Thesis submitted in fulfillment of the requirements for the joint Doctoral degree in

- Doctor of Medical Sciences – Doctor in de Medische Wetenschappen, Faculty of Medicine and Pharmacy at Vrije Universiteit Brussel
- Doctor of Medical Sciences – Doctor in de Medische Wetenschappen, Faculty of Medicine and Health sciences at University of Antwerp

DEPRESCRIBING MEDICATIONS IN NURSING HOMES

Using big data to study real-world implementation and effects on end-of-life-relevant outcomes

DEGEFAYE ZELALEM ANLAY

2025-2026

Promotors:
Prof. Dr. Joachim Cohen, Faculty of Medicine and Pharmacy, Vrije Universiteit Brussel
Prof. Dr. Tinne Dilles, Faculty of Medicine and Health sciences, University of Antwerp
Dr. Kristel Paque, Faculty of Medicine and Health sciences, University of Antwerp

PROMOTORS

PROF. DR. JOACHIM COHEN
End-of-Life Care Research Group (EOLC)
Vrije Universiteit Brussel, Belgium

PROF. DR. TINNE DILLES
Centre for Research and Innovation in Care (CRIC)
University of Antwerp, Belgium

DR. KRISTEL PAQUE
Centre for Research and Innovation in Care (CRIC)
University of Antwerp, Belgium

CHAIR OF THE JURY

PROF.DR. KATRIEN BEECKMAN
Nursing and Midwifery Research Group
Universitair Ziekenhuis Brussel & Vrije Universiteit Brussel, Belgium

Members of the jury

PROF. DR. PETRA DENIG
Clinical Pharmacy & Pharmacology
Universitair Medisch Centrum Groningen, Groningen, the Netherlands

PROF. DR. JOHAN WENS
Eerstelijns- en Interdisciplinaire Zorg Antwerpen(ELIZA)
University of Antwerp, Antwerp, Belgium

DR. MAARTEN WAUTERS
Centre for Research and Innovation in Care (CRIC)
University of Antwerp, Antwerp, Belgium

PROF. DR. KOEN PUTMAN
The Interuniversity Centre for Health Economics Research (I-CHER)
Vrije Universiteit Brussel, Brussels, Belgium

PROF. DR.TINNE SEMTS
End-of-Life Care Research Group (EOLC)
Vrije Universiteit Brussel, Brussels, Belgium

To Yeshi and Eyoab, whose love, patience, and unwavering support made this journey possible.

TABLE OF CONTENT

Abstract

Introduction

Nursing home (NH) residents often use many medications that are eligible for deprescribing, defined as the process of withdrawing inappropriate medications, including dose reduction or switching to safer alternatives to minimize harm. However, this population is largely excluded from clinical research, resulting in a limited evidence base to guide deprescribing practices.

Objectives

This dissertation aims to strengthen the evidence on the real-world implementation and effects of deprescribing potentially inappropraite medications (PIM) in NH residents through four aims: (1) establish a comprehensive evidence base by synthesizing tools and guidelines (2) investigate trends in deprescribing, the impact of existing guidelines on actual practice, barriers and enablers of deprescribing, and sustainability through the reinitiation of deprescribed medications in residents with limited life expectancy; (3) explore associations between changes in medication use and corresponding changes in end-of-life-care–relevant outcomes, and investigate the causal effect of proton pump inhibitor (PPI) deprescribing on these outcomes; and (4) analyse challenges in accessing and using big data.

Methods

For Aim 1, I conducted an umbrella review of systematic reviews on tools and guidelines supporting deprescribing. For Aim 2, I used linked healthcare reimbursement and Statistics Belgium data for a cohort of deceased NH residents (cohort 1), analysing trends with joinpoint regression, guideline impact with interrupted time series, and reinitiation with log binomial regression. Semi-structured qualitative interviews explored barriers and enablers. For Aim 3, I analysed a second dataset linking reimbursement and BelRAI long term care facility assessment data (cohort 2), examining one year changes in chronic and PIM use and end-of-life care–relevant outcomes, and their associations, a target trial emulation evaluated PPI deprescribing. For Aim 4, I conducted a case study based on both cohorts to identify challenges in data access and use, and develop recommendations.

Results

The umbrella review included 15 systematic reviews covering 95 tools and 9 guidelines. Fourteen tools targeted older adults with limited life expectancy, but the evidence base was limited, with substantial inconsistencies in medication appropriateness classification. Deprescribing of at least one PIM occurred in 30% of residents with small decline over time (0.47% per quarter), with no significant guideline impact on commonly used medicines. Reinitiation occurred in 17% of residents, varying by medication type (11 % in preventive and 20.3% in symptomatic). Interviews with 28 healthcare professionals identified barriers and enablers at macro (healthcare system and policy), meso (nursing home), and micro (individual) levels. In a prospective cohort study (n = 1691), chronic medication use increased (94.6% to 96.9%) while PIM use decreased (72.7% to 56.0%); 13% transitioned into polypharmacy and 8% out. These transitions were associated with worsening activity of daily living (ADL) and cognition, while higher PIM exposure was linked to decline in ADL, increased aggression, and greater comorbidity burden. In a target trial of 3604 residents, PPI deprescribing showed no effect on quality of life related outcomes but reduced hospitalizations by 19% and showed time varying

survival differences. Data access was slow and complex, taking up to 3.5 years, limiting research efficiency.

Conclusion

Deprescribing in NH residents with limited life expectancy remains insufficiently embedded in routine practice. This is concerning, as prescribing practices appear poorly aligned with residents' evolving clinical needs. Evidence from PPI deprescribing suggests it can be done safely without worsening quality-of-life-related outcomes and may reduce hospital admissions. Future efforts should focus on stronger implementation strategies, improved evidence across medications, and more efficient access to healthcare data.

Samenvatting

Introductie

Bewoners van woonzorgcentra (WZC) gebruiken vaak verscheidene geneesmiddelen die in aanmerking komen voor deprescribing, gedefinieerd als het proces van het stopzetten van ongeschikte geneesmiddelen, waaronder dosisverlaging of overschakeling naar veiligere alternatieven om schade te minimaliseren. Deze populatie wordt echter grotendeels uitgesloten van klinisch onderzoek, wat resulteert in een beperkte evidentiebasis om deprescribingpraktijken te sturen.

Doelstellingen

Dit proefschrift had tot doel de evidentie over de implementatie en effecten van deprescribing van potentieel ongeschikte medicatie (PIM) bij WZC-bewoners in de praktijk te versterken via vier doelstellingen: (1) het opbouwen van een uitgebreide evidentiebasis door het synthetiseren van tools en richtlijnen; (2) het evalueren van trends in deprescribing, de impact van bestaande richtlijnen op de praktijk, barrières en bevorderende factoren van deprescribing, en de duurzaamheid van deprescribing door het onderzoeken van het heropstarten van medicatie bij bewoners met een beperkte levensverwachting; (3) het onderzoeken van verbanden tussen veranderingen in medicatiegebruik en overeenkomstige veranderingen in uitkomsten relevant voor zorg aan het levenseinde, en het beoordelen van het causale effect van deprescribing van protonpompremmers (PPI's) op deze uitkomsten; en (4) het analyseren van uitdagingen omtrent toegang en gebruik van big data.

Methoden

Voor doelstelling 1 voerde ik een umbrella review uit van systematische reviews over tools en richtlijnen die deprescribing ondersteunen. Voor doelstelling 2 gebruikte ik gekoppelde gegevens van gezondheidszorgterugbetalingen en Statbel voor een cohort overleden WZC-bewoners (cohort 1), waarbij trends werden geanalyseerd met joinpoint-regressie, de impact van richtlijnen met interrupted time series, en de heropstart met log-binomiale regressie. Semigestructureerde kwalitatieve interviews verkenden barrières en bevorderende factoren. Voor doelstelling 3 analyseerde ik een tweede dataset die terugbetalingsgegevens koppelt aan BelRAI-gegevens van langdurige zorg (cohort 2), waarbij veranderingen (prospectief) over één jaar in chronisch en PIM-gebruik en relevante uitkomsten werden onderzocht, evenals hun associaties. Een target trial emulatie evalueerde de effecten van PPI-deprescribing. Voor doelstelling 4 voerde ik een casestudy uit op basis van beide cohorten om uitdagingen bij datatoegang en -gebruik te identificeren en aanbevelingen te formuleren.

Resultaten

De umbrella review omvatte 15 systematische reviews met 95 tools en 9 richtlijnen. Veertien tools waren gericht op ouderen met een beperkte levensverwachting, maar de evidentie was beperkt en er waren aanzienlijke inconsistenties in de classificatie van medicatiegeschiktheid. Deprescribing van minstens één PIM kwam voor bij 30% van de bewoners, met een lichte daling over de tijd (0,47% per kwartaal), en zonder een significante impact van richtlijnen op vaak gebruikte medicatie. Heropstart trad op bij 17% van de bewoners en varieerde per type medicatie (11% bij preventieve en 20,3% bij

symptomatische medicatie). Interviews met 28 zorgprofessionals identificeerden barrières en bevorderende factoren op macro- (zorgsysteem en beleid), meso- (woonzorgcentrum) en microniveau (individu). In een prospectieve cohortstudie (n = 1691) nam chronisch medicatiegebruik toe (94,6% naar 96,9%), terwijl PIM-gebruik daalde (72,7% naar 56,0%); 13% ging over naar polyfarmacie en 8% eruit. Deze veranderingen waren geassocieerd met verslechtering in activiteiten van het dagelijks leven (ADL) en cognitie, terwijl hogere PIM-blootstelling verband hield met achteruitgang in ADL, meer agressie en een grotere comorbiditeitslast. In een target trial emulatie bij 3604 bewoners had PPI-deprescribing geen effect op levenskwaliteitsgerelateerde uitkomsten, maar verminderde het hospitalisaties met 19% en toonde het tijdsafhankelijke verschillen in overleving. Toegang tot data was traag en complex en duurde tot 3,5 jaar, wat de efficiëntie van onderzoek beperkte.

Conclusie

Deprescribing bij WZC-bewoners met een beperkte levensverwachting is nog onvoldoende ingebed in de zorg. Dit is zorgwekkend, aangezien voorschrijfpraktijken slecht afgestemd lijken op de evoluerende klinische noden van bewoners. Evidentie rond PPI-deprescribing suggereert dat dit veilig kan worden toegepast zonder verslechtering van levenskwaliteit en wellicht ziekenhuisopnames vermindert. Toekomstige inspanningen moeten zich richten op sterkere implementatiestrategieën, betere evidentie voor verschillende medicaties en efficiëntere toegang tot gezondheidszorgdata.

Non-academic summary

Nursing home (NH) residents often take many medications every day. While some of these medicines are necessary and help treat symptoms or diseases, others may no longer be beneficial and may have limited value at the end of life. In some cases, these medicines can even cause harm. Medications with questionable benefits may therefore be suitable for deprescribing. Deprescribing means stopping a medication or reducing its dose. In recent years, increasing attention and efforts have been made to integrate deprescribing into routine practice, including the development of guidelines to support healthcare professionals. However, in daily practice, deprescribing is not always carried out consistently. This raises an important question: how are these efforts reflected in real-world practice? So far, there is still limited scientific evidence on what happens when medications with questionable benefits are stopped, particularly in terms of quality-of-life–related outcomes. This is especially important for nursing home residents, who often have a limited life expectancy and for whom quality of life is a key priority.

The research in this thesis aimed to examine real-world implementation of deprescribing in NH residents with limited life expectancy and evaluate its effects on health outcomes. These aims were addressed using several methodological approaches in separate studies. First, I reviewed existing research on tools and guidelines that help healthcare professionals decide which medicines to stop. In total, 95 tools and 9 guidelines were identified, of which 14 were specifically developed for people with limited life expectancy. However, the evidence for this group was often weak, and the tools did not always agree on which medications are appropriate or should be stopped.

Then, using national healthcare reimbursement and statistics agency data containing information about medicines, healthcare use, and sociodemographic data, I analysed how common deprescribing is, how it changed over time, and the rate of restarting after discontinuation. I found that nearly one in three residents had at least one unnecessary medicine stopped near the end of life, 1 in 5 residents restarted it again. More importantly and concerningly, although small, the rate of deprescribing decreased over time, and even after the publication of guidance, there was no change in trend. In another qualitative study, 28 healthcare professionals (doctors, nurses, and pharmacists) working in NHs shared their views on barriers and enablers to deprescribing and identified challenges at multiple levels, including the individual (patients and healthcare providers), the nursing home, and the healthcare system. These included, but were not limited to, extra time required without adequate compensation, lack of clear, context-specific guidance, fear of unintended consequences, poor communication across care settings and between professionals, and limited information sharing to support informed decision-making.

In a study using different data (national health care reimbursment data and nursing home assessment data “BelRAI”), I looked at how residents’ medication use and health changed over time, from their first assessment in the nursing home to one year later. Long-term medication use increased over time, and the use of medicines with questionable benefit decreased although only small. Taking more medicines was linked to no improvement or even worsening in health outcomes. In a separate study comparing residents who continued or stopped certain medications, stopping stomach acid medicines (proton pump inhibitors) did not worsen quality-of-life-related outcomes and reduced hospital visits by about 1 in 5, suggesting that some medicines can be safely stopped and may even improve outcomes. However, similar evidence for other medications is still limited, and more research is needed.

Finally, I conducted a study to identify the structural and practical challenges of accessing and using linked data for research based on the experience of the two data requests, which took up to 3.5 years, and showed that using large healthcare datasets is more difficult than expected and needs to be addressed.

Overall, the findings of this thesis show that deprescribing is not yet fully part of routine practice in NHs, even though it could benefit residents. More effort is needed to support deprescribing in practice, improve the evidence behind it, and make healthcare data easier and faster to access.

Niet-academische samenvatting

Bewoners van woonzorgcentra nemen vaak dagelijks meerdere geneesmiddelen. Sommige zijn noodzakelijk en helpen bij het behandelen van symptomen of ziekten, maar andere zijn mogelijk niet langer nuttig en hebben een beperkte waarde aan het einde van het leven. In sommige gevallen kunnen deze geneesmiddelen zelfs schadelijk zijn. Medicatie met twijfelachtig nut komt daarom in aanmerking voor deprescribing. Deprescribing betekent het stoppen van een medicijn of het verlagen van de dosis. In de afgelopen jaren is er meer aandacht en inspanning geweest om deprescribing in de standaard zorg te integreren, onder andere via de ontwikkeling van richtlijnen voor zorgverleners. Toch wordt deprescribing in de praktijk niet altijd consequent toegepast. Dit roept een belangrijke vraag op: hoe vertaalt dit zich in de dagelijkse praktijk? Tot nu toe is er nog beperkte wetenschappelijke evidentie over wat er gebeurt wanneer dergelijke medicatie wordt gestopt, vooral wat betreft levenskwaliteit. Dit is bijzonder belangrijk voor bewoners van woonzorgcentra, die vaak een beperkte levensverwachting hebben en voor wie levenskwaliteit een prioriteit is.

Het onderzoek in dit proefschrift had tot doel de implementatie van deprescribing in de praktijk te bestuderen bij WZC-bewoners met een beperkte levensverwachting en de effecten ervan op gezondheidsuitkomsten te evalueren. Deze doelstellingen werden onderzocht via verschillende studies met uiteenlopende methoden. Eerst voerde ik een overzicht uit van bestaande tools en richtlijnen die zorgverleners helpen beslissen welke medicatie gestopt kan worden. In totaal werden 95 tools en 9 richtlijnen geïdentificeerd, waarvan 14 specifiek ontwikkeld waren voor mensen met een beperkte levensverwachting. De evidentie voor deze groep was echter vaak zwak en de tools waren niet altijd eensgezind over welke medicatie geschikt is.

Vervolgens analyseerde ik gegevens, voor de hele Belgische bevolking, over zorg- en medicatieterugbetalingen en officiële sociodemografische gegevens. Hieruit bleek dat bijna één op drie bewoners minstens één onnodig geneesmiddel stopte aan het einde van het leven, maar één op vijf startte deze medicatie opnieuw. Belangrijk en zorgwekkend is dat het deprescribingpercentage licht daalde in de tijd en dat de publicatie van deprescribingrichtlijnen geen verandering bracht. In een andere studie deelden 28 zorgprofessionals (artsen, verpleegkundigen en apothekers) hun visie op barrières en bevorderende factoren. Ze identificeerden uitdagingen op individueel niveau, op niveau van het woonzorgcentrum en op niveau van het zorgsysteem, zoals tijdsgebrek zonder financiële compensatie, gebrek aan duidelijke richtlijnen, angst voor ongewenste gevolgen, slechte communicatie en beperkte gegevensdeling.

In een andere studie, met terugbetalingsgegevens en gegevens vanuit BelRAI-beoordelingen, onderzocht ik veranderingen in medicatiegebruik en gezondheidstoestand over één jaar. Langdurig medicatiegebruik nam toe, terwijl het gebruik van medicatie met twijfelachtig nut licht daalde. Het gebruik van meer medicatie was niet geassocieerd met betere gezondheidsuitkomsten en soms zelfs met verslechtering. In een aparte studie bleek dat het stoppen van maagzuurremmers (PPI's) geen negatieve invloed had op levenskwaliteit en de kans op ziekenhuisopname met ongeveer 20% verminderde. Dit suggereert dat sommige geneesmiddelen veilig kunnen worden gestopt en zelfs voordelen kunnen bieden. Voor andere geneesmiddelen is echter meer onderzoek nodig.

Tot slot onderzocht ik de structurele en praktische uitdagingen bij het verkrijgen en gebruiken van gekoppelde data voor onderzoek. De data-aanvragen duurden tot 3,5 jaar, wat aantoont dat het gebruik van grote gezondheidsdatasets complexer is dan verwacht en verbetering vereist.

Over het geheel genomen tonen de resultaten van dit proefschrift aan dat deprescribing nog geen vast onderdeel is van de routinezorg in woonzorgcentra, ondanks de mogelijke voordelen. Er is meer inspanning nodig om deprescribing te ondersteunen, de onderliggende evidentie te versterken en de toegang tot gezondheidsdata te verbeteren.

List of chapters

Chapters 2 to 8 of this thesis are based on the following publications.

Chapter 2

Anlay DZ, Paque K, Van Leeuwen E, Cohen J, Dilles T. Tools and guidelines to assess the appropriateness of medication and aid the deprescribing: an umbrella review. Br J Clin Pharmacol. 2023 Sep 11. doi: 10.1111/bcp.15906 [2022 IF 3.4; Ranking Q2; ranking 126/277 PHARMACOLOGY & PHARMACY]

Chapter 3

Anlay DZ, Paque K, Van den Eynden B, Dilles T, Cohen J. International Deprescribing Guidelines Did Not Impact Actual Practice in Deprescribing of Potentially Inappropriate Medications for Nursing Home Residents: An Interrupted Time Series Analysis. Drugs & Aging. 2025 May;42(5):485-499. 105122. doi: 10.1007/s40266-025-01197-2 [2023 IF 3.4; Ranking Q2; ranking 22/73 GERIATRICS & GERONTOLOGY]

Chapter 4

Anlay DZ, Peremans L, Cohen J, Dilles T, Paque K. Deprescribing for nursing home residents with limited life expectancy: A qualitative study to identify barriers and enablers for healthcare professionals. Geriatr Nurs. 2025 Feb 4;62(Pt B):1-11. doi: 10.1016/j.gerinurse.2025.01.049 [2023 IF 2.5; Ranking Q1; ranking 33/193 NURSING]

Chapter 5

Anlay DZ, Paque K, Brys ADH, Cohen J, Dilles T. Balancing palliative care needs and medication appropriateness: Initiation and reinitiation of medications at the end of life. Arch Gerontol Geriatr. 2025 Aug 23;139:105994. doi: 10.1016/j.archger.2025.105994. Epub ahead of print. PMID: 40916322. [2024 IF 3.8; Ranking Q2; ranking 22/73 GERIATRICS & GERONTOLOGY]

Chapter 6

Anlay DZ, de Almeida Mello J, Declercq A, Van Leeuwen E, Paque K, Cohen J, Dilles T. Evolution of Health and Medication Use in a Cohort of Nursing Home Residents: A Data Linkage Study. J Am Med Dir Assoc. 2026 Jul 2;27(8):106300. doi: 10.1016/j.jamda.2026.106300. Epub ahead of print. PMID: 42391777. [2025 IF 3.4; Ranking Q2; ranking 33/72 GERIATRICS & GERONTOLOGY in SCIE edition]

Chapter 7

Anlay DZ, Paque K, de Almeida Mello J, Declercq A, Van Leeuwen E, Dilles T, Cohen J. (submitted)The effect of deprescribing proton pump inhibitors on quality-of-life related patient outcomes among nursing home residents: a target trial emulation

Chapter 8

Anlay DZ, Paque K, Sabbe K, **Miranda R**, Dilles T, **Cohen J**. Structural challenges in accessing and using big data in health care: A case study based on palliative care research. Int J Med Inform. 2026 Jul 6;220:106593. doi: 10.1016/j.ijmedinf.2026.106593. Epub ahead of print. PMID: 42413364. [2025 IF 5; Ranking Q1; ranking 25/194 HEALTH CARE SCIENCES & SERVICES in SCIE edition]

PART I

GENERAL INTRODUCTION

Chapter 1

General introduction

1. Introduction

1.1. Aging population and demographic shift

As populations age, an increasing number of individuals live with multiple chronic conditions, often requiring the use of multiple medications.[1] European populations are undergoing a profound demographic shift driven by declining fertility rates and increasing life expectancy. [2] As a result, the proportion of older adults is rising rapidly across the European Union (EU). In 2024, individuals aged 65 years and older accounted for 21.6% of the EU population, a figure projected to increase to 32.5% by 2100. Belgium closely follows this trend, with 20 % of its population aged 65 years or older in 2024,[2] a proportion projected to exceed 25% by 2050. [3] Growth is particularly pronounced among ≥80 years, who represented 6.1% of the EU population and 5.5% of the Belgian population in 2024,[2] and projected to be 10.9 % in EU and 11% in Belgium by the year 2050. Life expectancy continues to increase alongside population ageing. In 2024, life expectancy at birth reached 81.7 years in the EU and 82.6 years in Belgium, exceeding levels observed in 2020 (80.4 years in the EU and 80.8 years in Belgium).[4]

While increased longevity reflects major public health achievements, the growing older population also leads to a higher prevalence of chronic diseases, multimorbidity (the co-existence of two or more chronic conditions in an individual, [5]) and functional limitations among older adults. These changes substantially increase the demand for long-term care (LTC), "*defined as a range of services required by persons with a reduced degree of functional capacity (physical or cognitive) and who are consequently dependent for an extended period of time on help with basic and/or instrumental activities of daily living (ADL.)*" [6] Long-term care can be delivered formally by healthcare professionals (HCPs) or informally by family or friends, either at home or in institutional settings such as nursing homes (NH). Monitoring the use of formal LTC services is an important indicator of the accessibility and sustainability of healthcare systems.[7] Home-based care is widely promoted, with NH based care generally reserved for situations in which extensive assistance is needed; nevertheless, a substantial share of older adults continue to reside NHs.[8] Approximately 6% of Belgians aged 65 years or older lived in NHs in 2018, exceeding the EU average of 3.0%.[9]

1.2. NHs and their residents characteristics: a frail population with limited life-expectancy

NHs provide care for older adults with multimorbidity, functional dependence, and cognitive impairment, whose needs can no longer be met at home. [10] Residents are typically frail, with high care dependency and limited life expectancy. [11-13] Admission occurs at advanced ages, with mean ages of 83.9 years in Europe and 84.6 years in Belgium as reported in 2015, [14] and this age profile has continued to increase over time, in Belgium reaching approximately 87 years for women and 84 years for men by 2021.[9] Following admission, the median length of stay prior to death in Europe is 73.4 weeks, with 42% of residents dying within one year, while in Belgium the median length of stay is 103.9 weeks and 32% of residents die within one year of admission. [14]

In this thesis, limited life expectancy (LLE) is defined as an expected survival of less than one year in a person with a life-limiting disease that cannot be treated with curative intent

Most residents have two or more chronic conditions at the time of death, ranging from 47.3% to 74.2% in Europe and 51.3% in Belgium, [14] with over 60% experiencing dementia. [15] Other life-limiting conditions, such as cancer (15.5%) and organ failure (34.7%), are also common, reflecting substantial palliative care needs. [15, 16] In Europe, 56.8% of residents receive palliative care, with the highest

proportion in Belgium (77.9%), although it is often initiated shortly, 2 weeks before death. [17] Treatment for multiple morbidity increases the treatment burden, poor medication adherence, adverse drug events, and complex treatment regimens, thereby amplifying the demand for long-term care. [18]

1.3. Medication burden in NH residents in the end of life context

Multimorbidity, which is common and often unavoidable among NH residents,[19] frequently necessitates treatment for multiple conditions, resulting in increased medication use. [20] This leads to polypharmacy, commonly defined as the concurrent use of five or more chronic medications,[21] which is particularly prevalent in NHs. Globally, the prevalence of polypharmacy is approximately 45% among older adults and reaches up to 70% among NH residents. [22] In Belgium, the prevalence is 43.4% among adults aged 65 years and older, [23] while 65% of NH residents aged 65 years and above are exposed to polypharmacy.[19]

Although polypharmacy may be clinically justified and is not inherently inappropriate,[19] as medications can be essential for symptom management and functional improvement,[24] ageing-related physiological changes increase vulnerability to medication-related harm. Reductions in hepatic and renal function, changes in body composition, and altered drug metabolism affect pharmacokinetics and pharmacodynamics, thereby increasing susceptibility to drug–drug interactions and adverse drug reactions (ADRs). [25, 26] NH residents are particularly vulnerable due to advanced age, frailty, complex health status, and the high number of medications often used. [24] Polypharmacy has been associated with a wide range of adverse outcomes, including falls, hospitalizations, cognitive impairment, functional decline, frailty, disability, renal failure, fractures, sarcopenia, and increased mortality, [24, 27, 28] with the risk of harm rising with each additional medication prescribed. [29] The association between high medication burden and unfavorable health outcomes indicates that polypharmacy is an important contributor to medication-related harm in NH residents. [24, 29] It is also essential to ensure that medications are not underused. Even when multiple drugs are prescribed, underuse of clearly indicated treatments has been linked to increased mortality and hospitalizations in older adults. [30, 31] This highlights the importance of regular medication review in NH residents to initiate beneficial treatments and discontinue unnecessary medications, thereby optimizing therapy and balancing benefits and risks.

The high prevalence of polypharmacy and its close relationship with multimorbidity, represents a major driver of potentially inappropriate medication (PIM) use [32-34]. PIMs are defined as "*medications lacking evidence-based indications, medications with treatment risks that may outweigh their benefits, medications significantly associated with adverse drug reactions, and those that may potentially interact with other medications or other diseases.*" [35]

1.4. NH residents and PIMs

PIMs are common and persisting challenges in NH settings, [36] largely driven by the high prevalence of multimorbidity and polypharmacy, and necessitate continuous efforts to optimize these medications. Residents often have a limited life expectancy or a life limiting disease requiring palliative care, [37] yet continue to receive complex medication regimens that were initiated earlier in the disease trajectory, [38] when long-term prevention and disease modification were the primary goals of care. As residents approach the end of life, the focus of treatment increasingly shifts from curative and preventive strategies toward symptom management and comfort. [39, 40] This transition should be reflected in medication use, as drugs intended for primary or secondary prevention may no longer offer

meaningful benefit within a limited life expectancy and may instead contribute to treatment burden or harm and be considered as PIMs. [41]

Although the prevalence of PIMs varies depending on the assessment tool and data source used, existing research consistently demonstrates a high use of PIM among NH residents, which increases with the number of prescribed medications [42] and substantially exceeds that observed in the general older population (36.7%). [43] Overall, reported PIM prevalence in NHs ranges widely, from 43.2% to 97.1%. [42, 44-48] Multi-country studies using Screening Tool of Older Persons Prescriptions in Frail adults with limited life expectancy (STOPP-Frail) criteria report that approximately 88% of residents have at least one PIM, with an average of more than two PIMs per resident. [47] Similar patterns are observed in Belgium, where 64.1% [49] to 88.3%[48] of residents were exposed to at least one PIM.

Common PIMs in NH residents include several medication classes that are consistently reported across studies to be associated with specific risks when used long term. Proton pump inhibitors (PPI), with a prevalence of 18.0% to 57.6%, [42, 44, 48-50] are indicated for acid related disorders and gastroprotection but are also associated with fractures, renal impairment, infections, and micronutrient deficiencies. [51] Benzodiazepines, used by 46.7% of residents, [45, 47, 50)] are mainly prescribed for insomnia but increase the risk of falls, fractures, cognitive impairment, and dependence. [52] Antipsychotics, with a prevalence ranging from 7.5% to 22.5%, [49, 50, 53] are commonly used for insomnia, psychosis, and behavioural and psychological symptoms of dementia, but are linked to cerebrovascular events, cognitive and functional decline, and increased mortality. [54] Antidepressants, used by 48.3% of residents, [44, 48] are indicated for mood and anxiety disorders and are associated with falls, hyponatremia, and anticholinergic burden. [55] In addition, long term preventive therapies such as lipid lowering agents, used in 11.4% to 21.5%, [49, 50] and calcium supplements, used in 16.3% of residents, [49] are frequently continued despite limited short term benefit in individuals with advanced frailty or limited life expectancy, contributing to the persistently high prevalence of PIMs in this population.

While overuse of medications is a major concern, underuse of clinically indicated treatments is also a significant challenge in NH residents. In Belgium, at least one potentially inappropriate omission has been reported in up to 85% of residents, [48] with similar findings in other countries, such as the underuse of PPIs in Australian NHs (38.5%).[56] At the same time, as residents approach the end of life, medications aimed at relieving symptoms and improving quality of life become increasingly important and are used more frequently, [57, 58] while preventive treatments are often continued. [58] These patterns highlight the need to balance overuse, underuse, and changing goals of care in this population. To optimise medication regimens, re-prescribing, which requires sound knowledge of each drug and is supported by regular medication review and monitoring, is essential, as it involves both initiating necessary treatments to address patients' current needs and discontinuing medications that are no longer appropriate. [59, 60]

1.5. **NH residents and deprescribing**

Deprescribing is a promising approach to address polypharmacy and reduce the use of PIMs and is defined as "*the process of withdrawal of an inappropriate medication, supervised by a health care professional with the goal of managing polypharmacy and improving outcomes."* Dose reduction and switching to safer alternative medications, aimed at maintaining effectiveness while minimizing harm, are also considered deprescribing strategies. [61, 62] However, evidence on the outcomes of deprescribing medications at the end of life remains limited and warrants further investigation.

Deprescribing has gained increasing recognition as a core component of patient safety and appropriate medication management in older adults and has been formally embedded within the global health agenda following the World Health Organization's call to reduce medication related harm by 50% within five years. [63] Despite growing awareness, the availability of deprescribing algorithms, clinical guidelines, and educational resources, the management of polypharmacy and PIMs remains challenging in NH settings. [24, 64, 65]

Evidence indicates that deprescribing interventions, including structured medication reviews, HCP education, and multidisciplinary approaches, can be effective. [66-69]Meta analytical evidence demonstrates substantial benefits, including reductions in PIMs by 59%, all-cause mortality by 26%, and the number of fallers by 24%. [70] Importantly, patients and caregivers are generally receptive to deprescribing; approximately three quarters of caregivers and up to 88% of patients report willingness to stop medications when advised by a physician. [71, 72]

However, real world implementation remains limited. Studies consistently report low deprescribing rates in NHs, with high prevalence of continued use of PIMs until the end of life and frequent new initiations. In Belgium, studies applying STOPPFrail criteria show that for only 20–31% of residents PIMs are discontinued in their last years of life without new inappropriate initiations, [49, 50, 73] while nearly half are continued [50] and approximately 30% involve new initiations. [73] Similar patterns have been observed across European NHs, where only 35.7% of PIMs were discontinued. [74] Near the end of life, not specific to NHs, continuation and initiation of PIMs remain common, including among residents with life-limiting conditions receiving palliative care. For example, in Sweden, 32.0% of older adults continued and 14.0% initiated at least one PIM near the end of life, [75] while in the United Kingdom only 4.46% of preventive medications were deprescribed. [76] Moreover, deprescribing often occurs reactively in response to adverse effects rather than proactively aligned with goals of care; in hospice settings, 87.5% of medication discontinuations in the final two weeks of life were reactive, compared with only 12.5% that were proactive. [77]

These findings from previous research highlight a substantial gap between evidence, patient willingness, and clinical practice, underscoring the need to better understand the barriers and enablers influencing deprescribing in NH settings.

1.6. NH residents and medication review

Medication review represents a key strategy to operationalise deprescribing by translating its principles into structured clinical practice. [78, 79] According to the Pharmaceutical Care Network Europe (PCNE), medication review is defined as "*a structured evaluation of a patient's medicines with the aim of optimising medicines use and improving health outcomes, through the identification of drug-related problems and the recommendation of interventions*." [80] Medication review adopts a broader, patient-centred approach that also includes the initiation of necessary treatments, dose optimisation, and alignment with current goals of care.

In NH residents, medication review and deprescribing interventions have consistently demonstrated effectiveness in reducing polypharmacy and the use of PIMs. [81] However, their impact on clinical outcomes remains variable and less conclusive. While earlier studies suggested potential benefits in outcomes such as falls and mortality, [82] more recent meta-analyses indicate that reductions in inappropriate prescribing do not consistently translate into significant improvements in these endpoints. [81] Furthermore, a recent systematic review synthesising evidence on outcomes of

deprescribing among individuals with life limiting illness emphasised the need to strengthen the evidence base on the effects of deprescribing for specific medication classes. Although reductions in PIMs are well established, patient-centred outcomes, remain underrepresented and warrant greater prioritisation. [83] This underscores the need for further high-quality research to better evaluate the effect of deprescribing in this vulnerable population.

1.7. Reasons for deprescribing

Deprescribing is essential when medications no longer provide meaningful benefit or may cause harm, as their continued use can negatively impact patient outcomes and quality of care. Beyond individual safety, unnecessary treatments contribute to increased healthcare costs and represent low-value care that should be actively addressed. [62, 84] Low-value care "encompasses overuse, misuse, and underuse of healthcare services and can lead to negative consequences for patients, their caregivers, the healthcare workforce, the health system as a whole, and the wider environment."[85] Furthermore, reducing avoidable medication use can help limit pharmaceutical waste and associated greenhouse gas emissions, supporting more environmentally sustainable healthcare. [86] Therefore, continuous and proactive efforts should be made to deprescribe medications that no longer provide value, supported by robust evidence to guide safe and effective clinical decision-making.

1.8. Barriers to deprescribing

Admission to NHs may offer favorable conditions for deprescribing, as residents have relatively longer stays and the time of admission to a NH provides a key opportunity for comprehensive medication review. [87] Despite evidence showing that deprescribing PIMs is safe, feasible, and often beneficial, with reductions in mortality, hospitalizations, and falls, [88-90] deprescribing is not yet routinely implemented in NH practice. Commonly reported barriers include incomplete access to patients' medical profiles, concerns about potential negative consequences of discontinuing medications, limited availability of clear deprescribing guidance, and beliefs in the ongoing benefit of certain treatments.[91] Additional barriers include communication difficulties with residents, relatives, and medical specialists, as well as insufficient multidisciplinary collaboration and resource constraints, which further hinders deprescribing efforts. [92, 93]

An international expert review has emphasized the need to strengthen the implementation and translation of deprescribing into routine clinical care and highlighted the importance of identifying context-specific barriers and enablers across settings and countries. [94] Understanding these factors is particularly relevant for NH residents, who have complex and unique healthcare needs and often limited life expectancy. [95] However, most existing research on barriers and enablers to deprescribing has focused on primary care or NH settings without a specific end-of-life focus, [96-99] limiting transferability to NH residents approaching the end of life. [100] Evidence in this population remains scarce, particularly for residents with limited life expectancy or palliative care needs. [41, 101] In Belgium, research on barriers to deprescribing in NHs has explored specific medication classes, such as benzodiazepine receptor agonists, [102] and antidepressants, [103] with little attention to broader barriers and enablers in end-of-life care. Addressing these gaps by exploring barriers and enablers to deprescribing as experienced by HCPs in NHs is essential to inform theory-driven intervention development and improve medication management for residents nearing the end of life.

1.9. Existing deprescribing tools and guidelines for limited life expectancy

Growing attention to PIMs and deprescribing in geriatrics and pharmacology has led to the development of several expert validated tools and guidelines. [104] However, only a limited number

specifically address end of life care, and these typically cover a limited set of medications. [105, 106] Tools designed for individuals with limited life expectancy include STOPPFrail (2017, updated 2021), [20, 107] the Morin et al. list for patients with a life expectancy of three months or less (2018). [108]

However, the classification of medication appropriateness at the end of life is largely based on expert opinion and clinical experience rather than high-level evidence. [106] This is reflected in the discrepancies between existing tools regarding the appropriateness of medications for use at the end of life. [105] Moreover, medications considered inappropriate in older adults with normal or limited life expectancy may still be appropriate for symptom relief in palliative care, yet existing tools do not always clearly distinguish appropriateness within the palliative care context at the end of life (e.g.;PPI, antipsychotics). [109]

Despite the contributions of international experts in developing and promoting deprescribing guidelines, [110] and advocacy for their integration into clinical practice guidelines, [111] these recommendations remain largely standalone and are not routinely embedded within clinical guidelines. [51, 52, 54] Only around 29% of clinical practice guidelines include deprescribing recommendations. Even when deprescribing recommendations are included in clinical guidelines, they often lack clear and actionable steps, limiting their uptake in routine practice, [112] and insufficient pharmacological guidance has been identified as a major barrier for physicians to initiate deprescribing. [91] The ultimate purpose of deprescribing guidelines is to drive meaningful changes in clinical practice. However, the publication of guidelines and tools alone may be insufficient to achieve substantial changes in clinical practice without dedicated implementation strategies. Their effectiveness, for example through STOPPFrail-guided interventions, has been demonstrated in a randomized controlled trial [113] and small-scale pre-post study[114], showing reductions in PIMs and associated costs. Nevertheless, trends in deprescribing rates overtime in real-world settings remains unclear. In addition, it has not been established whether the publication of these guidelines has influenced these trends.

1.10. Need for high-level evidence on the effects of deprescribing at the end of life

NH residents are consistently underrepresented in clinical research, which constrains the evidence base informing deprescribing practices in this population. Generating robust evidence on deprescribing in NH populations, particularly near the end of life, is constrained by practical and ethical challenges that often make real-life randomized controlled trials infeasible. Practically, residents frequently present with high clinical complexity, including multiple chronic conditions, and marked heterogeneity in physical and cognitive functioning, which complicates recruitment and retention of sufficiently large sample sizes and limits the feasibility of conducting RCTs with good internal and external validity. Ethically, safeguarding this highly vulnerable population and navigating complex consent procedures, which often involve family members or legal proxies, is required due to potential risks associated with deprescribing, further complicating recruitment. The current practice in deprescribing medications near the end of life therefore largely relies on extrapolated evidence, expert consensus, and clinical experiences rather than high-level evidence from randomized controlled trials and the impact of deprescribing on clinical outcomes is currently unclear. [115] Given the assumed impact of inappropriate prescribing on patient outcomes, a need for robust, high-level evidence to appraise the appropriateness of medications at the end of life occurs in order to validate existing tools and guidelines, to adapt them to palliative care, and to support the development of new deprescribing guidelines. Furthermore, this information can be used to guide and support clinicians in

prescribing beneficial and deprescribing medications with questionable benefits at the end of life, and for the development of quality improvements projects in NHs.

Importantly, the success and sustainability of deprescribing depend on outcome measures that are clinically meaningful and centered on patients and care providers. [116] At the end of life, patient centered outcomes such as quality of life, encompassing physical, mental, cognitive, and functional domains, are highly valued, yet they have received limited attention in health evaluations. [117, 118]

Given all the challenges of conducting RCTs and the pressing need for evidence, alternative research approaches that approximate RCTs are required to advance the evidence base. This underscores the growing importance of real-world data and large-scale observational datasets to study deprescribing at the end of life.

1.11. Big data to study deprescribing at the end of life

The concept of "Big Data" is continually evolving and is characterized by 5 V's, which highlight its essential characteristics: *volume*, representing the massive amounts of data generated; *velocity*, describing the high speed at which data is created, processed, and transmitted; *variety*, which refers to the diverse formats and sources of data, including structured, semi-structured, and unstructured types; *value*, focusing on the meaningful insights and benefits that can be derived from analyzing the data; and *veracity*, addressing the uncertainty, inconsistencies, and reliability challenges associated with data quality. [119] In the context of end of life, big data offers substantial opportunities in palliative and end-of-life care research. [120] By analyzing large, linked datasets, it enables the study of complex clinical and healthcare patterns in populations where randomized trials are often impractical. [121] This approach provides real-world insights into medication use, treatment outcomes, and healthcare utilization, helping to inform clinical practice and guide evidence-based decision-making. [122] The big promise of big data in end of life care research seems to be that it can offer a lot to end of life research in a short time, with little effort, and big impact. As a result, researchers are increasingly utilizing big data across various disciplines to explore interdisciplinary challenges and gain new insights by linking and analyzing large and diverse datasets. However, the use of big data presents significant challenges that researchers must navigate to ensure data quality and integrity, protect privacy and security, and manage the sheer volume, variety, and complexity of the data. [123-125] Researchers also face practical barriers when accessing and utilizing data, such as lengthy turnaround times, inconsistent access procedures, and difficulties in data linkage. [126, 127]

In Belgium, several databases have been identified to study end-of-life care research on a population level including InterMutualistisch Agentschap-Agence InterMutualiste (IMA-AIM) national registry of health care claims data, the Cancer Registry, and databases managed by Statistics Belgium including socio-economic data, fiscal data and death certificate database. [128] Prior studies used these data to study appropriateness of end of life care [129] and also deprescribing. [109] In the context of deprescribing, regardless of the population studied, large-scale RCTs of deprescribing are unlikely, as deprescribing lacks commercial incentive and therefore rarely attracts pharmaceutical industry funding. In addition, practical challenges related to the frail and heterogeneous nature of the population often hinder the conduct of non-commercial trials. Moreover, given the large number and diversity of PIMs, it is unlikely that randomised controlled trials can be conducted to generate causal evidence for each individual medication. As a result, research based on routinely collected health care data has become one of the most essential and practical options for studying deprescribing. In this context, the use of large-scale real world data offers important opportunities to generate evidence across multiple

medications and populations. However, it required innovative use of data to distinguish intentional deprescribing from other forms of medication discontinuation to improve quality of evidence, [130, 131] as deprescribing is not routinely documented in current clinical practice. [132]

Collecting clinical and medication data at multiple time points from a large sample of NH residents with limited life expectancy would be resource-intensive, making the efficient and innovative use of linked routinely collected big health data both a solution and a challenge. While administrative databases provide detailed information on medication use, diagnoses, and health care utilization, they generally lack structured information on patient centered outcomes. Advances in health information systems have created opportunities to collect such outcomes more systematically and repeatedly over time, supporting a learning health care system in which emerging evidence can be more rapidly translated into clinical practice. [133] Patient reported outcomes capture patients' own perspectives [134] or patient-relevant outcomes via proxy reports or observations from caregivers, HCPs, or parents and guardians are particularly meaningful at the end of life. [135] In long term care settings, the interRAI Long Term Care Facility (LTCF) assessment offers a unique source of standardized, longitudinal data across multiple health domains, including physical, cognitive, psychological, and functional status. Linking interRAI data with administrative medication data enables the study of medication use over time in relation to changes in residents' health outcomes and the effect of deprescribing medications on quality of life related patient outcomes for which the evidence needed currently. In this dissertation, Belgian health insurance data were linked with the Belgian versions of interRAI (BelRAI LTCF) assessments, representing a pioneering effort to link these complementary data sources for the purpose of studying deprescribing and its effect.

In summary, building on the key concepts and evidence presented in the previous section (introduction), the main points are outlined below (Table 1), structured around what is already known, what additional knowledge is needed and addressed in this thesis, and why this knowledge is important.

Table 1. Summary of current knowledge, research gaps, and rationale for this thesis

What is already known	What additional knowledge is needed	Why this knowledge is needed
Tools and guidelines have been developed to assist clinicians in assessing medication appropriateness, deprescribing PIMs, and prescribing beneficial medications, particularly for vulnerable populations. Due to cultural, societal, and medical differences, a variety of tools and guidelines have been developed for diverse healthcare settings to support clinicians' decision-making and enhance their self-efficacy in medication management. [136] *Systematic reviews have summarized these tools and guidelines over time.* [137] however, only a few have integrated the medications included within them. [138-142]	*Existing reviews have not compiled medication lists based on appropriateness for older adults with limited life expectancy, nor have they clearly described the level of evidence supporting the medications included in the tools and guidelines.*	*The review can inform the development of widely applicable, evidence-based medication lists, highlight areas requiring further research, and facilitate evidence generation. Particularly for this thesis, the synthesis of evidence is essential because our subsequent quantitative studies depend on the review; therefore, this study serves as a preparatory phase for a subsequent quantitative study by guiding the selection of tools, guidelines, and medications for inclusion in further analyses.*
The ultimate purpose of deprescribing guidelines is to drive meaningful changes in clinical practice. *The effectiveness of deprescribing guidelines, such as STOPPFrail guided interventions, has been demonstrated in RCT and small-scale pre-post studies, showing positive outcomes in reducing PIMs and costs.* [113, 114]	*Whether the publication of STOPPFrail and other deprescribing guidelines for residents with limited life expectancy has influenced real world deprescribing practices,* [20, 51, 54] *and how deprescribing rates have evolved over time, remains unclear.*	*Assessing deprescribing trends is crucial for understanding how PIMs management is evolving in nursing homes and for determining whether the publication of international deprescribing guidelines has contributed to changes in practice. Tracking these patterns over time provides evidence-based insights to inform deprescribing efforts and shows whether practices are changing. Such insights can help stakeholders develop targeted interventions and policies to enhance deprescribing, ultimately improving safety and quality of care for nursing home residents approaching the end of life.*
Deprescribing is not routinely implemented, and effective translation into routine care requires understanding context specific barriers and enablers across settings and countries. [94] *At the end of life, as care goals shift,* [39, 40] *medications that were appropriate may become inappropriate, creating a need to deprescribe multiple medications.* [41] *Existing research has largely focused on primary care or on specific medications.* [96-99, 102, 103]	*Despite the high burden of drug use in nursing home residents,* [57, 58] *limited attention has been given to exploring barriers and enablers of deprescribing in the context of end-of-life.*	*Exploring barriers and enablers to deprescribing using a theory-informed approach can support the development of context-based interventions that are more likely to be successfully implemented and sustained.* [143, 144]
Previous research on PIMs in older adults has largely focused on patterns of initiation, continued use, or deprescribing during the disease trajectory, but they provides limited insight into reinitiation at the end of life. [73, 105] *In this context, medications considered inappropriate earlier in the disease trajectory may become appropriate due to changes in goals of care. There is also recognised uncertainty regarding medication appropriateness at the end of life, as existing deprescribing tools and criteria often diverge in their recommendations.* [105]	*Empirical evidence is lacking on how often medications deemed inappropriate earlier in the disease trajectory are reinitiated after prior discontinuation near the end of life.*	*Reinitiation may reflect appropriate palliative use, unsuccessful deprescribing, or gaps in medication appropriateness assessment that lead to unnecessary prescribing. Understanding these patterns is important for strengthening the evidence base that supports deprescribing decisions.*
Medication use in nursing home residents, including chronic and PIMs, remains high.[145] *While patient-centred care is increasingly promoted,*[146] *research has mainly focused on*	*Longitudinal evidence quantifying changes in chronic medication use and PIMs (continued,*	*Understanding how medication use aligns with or diverges from patients' needs and priorities, particularly in relation to multidimensional quality-of-life-releted outcomes in nursing*

prescribing patterns and their association with well-established outcomes such as healthcare utilisation and mortality, [83] with limited attention to quality-of-life related outcomes, despite their relevance to nursing home residents. [116-118] Moreover, most studies rely on single time-point assessments [147] and seldom examine longitudinal changes after admission to nursing home or how medication use evolves, alongside changes in these outcomes, largely due to feasibility constraints.	*discontinued, newly initiated, or no use), and examining how these changes are associated with multidimensional quality of life related outcomes outcomes (decline, no change, or improvement) remains limited.*	*home residents, is essential to support more goal oriented medication management. Leveraging innovative data linkage approaches offers a unique opportunity to generate longitudinal evidence on these relationships, while also providing insight on the feasibility of using such linked real-world data for future research.*
PPIs continue to be widely and persistently prescribed among nursing home residents worldwide, [56, 148-154] often beyond recommended durations of use (typically less than 8 weeks), while deprescribing rates remain low. [155] Long-term use without a clear indication increases treatment burden and costs and has been associated with adverse effects such as nutrient deficiencies, kidney disease, and infections. [156-158] At the same time, underuse in high-risk patients has also been reported, [56] highlighting PPIs as a key target for medication optimisation in older adults as well as for further research. [159]	*Robust causal comparative evidence on the effects of deprescribing versus continued long-term PPI use on quality of life related outcomes in nursing home residents is lacking.*	*Comparative evidence on PPI deprescribing versus continued use in clinically relevant outcomes is essential to guide clinical decision-making in nursing home residents, where trade-offs between quality-of-life related outcomes, individual treatment goals, and costs need to be carefully balanced.*
Big data offers transformative potential for end-of-life and palliative care research, where RCTs are often infeasible. [128]	*Practical and structural challenges related to accessing and using national-level datasets remain insufficiently documented, despite being crucial for guiding data users, data holders (agencies providing data), and policymakers*	*Drawing on experience from multiple end-of-life care research projects, persistent practical and structural challenges in accessing and utilising national-level datasets are evident, with important implications. Articulating these challenges provides a more realistic understanding of the potential and limitations of big data, moving beyond expectations of rapid and low-cost insights, and offers actionable guidance to researchers, policymakers, and data holders to improve data access, use, and governance*

2. Aims of the doctoral study

*The **overall aim** of this thesis is to strengthen the evidence on the real-world implementation of deprescribing in nursing home residents with limited life expectancy and on the effects of deprescribing medications on outcomes relevant to end-of-life care, addressing the evidence gaps identified in existing deprescribing tools and guidelines through the use of linked population-level health-care data.*

To achieve this overarching aim, the thesis is structured into four specific aims.

Aim 1: To establish a comprehensive evidence base for deprescribing by identifying available tools and guidelines for assessing medication appropriateness and aiding deprescribing of PIMs, evaluating their development and validation methods, developing a comprehensive thematic list of medications extracted from identified tools and guidelines categorized based on the target populations (older adults with limited life expectancy, older adults with normal life expectancy) and describing the available level of evidence supporting the medications included in the identified tools and guidelines. Therefore, the work conducted under this aim serves as a foundational component of the thesis, as it informs the selection of relevant tools, guidelines, and medications for subsequent quantitative analyses.

Aim 2: To investigate the real-world implementation of deprescribing in nursing home residents with limited life expectancy by analysing trends in deprescribing and the impact of international deprescribing guidelines (STOPPFrail, proton pump inhibitors, and antipsychotics) on these trends; identifying barriers and enablers influencing healthcare professionals' deprescribing practices; and evaluating the sustainability of deprescribing decisions through patterns of initiation and reinitiation of medications deemed inappropriate according to STOPPFrail criteria.

Aim 3: To assess the effects of deprescribing medications on end-of-life care–relevant outcomes by exploring the associations between longitudinal changes in chronic medication use and PIMs and changes in quality-of-life–related health outcomes over time, and by investigating the effect of deprescribing specific medication classes, particularly proton pump inhibitors, on these outcomes.

Aim 4: To analyse the practical and structural challenges in accessing and using linked national healthcare administrative data for end-of-life research, using the data requested for this PhD project as a case study, and to formulate actionable recommendations for researchers, data holders, and policymakers based on this analysis and informed by first-hand experience.

3. Methods used within this dissertation

To address the aims of this dissertation, a multi-method study design was employed, comprising a review (Chapter 2), quantitative studies (Chapters 3, 5, 6, and 7), a qualitative study (Chapter 4), and a case study (Chapter 8), drawing on multiple data sources.

3.1 Synthesis of medication appropriateness lists

An umbrella review was conducted (Chapter 2) to systematically review existing systematic reviews summarizing tools and guidelines used to evaluate medication appropriateness and support deprescribing decisions. Although the significant number of available systematic reviews provided a foundation for the umbrella review, their limitations, particularly the frequent omission of detailed medication lists from the included tools, necessitated a complementary approach. Therefore, the reviews were primarily used to identify and access the underlying tools and guidelines, which were then analyzed in detail.

In this dissertation, a distinction was made between "tools" and "guidelines" based on their specific purposes, although these terms are often used interchangeably in the literature. Tools were defined as resources primarily aimed at identifying the appropriateness of medications and may be explicit, providing predefined criteria or medication lists, implicit, relying on clinical judgment and individualized assessment, or mixed, combining explicit criteria with implicit evaluation. [160] Guidelines were defined as resources that support clinicians in identifying and deprescribing PIMs by providing explicit advice on when, why, and how to stop or taper medications.

The identified tools and guidelines were synthesized and thematically categorized by target population (i.e., older adults aged 65 years or more with normal life expectancy, individuals with limited life expectancy, and paediatric populations). Medications listed in explicit and mixed tools were systematically extracted and compiled into comprehensive medication lists for each population group. To avoid duplication, the genealogy of tool development was assessed, [161] and for tools with multiple versions, only the medications included in the latest version were extracted.

3.2 Qualitative study

A qualitative descriptive study was conducted using semi-structured interviews, guided by the literature and the Theoretical Domains Framework (TDF), with a purposive sample of 28 HCPs (physicians, nurses, and pharmacists) involved in the care of NH residents in Flanders, Belgium.

Data analysis was guided by reflexive thematic analysis, [162] allowing for a flexible and in-depth exploration of barriers and enablers of deprescribing within the complex, context-specific end-of-life care setting of NHs, without imposing rigid analytical constraints. Using the TDF as a lens, the inductively identified barriers and enablers were mapped to the TDF domains, which were then linked to corresponding behavior change techniques (BCTs) to inform deprescribing interventions. This theory-informed approach was used because it can support the development of interventions that are more likely to be successfully implemented. [143, 144]

3.3. Measuring deprescribing trends and guideline impact and PIM reinitiation

3.3.1. Data source: administrative databases

To evaluate deprescribing trends, the impact of international deprescribing tools and guidelines, and the rates of initiation and reinitiation of PIMs, we requested and accessed linked population-level

administrative databases previously identified as suitable for end-of-life care research. [128] Data were obtained from the Intermutualistic Agency of Belgium (IMA) and Statistics Belgium (Statbel).

The IMA-AIM provided 5 databases:

1. ***Population database*** with socio-demographic characteristics of all insured persons. In Belgium, where healthcare insurance is legally mandatory, data include more than 99% of the population,
2. ***Healthcare claims database*** containing all reimbursed treatments and medications from seven healthcare insurers, except medications delivered at the community pharmacies,
3. ***Pharmanet database*** containing all reimbursed medication data dispensed at community pharmacies,
4. ***Hospitalization database*** containing all hospital admissions, and
5. ***Katz-scale database*** containing all mandatory evaluations of independence in activities of daily living for patients in outpatient nursing care or staying in NHs.

Statbel provided 3 additional linked databases:

1. ***Death certificate database*** with place and all causes of death
2. ***National demographic database***, containing socio-economic survey data and national census data including educational levels
3. ***National fiscal database*** includes net taxable income

For each NH resident, the databases were deterministically linked using a unique identifier based on multiple encrypted social security numbers. Using these linked data, we conducted decedent-based studies (Chapters 3 and 5). Measures of medication deprescribing, reinitiation, and initiation in the quantitative analyses were derived from administrative reimbursement data and therefore did not capture medications not reimbursed by the Belgian health care system or over-the-counter medications.

3.3.2. Analysis of deprescribing trend and impact of deprescribing guidelines

Using a cohort of deceased NH residents with limited life expectancy over a six-year period (2014–2019), aged 65 years or older at the time of death and having received at least one reimbursed healthcare service, we aggregated residents who died in the same month and year and included all reimbursed medications dispensed during the year preceding death. A decedent cohort design was used to assess underlying changes in deprescribing rates over time. Joinpoint linear regression models were applied to identify statistically significant changes in trends by detecting “joinpoints”, defined as time points at which trends significantly changed. For each linear segment, quarterly percent change (QPC) was estimated, and the average quarterly percent change (AQPC) with 95% confidence intervals (CI) was calculated as a weighted summary measure of overall trends. [163] To assess the impact of the publication of deprescribing guidelines (STOPPFrail, proton pump inhibitor, and antipsychotic guidelines), an interrupted time series analysis was conducted using autoregressive integrated moving average (ARIMA) modelling. [164]

3.3.3. Analysis of initiation and reinitiation rate of PIMs

A decedent cohort study was conducted among NH residents aged ≥65 years who died between 2015 and 2019 with a condition potentially amenable to palliative care. A log-binomial regression model was used to assess the association of socio-demographic and clinical factors with reinitiation (restarting after prior discontinuation) or initiation (starting regardless of prior use) of STOPPFrail-listed medications in the last three months of life, estimating relative risks with 95% CIs.

3.4. Measuring the evolution of chronic medication use, PIMs and quality-of-life-related patient outcomes: effects of deprescribing

3.4.1. Data sources: administrative databases and BelRAI clinical assessment data

To describe the evolution of chronic medication use and quality-of-life-related patient outcomes, and to investigate the effects of deprescribing long-term PPIs, we used linked IMA-AIM administrative data (Section 3.3.1) and BelRAI LTCF assessment data provided by Pyxicare.

BelRAI LTCF is the Belgian implementation of the international InterRAI LTCF assessment as part of the interRAI Suite of instruments, [165] a standardized, multi-domain instrument developed by an international network of researchers and practitioners. [166] It systematically captures residents' health across key domains, identifies clinical triggers for intervention, and includes validated outcome scales for monitoring changes over time. In Belgium, the implementation of BelRAI has evolved through successive pilot studies and early adoption initiatives. Following earlier testing phases of interRAI instruments, BelRAI LTCF was introduced across multiple care settings through multidisciplinary pilot projects, including those initiated from 2016 onwards, as preparation for wider implementation. In 2018, federal and regional entities formally agreed on a national rollout of the BelRAI system; however, the pace and extent of implementation have varied across regions. Flanders is currently the only region where the use of interRAI LTCF has become mandatory in all NHs, as of June 1, 2023, with all residents having at least one assessment by June 1, 2025. The data used in this thesis, covering the period from 2016 to the end of 2022, therefore originate from pilot settings and early-adopting NHs that had integrated BelRAI LTCF into routine practice before its formal mandate. The region of Flanders mandates a baseline assessment for all NH residents by day 4, following a 3-day observation period, with follow-up assessments conducted every six months or after any significant changes in the resident's condition.

The BelRAI LTCF instrument includes validated outcome scales across key health domains. These scales are automatically calculated from resident assessment items and provide multidimensional measures, including physical function (Activities of Daily Living [ADL]), cognitive function (Cognitive Performance Scale), social function (Revised Index of Social Engagement [RISE]), mood and behavior (Aggressive Behavior Scale, Depression Rating Scale), and health status (Changes in Health, End-stage disease, Symptoms and Signs [CHESS Scale], Fall Risk Scale, Pain Scale). In addition, BelRAI LTCF contains sections relevant to this thesis, such as identification information (e.g., legal status) and disease diagnoses (e.g., chronic conditions).[166]

3.4.2. Evolution of chronic medication use, PIMs, and quality-of-life-related patient outcomes

A cohort study was conducted using the prospectively collected IMA-BelRAI linked data described above, including NH residents whose first BelRAI assessment occured between 2016 and 2022. NH residents aged ≥65 years were assessed at baseline (defined as the first BelRAI assessment after NH admission) and again one year later. Changes in medication use and outcome scales between the two

time points were assessed using the McNemar test for variables with two categories and the Stuart–Maxwell test for variables with more than two categories. Wilcoxon rank-sum tests were used for non-normally distributed continuous variables, and paired t-tests were applied for normally distributed continuous variables. Trends in chronic medication use and PIMs between 2016 and 2022 were evaluated using the Cochran–Armitage trend test. Associations between changes in medication use and changes in outcome scales were examined using χ^2 tests (when expected cell counts were ≥5 in all cells) or Fisher's exact tests (when expected cell counts were <5 in any cell), as appropriate.

3.4.3. Effect of deprescribing proton pump inhibitors (PPI)

A two-arm pragmatic randomized trial was emulated using linked BelRAI LTCF assessments and national health insurance claims data. [167] Residents aged ≥65 years with at least three months of continuous PPI use prior to baseline (first BelRAILTCF assessment after NH admission) were eligible. At baseline, residents were assigned to either deprescribing (no active PPI supply, with the last dispensing ending within 30 days before assessment) or continued use. The primary causal contrast was the intention-to-treat effect of deprescribing versus continuation.

Outcomes were assessed over 12 months (at 0, 3, 6, and 12 months), including six quality-of-life–related measures (activities of daily living, cognition, depressive symptoms, pain, falls, and self-reported health) as primary outcomes, and all-cause mortality and number of hospitalizations as secondary outcomes. Confounder selection was guided by a directed acyclic graph (DAG), and inverse probability of treatment weighting (IPTW) was applied to balance baseline confounders between the deprescribing and continuation groups. [168] Average treatment effects were estimated using marginal structural models, applying weighted generalized estimating equations (wGEE) for the primary outcomes, negative binomial regression for hospitalization counts, and restricted mean survival time (RMST) for mortality. Missing covariate and outcome data were handled using multiple imputation (MI) with fully conditional specification.

3.5. Case study of structural challenge of big data access and use

Using a case study within this PhD project, we examined two national-level data requests to identify structural challenges in data access and their implications. These included Cohort 1, linking IMA-AIM data with data from Statistics Belgium, and Cohort 2, linking IMA-AIM with BelRAI LTCF. We conducted a document analysis using an adapted READ approach (Ready materials, Extract data, Analyse data, Distil findings) on materials generated throughout the data access process, including email correspondence, meeting minutes, and data application and approval documents.

For each cohort, we extracted time intervals between key stages of data access: first contact with the data holders and submission to the Information Security Committee (ISC) for authorization, ISC submission and approval, ISC approval and data delivery to the researcher, period from data delivery to identification of errors by the researcher, and time from error identification to redelivery of corrected data. These timelines were illustrated graphically.

Challenges related to data access and use were grouped into key themes. The identified challenges and their implications were discussed with data holders to incorporate their perspectives. Based on these insights, recommendations were developed for researchers, data holders, and governments.

4. Outlines of this dissertation

This dissertation consists of six parts: **PART I** (general introduction), **PARTS II to V** (main findings), and **PART VI** (general discussion). Chapters 2–8 within parts II to V are based on articles that have been published or submitted to international peer-reviewed journals. **PART I** introduces the dissertation by outlining the introduction, the aims of the thesis, and the methods used within this dissertation (**Chapter 1**).

PART II present the evidence foundation for deprescribing research and practice. **Chapter 2** synthesizing existing medication appropriateness tools and deprescribing guidelines through an umbrella review, compiles comprehensive medication lists, and evaluates the level of supporting evidence for older adults with limited life expectancy and other target populations.

PART III provides insight into the real-world implementation of deprescribing in NH residents with limited life expectancy, encompassing deprescribing trends, guideline impact, barriers and enablers to deprescribing for HCPs', and initiation and reinitiation of medications deemed inappropriate at the end of life. **Chapter 3** describe deprescribing trends over time and assesses changes following the publication of international deprescribing guidelines using interrupted time series analyses. **Chapter 4** explores HCPs' barriers and enablers to deprescribing through a qualitative descriptive study informed by the Theoretical Domains Framework (TDF), and **chapter 5** determines the rate of reinitiation and initiation of medications deemed inappropriate by STOPPFrail criteria near the end of life.

PART IV provides longitudinal evidence on individual trajectories of the use of chronic medication and PIMs, their associations with quality of life related patient outcomes, and investigate the effect of deprescribing on these outcomes. **Chapter 6** describe longitudinal evidence on individual trajectories of chronic medication use and PIMs, comparing baseline and one-year follow-up assessments, and exploring the associations between changes in medication use and quality-of-life-related outcomes. **Chapter 7** present the comparative effects of deprescribing versus continued use of long-term proton pump inhibitors on quality-of-life-related outcomes using a target trial emulation.

PART V outlines data access and structural challenges in big data healthcare research. **Chapter 8** presents a case study of two national-level data requests, illustrating the potential of big data for end-of-life and palliative care research. It traces the process of data access, highlighting the practical and structural challenges encountered in accessing, linking, and using administrative and clinical datasets. Based on this analysis, the chapter provides actionable recommendations for researchers, data holders, and policymakers

PART VI concludes the dissertation by providing a general discussion of the main findings, reflects on methodological strengths and limitations, and presents implications for policy, practice, and future research, concluding the dissertation **(Chapter 9)**.

References

1. World Health Organization. Medication safety in polypharmacy: technical report. World Health Organization; 2019.
2. Eurostat. Population structure and ageing [updated February 2025. Available from: https://ec.europa.eu/eurostat/statistics-explained/index.php?title=Population_structure_and_ageing.
3. Statbel en het Federaal Planbureau. Bevolkingsvooruitzichten 2023-2070 [updated February 13, 2024; cited 2024 April 08]. Available from: https://www.plan.be/databases/data-35-nl-bevolkingsvooruitzichten_2022_2070.
4. Eurostat. Life expectancy by age and sex [updated 11/09/2025 Available from: https://ec.europa.eu/eurostat/databrowser/product/page/DEMO_MLEXPEC.
5. Skou ST, Mair FS, Fortin M*, et al.* Multimorbidity. Nat Rev Dis Primers. 2022;8(1):48.
6. European Commission. The 2015 Ageing Report: Economic and budgetary projections for the 28 EU Member States (2013-2060). 2015.
7. For a healthy Belgium: Care for older people [updated 01 February 2024; cited 2024 April 09]. Available from: https://www.healthybelgium.be/en/health-system-performance-assessment/specific-domains/care-for-the-elderly.
8. Elderly care homes: Belgium is 4th biggest spender in Europe. The Brussels Times. 2022 May 25.
9. S Gerkens, M Lefèvre, N Bouckaert, M Levy, C Maertens de Noordhout, C Obyn, C Devos, A Scohy, A Vlayen, H Yaras, C Janssens, P Meeus. Performance of the Belgian health system: Report 2024. Health Services Research (HSR) Brussels: Belgian Health Care Knowledge Centre (KCE). 2025. KCE Reports 376C. D/2025/10.273/44. https://www.kce.fgov.be/sites/default/files/2024-01/KCE376C_HSPA2024__Report.pdf.
10. Kojima G. Prevalence of frailty in nursing homes: a systematic review and meta-analysis. Journal of the American Medical Directors Association. 2015;16(11):940-5.
11. Van Dijk PT, Mehr DR, Ooms ME*, et al.* Comorbidity and 1-year mortality risks in nursing home residents. Journal of the American Geriatrics Society. 2005;53(4):660-5.
12. Roh E, Cota E, Lee JP, Madievsky R, Eskildsen MA. Polypharmacy in Nursing Homes. Clin Geriatr Med. 2022;38(4):653-66.
13. Brent RJ. Life expectancy in nursing homes. Applied Economics. 2022;54(16):1877-88.
14. Collingridge Moore D, Payne S, Keegan T*, et al.* Length of stay in long-term care facilities: a comparison of residents in six European countries. Results of the PACE cross-sectional study. BMJ Open. 2020;10(3):e033881.
15. Honinx E, van Dop N, Smets T*, et al.* Dying in long-term care facilities in Europe: the PACE epidemiological study of deceased residents in six countries. BMC Public Health. 2019;19(1):1199.
16. Morin L, Aubry R, Frova L*, et al.* Estimating the need for palliative care at the population level: a cross-national study in 12 countries. Palliat Med. 2017;31(6):526-36.
17. Ten Koppel M, Onwuteaka-Philipsen BD, Van den Block L*, et al.* Palliative care provision in long-term care facilities differs across Europe: Results of a cross-sectional study in six European countries (PACE). Palliat Med. 2019;33(9):1176-88.
18. World Health Organization. Multimorbidity: Technical Series on Safer Primary Care. Geneva: World Health Organization; 2016. Licence: CC BY-NC-SA 3.0 IGO. https://www.who.int/publications/i/item/9789241511650.
19. Agence InterMutualiste (AIM-IMA). Polyfarmacie in België. Brussels: AIM-IMA; 2024 [cited 2025 Jan 26]. Available from: https://www.aim-ima.be/Polyfarmacie-in-Belgie-461 [
20. Lavan AH, Gallagher P, Parsons C, O'Mahony D. STOPPFrail (Screening Tool of Older Persons Prescriptions in Frail adults with limited life expectancy): consensus validation. Age Ageing. 2017;46(4):600-7.
21. Veehof L, Stewart R, Haaijer-Ruskamp F, Jong BM-d. The development of polypharmacy. A longitudinal study. Family practice. 2000;17(3):261-7.
22. Kim S, Lee H, Park J*, et al.* Global and regional prevalence of polypharmacy and related factors, 1997–2022: An umbrella review. Arch Gerontol Geriatr. 2024;124:105465.
23. Van der Linden L, Tournoy J. Prevalence and trends in polypharmacy and excessive polypharmacy: a retrospective national database analysis (2012-2021). Int J Clin Pharm. 2024;46(4):987-91.
24. Visser AGR. Deprescribing in nursing home residents: when less is more? 2024.
25. Taxis K, Kochen S, Wouters H*, et al.* Cross-national comparison of medication use in Australian and Dutch nursing homes. Age Ageing. 2017;46(2):320-3.
26. Ngcobo NN. Influence of Ageing on the Pharmacodynamics and Pharmacokinetics of Chronically Administered Medicines in Geriatric Patients: A Review. Clin Pharmacokinet. 2025;64(3):335-67.
27. Hellemans L, Nuyts S, Hias J*, et al.* Polypharmacy and excessive polypharmacy in community-dwelling middle aged and aged adults between 2011 and 2015. Int J Clin Pract. 2021;75(4):e13942.
28. Wastesson JW, Morin L, Tan ECK, Johnell K. An update on the clinical consequences of polypharmacy in older adults: a narrative review. Expert Opin Drug Saf. 2018;17(12):1185-96.
29. Gnjidic D, Hilmer SN, Blyth FM*, et al.* Polypharmacy cutoff and outcomes: five or more medicines were used to identify community-dwelling older men at risk of different adverse outcomes. J Clin Epidemiol. 2012;65(9):989-95.
30. Meid AD, Quinzler R, Freigofas J*, et al.* Medication underuse in aging outpatients with cardiovascular disease: prevalence, determinants, and outcomes in a prospective cohort study. PLoS one. 2015;10(8):e0136339.
31. Wauters M, Elseviers M, Vaes B*, et al.* Too many, too few, or too unsafe? Impact of inappropriate prescribing on mortality, and hospitalization in a cohort of community-dwelling oldest old. British journal of clinical pharmacology. 2016;82(5):1382-92.

32. Miller GE, Sarpong EM, Davidoff AJ*, et al.* Determinants of potentially inappropriate medication use among community-dwelling older adults. Health services research. 2017;52(4):1534-49.
33. Morin L, Laroche M-L, Texier G, Johnell K. Prevalence of potentially inappropriate medication use in older adults living in nursing homes: a systematic review. Journal of the American Medical Directors Association. 2016;17(9):862. e1-. e9.
34. Nothelle SK, Sharma R, Oakes AH, Jackson M, Segal JB. Determinants of potentially inappropriate medication use in long-term and acute care settings: a systematic review. Journal of the American Medical Directors Association. 2017;18(9):806. e1-. e17.
35. Sharma M, Loh KP, Nightingale G, Mohile SG, Holmes HM. Polypharmacy and potentially inappropriate medication use in geriatric oncology. J Geriatr Oncol. 2016;7(5):346-53.
36. Cateau D, Bugnon O, Niquille A. Evolution of potentially inappropriate medication use in nursing homes: Retrospective analysis of drug consumption data. Research in Social and Administrative Pharmacy. 2021;17(4):701-6.
37. Liu J, Zhu Y, Tan JK*, et al.* Factors Associated with Frailty in Older Adults in Community and Nursing Home Settings: A Systematic Review with a Meta-Analysis. Journal of Clinical Medicine. 2024;13(8):2382.
38. Mangin D, Bahat G, Golomb BA*, et al.* International Group for Reducing Inappropriate Medication Use & Polypharmacy (IGRIMUP): Position Statement and 10 Recommendations for Action. Drugs Aging. 2018;35(7):575-87.
39. Hertogh CMPM, Ribbe MW. [Palliative care and the health care for the elderly]. Tijdschr Gerontol Geriatr. 2008;39(6):220-3.
40. Holmes HM, Hayley DC, Alexander GC, Sachs GA. Reconsidering medication appropriateness for patients late in life. Arch Intern Med. 2006;166(6):605-9.
41. Paque K, Vander Stichele R, Elseviers M*, et al.* Barriers and enablers to deprescribing in people with a life-limiting disease: a systematic review. Palliat Med. 2019;33(1):37-48.
42. Plácido AI, Aguiar A, Piñeiro-Lamas M*, et al.* Assessment of Potentially Inappropriate Medications Using the EU (7)-PIM List, in a Sample of Portuguese Older Adults' Residents in Nursing Homes. Risk Manag Healthc Policy. 2022;15:1343-52.
43. Tian F, Chen Z, Zeng Y, Feng Q, Chen X. Prevalence of Use of Potentially Inappropriate Medications Among Older Adults Worldwide: A Systematic Review and Meta-Analysis. JAMA Network Open. 2023;6(8):e2326910-e.
44. Morin L, Laroche M-L, Texier G, Johnell K. Prevalence of Potentially Inappropriate Medication Use in Older Adults Living in Nursing Homes: A Systematic Review. J Am Med Dir Assoc. 2016;17(9):862.e1-.e9.
45. Chae HW, Kim Y, Suh Y*, et al.* Prevalence of potentially inappropriate medications based on the STOPPFrail criteria in frail older patients with limited life expectancy: a cross-sectional study. BMC Geriatr. 2022;22(1):367.
46. Alwidyan T, McCorry NK, Parsons C. Healthcare professionals' perspectives of deprescribing in older patients at the end of life in hospice care: a qualitative study using the Theoretical Domains Framework. Int J Pharm Pract. 2023;31(3):305-13.
47. Malek Makan A, van Hout H, Onder G*, et al.* Prevalence of potentially inappropriate medications according to STOPP-Frail criteria in nursing home residents, the SHELTER study. BMC Geriatr. 2024;24(1):882.
48. Anrys PMS, Strauven GC, Foulon V*, et al.* Potentially Inappropriate Prescribing in Belgian Nursing Homes: Prevalence and Associated Factors. J Am Med Dir Assoc. 2018;19(10):884-90.
49. Fournier A, Anrys P, Beuscart J-B*, et al.* Use and Deprescribing of Potentially Inappropriate Medications in Frail Nursing Home Residents. Drugs Aging. 2020;37(12):917-24.
50. Paque K, De Schreye R, Elseviers M*, et al.* Discontinuation of medications at the end of life: A population study in Belgium, based on linked administrative databases. Br J Clin Pharmacol. 2019;85(4):827-37.
51. Farrell B, Pottie K, Thompson W*, et al.* Deprescribing proton pump inhibitors. Can Fam Physician. 2017;63(5):354.
52. Pottie K, Thompson W, Davies S*, et al.* Deprescribing benzodiazepine receptor agonists: Evidence-based clinical practice guideline. Can Fam Physician. 2018;64(5):339-51.
53. Vandenberghe I, Kestens W, Bruyneel L, Van der Linden L, Tournoy J. Patterns of Antipsychotic Use in Belgian Nursing Homes 2017-2022: Admission is a Decision Point. J Am Med Dir Assoc. 2024;25(10):105222.
54. Bjerre LM, Farrell B, Hogel M*, et al.* Deprescribing antipsychotics for behavioural and psychological symptoms of dementia and insomnia: Evidence-based clinical practice guideline. Can Fam Physician. 2018;64(1):17-27.
55. Van Leeuwen E, van Driel ML, Horowitz MA*, et al.* Approaches for discontinuation versus continuation of long-term antidepressant use for depressive and anxiety disorders in adults. Cochrane Database Syst Rev. 2021;4(4):Cd013495.
56. Wabe N, Urwin R, Meulenbroeks I*, et al.* Over- and Underuse of Proton Pump Inhibitors in Nursing Homes: A Multisite Longitudinal Cohort Study. J Am Med Dir Assoc. 2025;26(2):105393.
57. Paque K, Elseviers M, Vander Stichele R*, et al.* Changes in medication use in a cohort of patients with advanced cancer: The international multicentre prospective European Palliative Care Cancer Symptom study. Palliat Med. 2017;32(4):775-85.
58. Van der Meer HG, Taxis K, Pont LG. Changes in prescribing symptomatic and preventive medications in the last year of life in older nursing home residents. Front Pharmacol. 2018;8:990.
59. Wehling M, Petrovic M. Deprescribing or represcribing: not just a semantic dilemma. Eur Geriatr Med. 2022;13(3):529-30.
60. Griese-Mammen N, Hersberger KE, Messerli M*, et al.* PCNE definition of medication review: reaching agreement. Int J Clin Pharm. 2018;40(5):1199-208.

61. Reeve E, Thompson W, Farrell B. Deprescribing: A narrative review of the evidence and practical recommendations for recognizing opportunities and taking action. Eur J Intern Med. 2017;38:3-11.
62. Scott IA, Hilmer SN, Reeve E*, et al.* Reducing inappropriate polypharmacy: the process of deprescribing. JAMA Intern Med. 2015;175(5):827-34.
63. Sheikh A, Dhingra-Kumar N, Kelley E, Kieny MP, Donaldson LJ. The third global patient safety challenge: tackling medication-related harm. Bull World Health Organ. 2017;95(8):546.
64. Deprescribing Guidelines and Algorithms. https://deprescribing.org/resources/deprescribing-guidelines-algorithms/ [cited 2022 /06/12].
65. Belgisch Centrum voor Farmacotherapeutische Informatie (BCFI). Goed en veilig gebruik van geneesmiddelen: deprescribing; [cited 2025 Jul 14]. Available from: https://www.bcfi.be/nl/chapters/1?frag=9991233&matches=deprescribing [
66. Strauven G, Anrys P, Vandael E*, et al.* Cluster-controlled trial of an intervention to improve prescribing in nursing homes study. J Am Med Dir Assoc. 2019;20(11):1404-11.
67. Fog AF, Kvalvaag G, Engedal K, Straand J. Drug-related problems and changes in drug utilization after medication reviews in nursing homes in Oslo, Norway. Scand J Prim Health Care. 2017;35(4):329-35.
68. Wouters H, Scheper J, Koning H*, et al.* Discontinuing Inappropriate Medication Use in Nursing Home Residents: A Cluster Randomized Controlled Trial. Ann Intern Med. 2017;167(9):609-17.
69. Cool C, Cestac P, McCambridge C*, et al.* Reducing potentially inappropriate drug prescribing in nursing home residents: effectiveness of a geriatric intervention. Br J Clin Pharmacol. 2018;84(7):1598-610.
70. Kua C-H, Mak VSL, Huey Lee SW. Health Outcomes of Deprescribing Interventions Among Older Residents in Nursing Homes: A Systematic Review and Meta-analysis. J Am Med Dir Assoc. 2019;20(3):362-72.e11.
71. Chock YL, Wee YL, Gan SL*, et al.* How Willing Are Patients or Their Caregivers to Deprescribe: a Systematic Review and Meta-analysis. J Gen Intern Med. 2021;36(12):3830-40.
72. Roux B, Rakheja B, Sirois C*, et al.* Attitudes and beliefs of older adults and caregivers towards deprescribing in French-speaking countries: a multicenter cross-sectional study. Eur J Clin Pharmacol. 2022;78(10):1633-46.
73. Paque K, Elseviers M, Vander Stichele R*, et al.* Balancing medication use in nursing home residents with life-limiting disease. Eur J Clin Pharmacol. 2019;75:969-77.
74. Onder G, Vetrano DL, Villani ER*, et al.* Deprescribing in Nursing Home Residents on Polypharmacy: Incidence and Associated Factors. J Am Med Dir Assoc. 2019;20(9):1116-20.
75. Morin L, Wastesson JW, Laroche M-L, Fastbom J, Johnell K. How many older adults receive drugs of questionable clinical benefit near the end of life? A cohort study. Palliat Med. 2019;33(8):1080-90.
76. Hickman E, Gillies C, Khunti K, Seidu S. Deprescribing of preventive medications in palliative care patients living with multiple long-term conditions in their final 12 months of life: A retrospective cohort Clinical Practice Research Datalink study. Prim Care Diabetes. 2025;19(3):288-95.
77. Alwidyan T, McCorry NK, Black C*, et al.* Prescribing and deprescribing in older people with life-limiting illnesses receiving hospice care at the end of life: A longitudinal, retrospective cohort study. Palliat Med. 2024;38(1):121-30.
78. Carollo M, Boccardi V, Crisafulli S*, et al.* Medication review and deprescribing in different healthcare settings: a position statement from an Italian scientific consortium. Aging Clin Exp Res. 2024;36(1):63.
79. Crisafulli S, Poluzzi E, Lunghi C*, et al.* Deprescribing as a strategy for improving safety of medicines in older people: Clinical and regulatory perspective. Frontiers in Drug Safety and Regulation. 2022;Volume 2 - 2022.
80. Griese-Mammen N, Hersberger KE, Messerli M*, et al.* PCNE definition of medication review: reaching agreement. Int J Clin Pharm. 2018;40(5):1199-208.
81. Carollo M, Cristini I, Crisafulli S*, et al.* Evaluating the impact of medication review and deprescribing on prescribing appropriateness and clinical outcomes in older people residing in long-term care facilities: a systematic review and meta-analysis. Age Ageing. 2026;55(4).
82. Kua CH, Mak VSL, Huey Lee SW. Health Outcomes of Deprescribing Interventions Among Older Residents in Nursing Homes: A Systematic Review and Meta-analysis. J Am Med Dir Assoc. 2019;20(3):362-72.e11.
83. Shrestha R, Shaw E, Mullen L*, et al.* Outcomes of deprescribing for people with life-limiting conditions: A systematic review. Palliat Med. 2026;0(0):02692163261416281.
84. Gnjidic D, Johansson M, Meng DM*, et al.* Achieving sustainable healthcare through deprescribing. Cochrane Database Syst Rev. 2022;10(10):Ed000159.
85. Achstetter K, Steinbeck V, Busse R. Identifying, Measuring, and Reducing Low-Value Care in Health System Performance Assessment. 2025.
86. Cussans A, Harvey G, Kemple T, Tomson M. Interventions to Reduce the Environmental Impact of Medicines: A UK perspective☆. The Journal of Climate Change and Health. 2021;4:100079.
87. Harriman K, Howard L, McCracken R. Deprescribing medication for frail elderly patients in nursing homes: a survey of Vancouver family physicians. BC Med J. 2014;56(9):436-41.
88. Gnjidic D, Reeve E. Deprescribing: What do we know, and where to next? Br J Clin Pharmacol. 2021;87(3):722-4.
89. Liacos M, Page AT, Etherton-Beer C. Deprescribing in older people. Aust Prescr. 2020;43(4):114-20.
90. Roux B, Rakheja B, Sirois C*, et al.* Attitudes and beliefs of older adults and caregivers towards deprescribing in French-speaking countries: a multicenter cross-sectional study. Eur J Clin Pharmacol. 2022;78(10):1633-46.
91. Malek Makan A, Lee MC, van Hein H, van Marum R. Barriers and enablers of elderly care specialists towards deprescribing practices in the nursing homes: a focus group study. BMC Health Serv Res. 2025;25(1):1466.

92. Hickman E, Almaqhawi A, Gillies C, Khunti K, Seidu S. Beliefs, practices, perceptions and motivations of healthcare professionals on medication deprescribing during end-of-life care: A systematic review. Prim Care Diabetes. 2024;18(3):249-56.
93. Visser AGR, de-Bruijn J, Spaetgens B*, et al.* Unlocking Deprescribing Potential in Nursing Homes: Insights from a Focus Group Study with Healthcare Professionals. Drugs Aging. 2024;41(3):261-70.
94. Sawan M, Reeve E, Turner J*, et al.* A systems approach to identifying the challenges of implementing deprescribing in older adults across different health-care settings and countries: a narrative review. Expert Rev Clin Pharmacol. 2020;13(3):233-45.
95. Spinewine A, Evrard P, Hughes C. Interventions to optimize medication use in nursing homes: a narrative review. Eur Geriatr Med. 2021;12(3):551-67.
96. Okeowo DA, Zaidi STR, Fylan B, Alldred DP. Barriers and facilitators of implementing proactive deprescribing within primary care: a systematic review. Int J Pharm Pract. 2023;31(2):126-52.
97. Doherty AJ, Boland P, Reed J*, et al.* Barriers and facilitators to deprescribing in primary care: a systematic review. BJGP Open. 2020;4(3).
98. Brunner L, Rodondi N, Aubert CE. Barriers and facilitators to deprescribing of cardiovascular medications: a systematic review. BMJ Open. 2022;12(12):e061686.
99. Heinrich CH, Hurley E, McCarthy S, McHugh S, Donovan MD. Barriers and enablers to deprescribing in long-term care facilities: a 'best-fit' framework synthesis of the qualitative evidence. Age Ageing. 2022;51(1).
100. Evrard P, Henrard S, Spinewine A. Development of a Behavior-Change Intervention toward Benzodiazepine Deprescribing in Older Adults Living in Nursing Homes. J Am Med Dir Assoc. 2024;25(8):105053.
101. Lundby C, Graabaek T, Ryg J*, et al.* Health care professionals' attitudes towards deprescribing in older patients with limited life expectancy: A systematic review. Br J Clin Pharmacol. 2019;85(5):868-92.
102. Evrard P, Damiaens A, Patey AM, Grimshaw JM, Spinewine A. Barriers and enablers towards benzodiazepine-receptor agonists deprescribing in nursing homes: A qualitative study of stakeholder groups. Exploratory Research in Clinical and Social Pharmacy. 2023;9:100258.
103. Van Leeuwen E, Anthierens S, van Driel ML*, et al.* General practitioners' perspectives on discontinuation of long-term antidepressants in nursing homes. Eur J Gen Pract. 2022;28(1):23-31.
104. van Poelgeest E, Seppala L, Bahat G*, et al.* Optimizing pharmacotherapy and deprescribing strategies in older adults living with multimorbidity and polypharmacy: EuGMS SIG on pharmacology position paper. Eur Geriatr Med. 2023;14(6):1195-209.
105. Anlay DZ, Paque K, Van Leeuwen E, Cohen J, Dilles T. Tools and guidelines to assess the appropriateness of medication and aid deprescribing: An umbrella review. Br J Clin Pharmacol. 2024;90(1):12-106.
106. Thompson W, Lundby C, Graabaek T*, et al.* Tools for Deprescribing in Frail Older Persons and Those with Limited Life Expectancy: A Systematic Review. J Am Geriatr Soc. 2019;67(1):172-80.
107. Curtin D, Gallagher P, O'Mahony D. Deprescribing in older people approaching end-of-life: development and validation of STOPPFrail version 2. Age Ageing. 2021;50(2):465-71.
108. Morin L, Laroche ML, Vetrano DL, Fastbom J, Johnell K. Adequate, questionable, and inadequate drug prescribing for older adults at the end of life: a European expert consensus. Eur J Clin Pharmacol. 2018;74(10):1333-42.
109. Paque K. Deprescribing of medications at the end of life: data of older adults living at home or in a nursing home, and patients with advanced cancer receiving palliative care: Ghent University; 2019.
110. Farrell B, Conklin J, Dolovich L*, et al.* Deprescribing guidelines: An international symposium on development, implementation, research and health professional education. Research in Social and Administrative Pharmacy. 2019;15(6):780-9.
111. Moriarty F, Pottie K, Dolovich L*, et al.* Deprescribing recommendations: An essential consideration for clinical guideline developers. Research in Social and Administrative Pharmacy. 2019;15(6):806-10.
112. Langford AV, Warriach I, McEvoy AM*, et al.* What do clinical practice guidelines say about deprescribing? A scoping review. BMJ Qual Saf. 2024;34(1):28-39.
113. Curtin D, Jennings E, Daunt R*, et al.* Deprescribing in older people approaching end of life: a randomized controlled trial using STOPPFrail criteria. J Am Geriatr Soc. 2020;68(4):762-9.
114. Hurley E, Dalton K, Byrne S, Foley T, Walsh E. Pharmacist-Led Deprescribing Using STOPPFrail for Frail Older Adults in Nursing Homes. J Am Med Dir Assoc. 2024;25(9):105122.
115. Shrestha S, Poudel A, Steadman K, Nissen L. Outcomes of deprescribing interventions in older patients with life-limiting illness and limited life expectancy: A systematic review. Br J Clin Pharmacol. 2020;86(10):1931-45.
116. Aubert CE, Kerr EA, Maratt JK, Klamerus ML, Hofer TP. Outcome Measures for Interventions to Reduce Inappropriate Chronic Drugs: A Narrative Review. J Am Geriatr Soc. 2020;68(10):2390-8.
117. van Leeuwen KM, van Loon MS, van Nes FA*, et al.* What does quality of life mean to older adults? A thematic synthesis. PLoS One. 2019;14(3):e0213263.
118. Ohura T, Higashi T, Ishizaki T, Nakayama T. Gaps between the subjective needs of older facility residents and how care workers understand them: a pairwise cross-sectional study. BMC Res Notes. 2016;9(1):52.
119. Keskar V, Yadav J, Kumar AH. 5V's of Big Data Attributes and their Relevance and Importance across Domains. International Journal of Innovative Technology and Exploring Engineering (IJITEE) ISSN. 2020:2278-3075.
120. Morin L, Onwuteaka-Philipsen BD. The promise of big data for palliative and end-of-life care research. Sage Publications Sage UK: London, England; 2021. p. 1638-40.

121. Huser V, Cimino JJ. Impending challenges for the use of big data. Elsevier; 2016. p. 890-4.
122. Schneeweiss S. Improving therapeutic effectiveness and safety through big healthcare data. Clin Pharmacol Ther. 2016;99(3):262-5.
123. Surbakti FPS, Wang W, Indulska M, Sadiq S. Factors influencing effective use of big data: A research framework. Information & Management. 2020;57(1):103146.
124. Berry RC, Johnston L. Big data and doctoral research: Opportunities, challenges, and cautions. Enhancing the Role of ICT in Doctoral Research Processes. 2019:67-83.
125. Stice-Lawrence L. Practical issues to consider when working with big data. Review of Accounting Studies. 2022;27(3):1117-24.
126. Lugg-Widger FV, Angel L, Cannings-John R*, et al.* Challenges in accessing routinely collected data from multiple providers in the UK for primary studies: Managing the morass. International Journal of Population Data Science. 2018;3.
127. Ho HKK, Görges M, Portales-Casamar E. Data Access and Usage Practices Across a Cohort of Researchers at a Large Tertiary Pediatric Hospital: Qualitative Survey Study. JMIR Med Inform. 2018;6(2):e32.
128. Maetens A, De Schreye R, Faes K*, et al.* Using linked administrative and disease-specific databases to study end-of-life care on a population level. BMC Palliat Care. 2016;15:1-10.
129. De Schreye R. Population-level evaluation of the appropriateness of end-of-life care in Belgium. 2020.
130. Wastesson JW, Kamgang KS, Lundby C, Pottegård A. Studying Deprescribing Using Routinely Collected Healthcare Data: Old Challenges and New Opportunities. Basic Clin Pharmacol Toxicol. 2025;137(5):e70131.
131. Spinewine A, Reeve E, Thompson W. Revisiting systematic reviews on deprescribing trials to better inform future practice and research. Br J Clin Pharmacol. 2023;89(12):3758-64.
132. Calfat AC, Gosselin M, Sirois C. Billing Deprescribing Interventions: Portrait of an Initiative in Québec, Canada. Basic Clin Pharmacol Toxicol. 2025;136(6):e70050.
133. Ahmed S, Ware P, Gardner W*, et al.* Montreal Accord on Patient-Reported Outcomes (PROs) use series – Paper 8: patient-reported outcomes in electronic health records can inform clinical and policy decisions. J Clin Epidemiol. 2017;89:160-7.
134. FDA. Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. Rockville, MD; 2009.
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM193282.pdf.
135. Powers JH, 3rd, Patrick DL, Walton MK*, et al.* Clinician-Reported Outcome Assessments of Treatment Benefit: Report of the ISPOR Clinical Outcome Assessment Emerging Good Practices Task Force. Value Health. 2017;20(1):2-14.
136. Farrell B, Richardson L, Raman-Wilms L*, et al.* Self-efficacy for deprescribing: A survey for health care professionals using evidence-based deprescribing guidelines. Res Social Adm Pharm. 2018;14(1):18-25.
137. Farhat A, Al-Hajje A, Csajka C, Panchaud A. Clinical and economic impacts of explicit tools detecting prescribing errors: A systematic review. J Clin Pharm Ther. 2021;46(4):877-86.
138. Aguiar JP, Brito AM, Martins AP, Leufkens HGM, Alves da Costa F. Potentially inappropriate medications with risk of cardiovascular adverse events in the elderly: A systematic review of tools addressing inappropriate prescribing. J Clin Pharm Ther. 2019;44(3):349-60.
139. Lucchetti G, Lucchetti A, G. rL. Inappropriate prescribing in older persons: A systematic review of medications available in different criteria. Arch Gerontol Geriatr. 2017;68:55-61.
140. Lee G, Lim J-F, Page AT*, et al.* Applicability of explicit potentially inappropriate medication lists to the Australian context: A systematic review. Australas J Ageing. 2022;41(2):200-21.
141. Motter FR, Fritzen JS, Hilmer SN, Paniz EV, Paniz VMV. Potentially inappropriate medication in the elderly: a systematic review of validated explicit criteria. Eur J Clin Pharmacol. 2018;74(6):679-700.
142. Schiavo G, Forgerini M, Lucchetta RC, Mastroianni PdC. A comprehensive look at explicit screening tools for potentially inappropriate medication: A systematic scoping review. Australas J Ageing. 2022.
143. Atkins L, Francis J, Islam R*, et al.* A guide to using the Theoretical Domains Framework of behaviour change to investigate implementation problems. Implement Sci. 2017;12(1):77.
144. Skivington K, Matthews L, Simpson SA*, et al.* A new framework for developing and evaluating complex interventions: update of Medical Research Council guidance. BMJ. 2021;374:n2061.
145. Anrys PM, Strauven GC, Foulon V*, et al.* Potentially inappropriate prescribing in Belgian nursing homes: prevalence and associated factors. J Am Med Dir Assoc. 2018;19(10):884-90.
146. Kuipers SJ, Cramm JM, Nieboer AP. The importance of patient-centered care and co-creation of care for satisfaction with care and physical and social well-being of patients with multi-morbidity in the primary care setting. BMC Health Serv Res. 2019;19(1):13.
147. De Wolf J, Dilles T, Vander Stichele R, Elseviers M. Evolution of Drug Utilization in Nursing Homes in Belgium. Clin Pharmacol Biopharm. 2014;3(124):2.
148. Rane PP, Guha S, Chatterjee S, Aparasu RR. Prevalence and predictors of non-evidence based proton pump inhibitor use among elderly nursing home residents in the US. Research in Social and Administrative Pharmacy. 2017;13(2):358-63.
149. Anlay DZ, Paque K, Van den Eynden B, Dilles T, Cohen J. International Deprescribing Guidelines Did Not Impact Actual Practice in Deprescribing of Potentially Inappropriate Medications for Nursing Home Residents: An Interrupted Time Series Analysis. Drugs Aging. 2025.

150. Pasina L, Novella A, Elli C, Nobili A, Ianes A. Overuse of proton pump inhibitors in nursing homes: An Italian multicenter observational study. Pharmacoepidemiol Drug Saf. 2020;29(4):461-6.
151. Hendrix I, Page AT, Korhonen MJ*, et al.* Patterns of High-Dose and Long-Term Proton Pump Inhibitor Use: A Cross-Sectional Study in Six South Australian Residential Aged Care Services. Drugs - Real World Outcomes. 2019;6(3):105-13.
152. Plácido AI, Aguiar A, Piñeiro-Lamas M*, et al.* Assessment of potentially inappropriate medications using the EU (7)-PIM list, in a sample of Portuguese older adults' residents in nursing homes. Risk Manag Healthc Policy. 2022:1343-52.
153. Doell A, Walus A, To J, Bell A. Quantifying Candidacy for Deprescribing of Proton Pump Inhibitors among Long-Term Care Residents. Can J Hosp Pharm. 2018;71(5):302-7.
154. Patterson Burdsall D, Flores HC, Krueger J*, et al.* Use of Proton Pump Inhibitors With Lack of Diagnostic Indications in 22 Midwestern US Skilled Nursing Facilities. J Am Med Dir Assoc. 2013;14(6):429-32.
155. Gendre P, Mocquard J, Artarit P*, et al.* (De)Prescribing of proton pump inhibitors: what has changed in recent years? an observational regional study from the French health insurance database. BMC Prim Care. 2022;23(1):341.
156. Ben-Eltriki M, Green CJ, Maclure M*, et al.* Do proton pump inhibitors increase mortality? A systematic review and in-depth analysis of the evidence. Pharmacol Res Perspect. 2020;8(5):e00651.
157. Maes ML, Fixen DR, Linnebur SA. Adverse effects of proton-pump inhibitor use in older adults: a review of the evidence. Ther Adv Drug Saf. 2017;8(9):273-97.
158. Bolt J, Thompson W, Inglis C. Appropriate Use of Proton Pump Inhibitors in Older Adults: Concerns and Solutions. Drugs Aging. 2025.
159. Wilsdon TD, Hendrix I, Thynne TR, Mangoni AA. Effectiveness of Interventions to Deprescribe Inappropriate Proton Pump Inhibitors in Older Adults. Drugs Aging. 2017;34(4):265-87.
160. Kaufmann CP, Tremp R, Hersberger KE, Lampert ML. Inappropriate prescribing: a systematic overview of published assessment tools. Eur J Clin Pharmacol. 2014;70(1):1-11.
161. Ivanova I, Elseviers M, Wauters M, Christiaens T, Vander Stichele R. European repository of explicit criteria of potentially inappropriate medications in old age. Geriatrics & gerontology international. 2018;18(8):1293-7.
162. Braun V, Clarke V. Supporting best practice in reflexive thematic analysis reporting in Palliative Medicine: A review of published research and introduction to the Reflexive Thematic Analysis Reporting Guidelines (RTARG). Palliat Med. 2024;38(6):608-16.
163. Clegg LX, Hankey BF, Tiwari R, Feuer EJ, Edwards BK. Estimating average annual per cent change in trend analysis. Stat Med. 2009;28(29):3670-82.
164. Box GEP, Jenkins GM, Reinsel GC. Time series analysis: forecasting and control. Hoboken, NJ: John Wiley & Sons, Inc.; 2008. https://doi.org/10.1002/9781118619193.
165. de Almeida Mello J, Wellens NI, Hermans K*, et al.* The Implementation of Integrated Health Information Systems - Research Studies from 7 Countries Involving the InterRAI Assessment System. Int J Integr Care. 2023;23(1):8.
166. InterRAI. Worldwide. Available from: https://interrai.org/applications/status-and-outcome-scales/ [Accessed 09 Jan 2026].
167. Hernán MA, Robins JM. Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available. Am J Epidemiol. 2016;183(8):758-64.
168. Chesnaye NC, Stel VS, Tripepi G*, et al.* An introduction to inverse probability of treatment weighting in observational research. Clin Kidney J. 2022;15(1):14-20.

PART II

EVIDENCE FOUNDATION FOR DEPRESCRIBING RESEARCH AND PRACTICE

Chapter 2

Tools and guidelines to assess the appropriateness of medication and aid the deprescribing: an umbrella review

Published:
Anlay DZ, Paque K, Van Leeuwen E, Cohen J, Dilles T. Tools and guidelines to assess the appropriateness of medication and aid the deprescribing: an umbrella review. Br J Clin Pharmacol. 2024 Jan;90(1):12-106. DOI: 10.1111/bcp.15906

ABSTRACT

AIMS

The aim of this umbrella review was to identify tools and guidelines to aid the deprescribing process of potentially inappropriate medications (PIM), evaluate development and validation methods, and describe evidence levels for medication inclusion.

METHODS

Searches were conducted on MEDLINE (Ovid), Embase.com, Cochrane CDSR, CINAHL (EBSCO), Web of Science Core Collection, and guideline databases from the date of inception to July 7, 2022 and checked for updated tools on July 17, 2023. We analysed the contents of tools and guidelines.

RESULTS

From 23 systematic reviews and guidelines, we identified 95 tools (72 explicit, 12 mixed, 11 implicit) and 9 guidelines. Most tools (83.2%) were developed to use for older persons, including 14 for those with limited life expectancy. Seven tools were for children <18 years (7.37%). Most explicit/mixed tools (78.57%) and all guidelines were validated. We found 484 PIMs and 202 medications with different appropriateness independent of disease for older persons with normal and limited life expectancy, respectively. Only two tools and eight guidelines reported the evidence level, and a quarter of medications had high-quality evidence.

CONCLUSION

Tools are available for a diversity of populations. There were discrepancies with the same medication being classified as inappropriate in some tools and appropriate in others, possibly due to low-quality evidence. Particularly, tools for patients with limited life expectancy were developed based on very limited evidence, and research to generate this evidence is highly needed. Our medication lists, along with the level of evidence, could facilitate efforts to strengthen the evidence.

Introduction

Deprescribing is a critical aspect of patient care, involving the supervised withdrawal of inappropriate medications by healthcare professionals. It aims to discontinue drugs when potential harms outweigh potential benefits, taking into account individual patient factors such as care goals, functioning, life expectancy, values, and preferences[1].

Recently, deprescribing has gained increased attention, particularly concerning vulnerable populations at higher risk of inappropriate medication use and its consequences. These vulnerable groups include older adults, paediatric patients, and individuals with limited life expectancy. The significant increase in the elderly population has led to a rise in comorbidities, which in turn has contributed to an increase in polypharmacy (defined as the use of five or more chronic medications) [2]. Being on polypharmacy and age-related changes in drug pharmacodynamics and pharmacokinetics further elevate the risks associated with medication use for older adults[3, 4].This has led to an increased risk of potentially inappropriate medications (PIMs) use, contributing to adverse drug effects, hospitalization[5], morbidity, mortality[6], and higher healthcare costs[7]. In the case of paediatric patients, unique issues arise due to their rapid growth and developmental changes, which influence how drugs are processed in their bodies [8]. Additionally, individuals with limited life expectancy necessitate a different approach to medication management, emphasizing symptom relief rather than long-term prevention or cure. This emphasis leads to certain medications being potentially inappropriate for individuals with limited life expectancy but appropriate for older persons without such limitations, and vice versa [9, 10].

In response to these challenges, tools and guidelines have been developed to assist clinicians in assessing medication appropriateness, deprescribing PIMs, and prescribing suitable medications, particularly for vulnerable populations. These tools and guidelines can either support the overall process of deprescribing (e.g., drug-specific deprescribing guidelines) or specific parts of the deprescribing process (e.g., tools for identifying PIMs) [11]. They can be explicit, providing pre-defined criteria or lists of medications, or implicit, relying on clinical judgment and expert opinion, or a mix of both explicit and implicit approaches for assessing the appropriateness of medications[12]. Due to cultural, societal, and medical differences, a wide range of tools and guidelines have been created to cater to diverse healthcare settings, aiding clinicians in making decisions and increasing their self-efficacy in medication management for improved care for vulnerable groups [13]. Systematic reviews to summarise these tools and guidelines have been conducted at different times [14].

Nevertheless, despite the importance of a comprehensive evaluation of medication appropriateness using tools and guidelines, only a few systematic reviews have successfully integrated medications from these tools and guidelines [15-19]. These reviews have compiled a list of PIMs for older persons, regardless of their specific disease or condition, and have also considered PIMs-interactions with other drugs or diseases. Additionally, they have provided information about therapeutic alternatives and clinical management strategies for identified PIMs reported in publications. However, certain crucial aspects are lacking in these reviews. For instance, they did not compile lists of medications based on their appropriateness for older persons with limited life expectancy. Furthermore, although the compilation of medications lacking consensus among experts regarding appropriateness offers a list of medications warranting further investigation, these reviews failed to provide such list.

Moreover, these reviews did not provide a clear description of the level of evidence supporting each medication included in the tools and guidelines. This limitation underscores the need for more thorough assessments of these tools and guidelines, considering all the aforementioned aspects, to enable informed clinical decision-making. By addressing these gaps, these lists can contribute to the creation of evidence-based medication lists that are widely applicable and can identify areas where further research and evidence are needed and allow to facilitate evidence generation. Therefore, this study aims to achieve the following objectives: 1) identify available tools and guidelines for assessing medication appropriateness and aiding deprescribing of PIMs; 2) evaluate the development and validation methods employed for explicit and mixed tools and guidelines; 3) develop a comprehensive thematic list of medications extracted from identified explicit and mixed tools and guidelines, categorized based on the target populations and rationale for evaluating medication use; and 4) describe the available level of evidence supporting the medications or medication classes included in the identified tools and guidelines

To achieve the aim of the study, we conducted an umbrella review. While the significant number of systematic reviews lays the foundation for the umbrella review, the limitations of these reviews necessitate a complementary approach, where we utilize them as a stepping stone to access and analyze the tools and guidelines included by these systematic reviews directly, resulting in a more comprehensive and rigorous high-level analysis.

Methods

This umbrella review was reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 (PRISMA), and PRISMA for Searching (PRISMA-S), [20] standardized guidelines to ensure quality and clarity [21]. The protocol for this review was developed according to the PRISMA protocol (PRISMA-P) 2015 [22], and registered on PROSPERO, the international prospective register of systematic reviews (**CRD42021235348**).

Eligibility criteria

The eligibility assessment for this study involved a three-stage process. In Stage 1, eligible systematic reviews and guidelines were identified. Stage 2 involved the screening of tools to assess the appropriateness of medications and guidelines to aid deprescribing, which were included in the identified systematic reviews. In Stage 3, we selected those tools/guidelines from stage 2 that were eligible for medication extraction based on the eligibility criteria for stage 3. The corresponding inclusion and exclusion criteria at each stage are presented in **Box 1**.

Box 1: The flow diagram provides a visual representation of the eligibility criteria and stages outlined in the study

Stage 1: Identification of Systematic Reviews and Guidelines	
Inclusion Criteria	**Exclusion Criteria**
• Peer-reviewed systematic reviews summarizing screening tools for assessment of the appropriateness of medication and/or guidelines in any population • Deprescribing guidelines (reported in accordance with the AGREE-Reporting Checklist [23] or following the GRADE approach [24]) that provide an algorithm or model to stop or taper the dose of specific PIM	• Systematic reviews describing aspects of use or introduction of tools and guidelines (compliance with the tools and guidelines, the effect of the use of the tools and guidelines, indicators of potentially inappropriate prescribing, prevalence of PIM, associations of PIM with various outcomes, factors influencing PIM use) • No language restrictions were applied for full texts, and there were no time or date restrictions. However, systematic reviews and guidelines published in a non-English language without available translation, even after contacting the authors, were excluded • No access (i.e., when retraction was not possible after trying to contact the authors through ResearchGate, including through email)
Stage 2: Identification of available Tools and Guidelines included in the systematic reviews	
• Explicit, implicit, and mixed tools to assess the appropriateness of medications • Guidelines that support deprescribing on specific medication classes/medications or lists of medications	• Computerized clinical decision support systems developed based on other tools or general frameworks • Medication review processes without specific drug lists • No access to the tools and guidelines (unable to retrieve after trying to contact the authors through ResearchGate, including through email, and publications are no longer available online)
Stage 3: Selection of Tools and Guidelines for Extraction of Medications	
• Most updated versions of tools (if multiple versions exist) • Validated tools and deprescribing guidelines developed based on the GRADE framework	• Implicit tools, non-validated tools, or tools without information about the validation process • Translation of original tools without changes in the medication list • Tools developed based on other tools without the addition of new drugs or only involving the deletion of medications are excluded. The genealogy of the tools is described based on Ivanova I, et al. [25] to minimize repeated extractions of the same medications and ensure comprehensive coverage of medications.

In this study, a distinction was made between "tools" and "guidelines" based on their specific purposes, although these terms are often used interchangeably in the literature. For the purpose of this study, "tools" are defined as resources primarily focused on identifying potentially inappropriate medications (PIMs). These tools employ a systematic approach or screening mechanism to assess the

appropriateness of medications, enabling the identification of medications that may require deprescribing. On the other hand, "guidelines" encompass resources that help clinicians identify and deprescribe PIMs by providing specific advice on when, why, and how to stop or taper certain medications.

Data sources and Search strategies

The search for relevant studies was conducted in five electronic databases: Medline and PubMed-not-Medline (via Ovid), Embase (via Embase.com), Web of Science (WoS Core Collection, Biosis Citation Index, Chinese Science Citation Database, Current Contents Connect, Data Citation Index, Derwent Innovations Index, KCI-Korean Journal Database, Medline, Russian Science Citation Index and SciELO Citation Index), Cochrane Database of Systematic Reviews (via Cochrane Library), and CINAHL (via EBSCO). The search covered studies from the inception of each database until July 7, 2022. Following the initial search, an additional check was performed to identify updated tools. Five tools that were updated in late 2022 and 2023 (until July 17, 2023) were identified and included in the updated versions of the tool lists and medication lists.

In addition to the article databases, five guideline databases were searched for relevant deprescribing guidelines: Guidelines International Network (G-I-N), Scottish Intercollegiate Guidelines Network (SIGN), Guideline Central, Trip Guidelines, and Richtlijnen databank (the Dutch guideline database). The Bruyère Research Institute website was also checked for any additional deprescribing guidelines [26]. Furthermore, a backward snowballing approach was employed by manually screening the bibliographic lists of the included systematic reviews to identify additional relevant studies.

The search strategy utilised a combination of controlled vocabulary and free text words related to the concepts of inappropriate/appropriate medication, systematic reviews, and guidelines. These terms were applied to titles, abstracts, and author keywords to ensure a comprehensive search within these concepts. To maintain the quality of the search strategies, a medical librarian (KT) was involved in developing and evaluating the search strings. For a more detailed description of the databases searched and the specific terms used in the search strategy, please refer to the additional details provided in the study (**Supplementary file 2.1**).

Data collection and analysis

Selection of studies

The references identified through the search were imported into EndNote X9 reference management software (Clarivate) and deduplicated. After removing the duplicates, the references were exported to Rayyan's free web application to facilitate the selection process [27]. In the first phase, studies were included for full-text review if the abstract was in English and the study design was clearly stated in the title and/or abstract as a systematic review or guideline. Articles or guidelines included for full-text review were also independently reviewed by KP and DZA as a second stage of screening. Conflicts throughout the selection process were first discussed by the two independent reviewers until consensus was reached. When consensus could not be reached, the research team was involved in the discussion.

Assessment of risk of bias in included systematic reviews

The assessments of the quality of eligible studies were conducted by two independent reviewers (DZA and KP) using the Joanna Briggs Institute (JBI) Critical Appraisal Checklist for Systematic Reviews [28]. This checklist contains 11 questions that assess specific domains of the systematic reviews to determine the potential risk of bias and could be answered either "yes," "no," "unclear," or "not applicable." Any disagreement in scoring was resolved by discussion and further discussion in the research group to reach a consensus. We calculated the final score by adding up all "yeses" and dividing this sum of scores by the number of items scored (eleven). The risk of bias in individual systematic reviews was determined using the following cutoffs: low risk of bias if the final score was ⩾70%, moderate risk if the score was 50 – 69%, and high risk of bias if the score was below 50%. For the included guidelines, the quality assessment was conducted using the AGREE II (Appraisal of Guidelines for Research and Evaluation II), consisting of 23 items within six quality domains. Each item was rated on a 7-point scale (from a score of 1 for strongly disagree to a score of 7 for strongly agree) [29]. The individual reviewer scores of all 23 items were summed for each study, and the average total score of two reviewers was obtained to derive the scaled all-domain score percentage. The quality of the study was classified based on the scaled all-domain score (high: ⩾ 70%, moderate: 50–69%, and low: <50%).

Data extraction and management

The data were extracted in three stepwise procedures. Firstly, we focused on the characteristics of the included systematic reviews and guidelines. Next, we examined the characteristics of tools and guidelines identified in the included systematic reviews. Finally, we collected information about the medications within the selected tools and guidelines for medication extraction. To ensure consistency and accuracy, we utilized a self-developed data extraction form, which underwent piloting and discussion among the authors. This process aimed to prevent the omission of important data and to ensure that all reviewers obtained comparable results. During the data extraction, one reviewer (DZA) was responsible for gathering data on various aspects, such as the objective of the systematic review and guidelines, databases searched, the number of included tools and guidelines in the systematic review, the nature of tools in the included systematic review, eligibility criteria for the systematic review, the name of the tool and guidelines, the country where the tool was developed, setting/context, target populations, aspects of inappropriateness or deprescribing covered by the tool and guidelines, the content of the tool and guidelines, and the development and validation technique of tools. To maintain quality, a second reviewer (KP) crosschecked all of the extracted data. In addition to the above, two reviewers (GV and DZA) independently collected data on outcomes related to medications. This included the Anatomical Therapeutic Chemical (ATC) class of each medication and the grading of recommendations if reported in the included explicit tools and guidelines. Any discrepancies that arose between the reviewers were thoroughly discussed within the review team until a consensus was reached.

Data synthesis and Compilation of drug lists

Data on complete lists of medications, characteristics of tools, development methods, validation methods, and aspects of inappropriate prescribing covered by tools were entered into Excel. Individual medications/medication classes reported in the tools and guidelines were also entered into Excel and grouped into ATC classes [30].

Separate lists of medications were developed according to the target populations covered, such as paediatric patients, older persons with normal life expectancy (≥ 65 years), and older persons with limited life expectancy (≥ 65 years). Limited life expectancy is defined throughout this document as an umbrella term representing frailty, advanced diseases, and end-of-life care situations. This definition also includes tools intended for frail older persons with limited life expectancy but do not provide frailty criteria or specify the duration of remaining life.

The medication/medication classes for each target population were then categorized based on aspects of the appropriateness of medications (PIM independent of disease/condition, PIM dependent on specific diseases, drug-drug interactions, drug-dose adjustments, medications questionable benefits, drugs to be used with caution, potentially inappropriate omissions, paediatric potentially inappropriate prescriptions, and fall risk drugs, paediatric potentially inappropriate medication lists, among others). For this review, drugs with questionable benefit are defined as medications for which the expert group did not reach a consensus on whether a specific medication is PIM or not. A separate description of the methodology used to develop these lists, considering each aspect of the appropriateness of medications, can be found in **Supplementary file 2.2.**

Results

Study selection and quality assessment

A comprehensive search strategy yielded 20,955 records from various databases and sources. After removing duplicates, 10,606 records underwent screening based on title and abstract, resulting in 66 records that were assessed in full-text form. A manual search of reference lists did not yield any additional relevant publications. Ultimately, 23 records, including 15 systematic reviews [12, 14-19, 31-38] and 8 guidelines [39-46], were included in this review **(Figure 1).** The detailed characteristics of these systematic reviews and guidelines can be found in **Table 1** and **Table 2**, respectively. The reasons for excluding records during full-text reading are provided in **Supplementary file 2.**

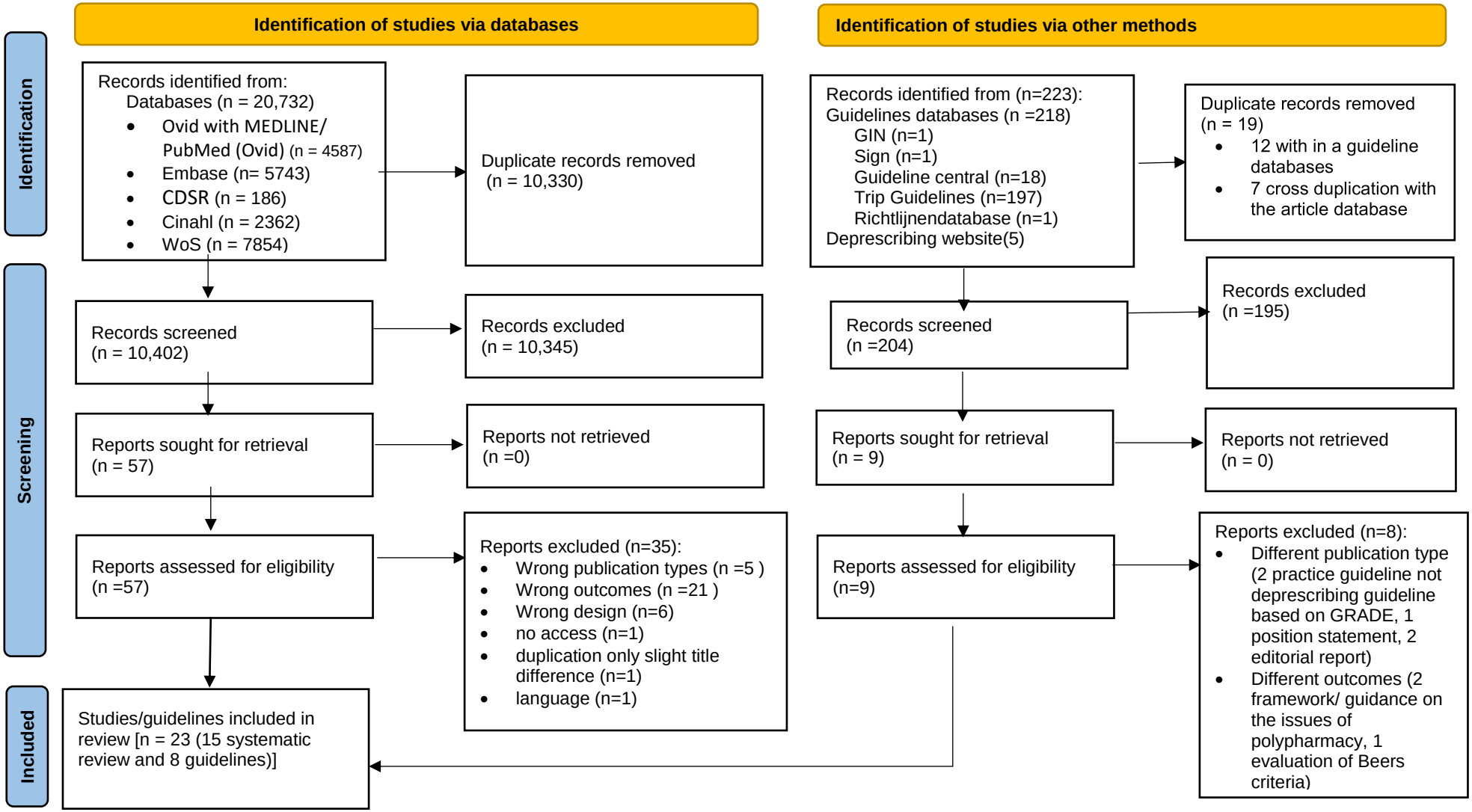


Figure 1: PRISMA 2020 flow diagram for the study selection process in the umbrella review, 2023 *From:* Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

Table 1: Summary of included systematic reviews listing tools to assess the appropriateness of medications

Reference	Objectives	Inclusion criteria	Exclusion criteria	Searched databases	Search period	Population	Types of included study	Tool type©	Number studies	Number tools	JBI score (11)
Aguiar JP, *et al*[15] (2019)	Identify PIMs with risk of cardiovascular adverse events from lists already published in the literature	Articles describing PIM-lists that included individuals aged 65 or older and objectively presented PIMs to be avoided by the elderly and drug-disease interactions with risk of CVS adverse events	Articles describing PIMs without any association with ADRs. Non-English and/or unavailable full-text articles	PubMed, Ovid® MEDLINE, Google Scholar, Manual search	1/1/1991-11/9/2017	65+	Original articles, Reviews, Systematic reviews	Explicit and mixed	24	19 lists and 5 updates	11
Darr-Foit S, *etal*[31](2019)	Addresses the concept of "deprescribing" in the context of recommendations for use of systemic drugs contained in current dermatological guidelines	Not clear (limited to all guidelines for which the German Dermatological Society (DDG) was responsible)	Not clear (under revision or did not propose systemic medication)	Online portal of the Association of the Scientific Medical Societies (AWMF)			Dermatology guideline	Guideline		16	3
Dimitrow MS, *et al*[32](2011).	Review existing criteria that measure inappropriate prescribing in individuals aged 65 and older and to define the circumstances of their use (explicit/ implicit), origins, development processes, and content.	Original articles describing criteria of measuring in appropriate prescribing written in English were included if they described the development of the criteria	Articles that described criteria applicable only in hospital settings, specific drugs, or a particular disease or condition were excluded. Articles assessing the quality of prescribing or medication use at the healthcare level were also excluded.	MEDLINE (Ovid) and PubMed manual search.	January 1, 1990 to July 17, 2010	65+	Original articles	Implicit and explicit	16	14 (10 explicit, 3 implicit and 1 mixed)	8

Farhat A, *et al*[14](2021).	Review of systematic reviews listing explicit tools developed to detect prescribing errors and to assess the impact of explicit tools on clinical and economic outcomes.	Systematic reviews listing explicit tools, dedicated to geriatrics or internal medicine populations. Any clinical setting was considered (e.g. hospital and nursing home). No restriction was imposed on the type of health centers	RCT targeted the frail, pediatric or specific populations, RCT applied other than an explicit tool	PubMed	Sept 1991 to 30 Sept 2020	65^{+}	Systematic review	Explicit	3	49 explicit tools	7
Kaufmann CP, *et al*[12](2014).	To create a comprehensive and structured overview of existing tools to assess inappropriate prescribing.	Tools or computerized decision support systems to assess inappropriate prescribing, updated versions of already published tools, and adaptations of an already published tool if its further development was based on new expert consensus. Studies report tools specifically in adults and published in English or German.	Tools restricted to specific therapeutic classes or specific diseases, tools targeted to children, adaption of already published tools to computerized decision support systems, medication review techniques which did not use a tool, educational interventions to improve prescribing practice, validation studies of previously published tools, and general guidelines or recommendations to assess inappropriate prescribing.	Pubmed	January 1, 1991, to March 19, 2013	Adults		Implicit, explicit, and mixed	46	46 (28 explicit, 8 implicit , 10 mixed)	9
Lee G, *et al*[17] (2022).	To determine the similarity of PIM specified in and between existing explicit lists and the availability in Australia of medications included on existing lists to determine their applicability to	Explicit lists of PIMs for older adults, the most recent version and having the complete list published in English were included. Lists modified and adapted from another list for a different clinical	Published lists based on an existing list if no changes were made from the original list, or if the new list consisted only of deletions, simplifications or rephrasing of the previous list, implicit tools	Ovid EMBASE Ovid MEDLINE and Elsevier Scopus, manually review of list of articles published in the previous seven systematic reviews	EMBASE (1974 – April 2021), MEDLINE (1946 – April 2021) and Elsevier Scopus (2004 –	Older adults	Original research	Explicit	35	35	11

	the Australian context	population or geographical location were included			April 2021).						
Lucchetti G, *et al*[16] (2017).	To review all PIM for older persons included in prescribing criteria published in the last decade	Articles describing the development of criteria for PIM Use in Older Adults. Latest version of the tool	Articles not addressing the target topic, investigating the use of these criteria in clinical and non-clinical settings, theoretical reviews of inappropriate prescribing, duplicate publications, prescription omission criteria (i.e. START) and criteria for institutionalized or hospitalized patients	PubMed and Medline	1st of January 2006 and to 31st of December 2015	Older adults		Explicit	14	14	6
Masnoon N, *et al*[33](2018).	To summarise available prescribing appropriateness assessment tools and criteria, and their associations with patient-related outcomes	Studies in English that were already published or in press	NS	MEDLINE, EMBASE and Informit (Health Collection)	2000 to 2016	Any age	Any study design	Implicit and explicit	42	42, 26 (explicit)	10
Motter FR, *et al*[18] (2018).	To summaries and compare validated PIMs lists for older peoples published in different countries between 1991 and 2017	Original studies describing the explicit criteria used to determine PIM, described the development and validation of the methods used in the PIM list. Interventions and observational studies that evaluated PIMs were also retained	Medication review techniques using implicit criteria to evaluate PIMs and lists of PIMs restricted to specific therapeutic classes orspecific diseases, studies of PIMs not validated by expert consensus and guidelines or recommendations for the assessment of inappropriate prescriptions, as well as letters, editorials, and duplicate studies.	PUBMED, AgeLine, Academic Search, Academic Search Premier, and CINAHL	January 1991 and April 2017	65+	Original studies	Explicit	36	36	11

Renn BN, *et al* [34](2018).	Examined published practice recommendations for discontinuation of Cholinesterase inhibitors (ChEI) in Alzheimer's disease (AD)	Guidelines that addressed patient care or treatment recommendations for dementia broadly or AD specifically. Five pertinent medical text books in the disciplines (neurology, geriatrics, psychiatry, medicine, pharmacology) and one specialty topic (dementia) reviewing diagnosis, treatment and practice in the relevant subspecialty	Exclusively pertained to a disorder other than AD, specific pharmacological treatments other than cholinesterase inhibitors, specific aspects of patient care or to a non-prescribing discipline, unrelated aspect of medicine or practice (e.g., nursing guides, pediatric psychiatry	PubMed Guidelines databases Seven relevant professional societies Google search engine.	Since 2005	Not specified	Practice guideline (16), and text book (36)	Guideline and text books on discontinuation	16	ChEI	5
Schiavo G, *et al*[19] (2022).	Identify explicit screening tools used to identify PIMs on older people, and identify the PIMs, PIMs–interactions (PIMs–drugs and PIMs–diseases), therapeutic alternatives and clinical management for PIMs reported in publications and in these explicit screening tools used to identify PIMs	Studies that developed and/or validated explicit screening tools to identify and report PIMs for older people; PIMs–interactions (PIMs–drugs and PIMs–diseases); and/or suggested strategies for clinical management and/or the use of therapeutic alternatives. The most recent versions of the tool were included	Editorials, commentaries, letters, reviews, news reports, abstracts from conference proceedings, theses and dissertations were excluded. Studies written in non-Roman alphabet languages (e.g., Russian, Japanese and Chinese)	PubMed and Scopus Records identified from reference of articles	Inception until May 2021).	60 +	Clinical trials, observational studies and studies conducted by a panel of experts.	Explicit tools	58	614 PIMs and 747 PIMs–interactions	8
Systematic reviews included tools used for paediatric age groups											
Li S, *et al*[35] (2022).	To systematically evaluate children's PIP screening tools and validation studies on these tools.	PIP screening tools for Children, validation studies on PIP screening tools, described as a clinical study which aims to assess the feasibility	Repeated publication, review, unobtainable full-texts, not the latest version, non-Chinese and non-English.	PubMed, Embase, Cochrane Library, CNKI, VIP and Wanfang Data	Not provided (retrieval before may 2021)	Children (0–18 year)	Original and Validation study of the tools	Explicit	Nine	5 (screening tool) and 4 (validation study)	11

		or reliability of PIP screening tools								
Corrick F, *et al*[36](2020)	Identify and provide an overview of all paediatric rational prescribing tools	Articles describing tools targeted at evaluating the rationality or appropriateness of prescriptions, updated and revised versions of previously published tools, and including tools limited to specific drugs, drug groups, diseases or disease groups	Tools targeting adults and no specified target patient groups, indicators that assess rates or percentages of prescription types, validation study of a previously published tool, educational interventions aimed at improving prescribing, and guidelines describing recommended prescribing	Ovid MEDLINE, Embase, International Pharmaceutical Abstracts (IPA) and CINAHL.	Earliest till July 2019	< 18	Explicit and mixed	5	3	9
Systematic reviews covered tools used to apply for limited life expectancy										
Thompson W, *et al*[37] (2019).	To summarize available tools that can assist clinicians in identifying and reducing or stopping (deprescribing) PIMs and that specifically consider frailty or LLE.	Studies had to state explicitly that the tool was designed for this population or include specific considerations relevant to this population.	Aimed exclusively at individuals with cancer in the palliative care setting.	MEDLINE (via Ovid SP), EMBASE (via Ovid SP), and CINAHL, along with grey literature	Inception to December 2017	Frail older persons and older persons with limited life expectancyLLE	Models/frameworks of deprescribing (2) Entire medication list approach (9) Medication specific approach (4)	15	15	10
Van Merendonk LN, *et al*[38] (2022).	Summarize and compare available guidelines and tools to deprescribe for palliative cancer patients.	Studies included palliative cancer patients. Applying a tool or certain criteria for screening of medications were included if they were applied to palliative cancer patients. Only electronic articles available in English were included	Studies focusing on a population without palliative cancer patients, Studies not applying a tool or guideline, Studies focusing on one specific medication category	SCOPUS and PubMed	Carried out a literature search in December 2020	Palliative cancer patients.	Implicit, Explicit, Guidelines	9	9	8

Footnote© Both tools and guidelines aid deprescribing process. Tools are used to identify PIM. These PIM tools can be explicit (i.e. criteria based, that providing a list of drugs as potentially inappropriate or as candidates for deprescribing), implicit (i.e. describing appropriateness based on users' clinical judgment) or mixed tools that combine both. Guidelines if the purpose is to identify PIM as well as provide guidance on how to deprescribe these medications. **RCT:** Randomised clinical trial

Table 2: Summary of guidelines to support deprescribing of potentially inappropriate medications

Reference (country, year)	Objectives	Evidence for the guideline development	Approach of the guideline development	Content ©	Target population: For whom the guideline apply	AGREE II quality (score)	Setting/ audience
Bjerre LM*, et al*[39] (Canada, 2018)	To develop an evidence-based guideline to help clinicians make decisions about when and how to safely taper and stop antipsychotics	Systematic review of clinical trial, review of review	GRADE	Recommendations on disease specific medication classes (antipsychotics) on how to stop the medication with tapering and without tapering. The cut-off for consensus of the final recommendations wording was based on ≥ 80% of GDT agreement. The GDT comprises 10 members (9 clinicians [4 pharmacists, 2 geriatrician, 2 family physician, 1 geriatric psychiatrist] and 1 Cochrane methodologist)	Adults including elderly who have been prescribed antipsychotics for insomnia or for behavioral and psychological symptoms of dementia (BPSD). BPSD treated for > 3 months' symptom controlled or no response to therapy and primary insomnia treated with any duration where underlying comorbidities are managed.	High (94.5%)	Canadian primary care and long-term care (LTC) physicians, pharmacists, nurse practitioners, and specialists who care for patients taking antipsychotics.
Farrell B*, et al*[46] (Canada, 2017).	To develop an evidence-based guideline to help clinicians make decisions about when and how to safely taper or stop proton pump inhibitors (PPIs)	Systematic review of PPI deprescribing, reviews of the harm of continued PPI use, syntheses of patient preferences and resource implication	GRADE	Recommendations on disease specific medication/ medication classes (PPIs) on stopping (abrupt or tapering), Stepping down (abrupt or tapering followed by prescription of H2 RA), and reducing the dose (on-demand or intermittent, lower dose use). The cut-off for consensus of the final recommendations wording was based on ≥ 80% of GDT agreement. The GDT comprises 10 members (5 voting [1 family physician, 3 pharmacists, and 1 gastroenterologist] and 5 non-voting member for the final recommendations).	18^{+}years (including the elderly) taking a continuous PPI for longer than 28 days for the purpose of treating GERD or esophagitis.	High (98.9%)	primary care physicians, pharmacists, nurse practitioners, and specialists who care for patients who might use PPIs
Pottie K*, et al*[42](Canada, 2018).	Develop an evidence-based guideline to help clinicians make decisions about when and how to safely taper and stop BZRA	Scoping review followed by systematic review	GRADE	Recommendation on disease specific medication classes/medications (BZRA) on Stopping, tapering dose, CBT, combining tapering and CBT, reducing BZRA use, Providing substitutive therapy. The cut-off for consensus of the final recommendations wording was based on ≥ 80% of GDT agreement. The GDT comprises 9members [8 clinicians (1 family physician, 2 psychiatrists, 1 clinical psychologist, 1 clinical pharmacologist, 2 clinical pharmacists, and 1 geriatrician) and a methodologist].	Primary insomnia or comorbid insomnia (adults aged 18 to 64 who take BZRAs for most days of the week for more than 4 weeks, and elderly adults 65^{+}regardless of duration)	High (98.9%)	primary care physicians, pharmacists, nurse practitioners, or other specialists who care for patients taking BZRAs for insomnia.

Department of Health[44] (Irish guideline, 2019)	To provide clear and evidence based recommendations on appropriate prescribing of psychotropic medication for non-cognitive symptoms in people with dementia	Systematic review of studies and guidelines	GRADE approach / evaluate by AGREE II	Recommendations on disease specific psychotropic medication classes/medications (antipsychotics, ChEI and memantine**,** antidepressant, anticonvulsant, and Z-drugs and melatonin) on appropriate verses non-appropriate use. Each recommendation was assigned a grade for quality of evidence and strength of recommendation by the GDG (32 multi-disciplinary team) and decision was reached based on consensus.	All adults (18 years and older) with a diagnosis of dementia, of any type with non-cognitive symptoms	High (90.3%)	For all settings that provide care for an adult with dementia doctors, nurses, pharmacists and health and social care professionals
Guidelines consider frail elderly and/limited life expectancy							
Kojima T*, et al*[45](Japan, 2016).	Update the list of PIM extracted from "Guidelines for medical treatment and its safety in the elderly 2005" based on the recently published "guidance statement on appropriate medical services for the elderly"	Asystematic review of 15 diseases, conditions and special areas pertinent to clinical care.	GRADE	Non disease specific list of medication classes/ medications (29 lists prescribing with special cautions/with flow charts to approach for deprescribing or starting with cautions if not better alternatives available, 8 lists consider for starting with flow charts to start if the patient was not taking but a possibility to improve quality of life). For each of the list the quality of evidence and strength of recommendation was assigned based on literatures and voted consensus by the multi-displinary authors (no specific GDT assigned). No specific cut-off point was provided to define consensus.	List of drugs to be prescribed with special caution for aged 75^{+} years or frail elderly < 75 years or in need of special care. List of drugs to consider starting" is oriented to elderly individuals of all ages	High (75.3%)	GP on the front lines, Pharmacists, and nurses involved in pharmacotherapy
Farrell B*, et al*[40] (Canada, 2017).	To develop an evidence-based guideline to help clinicians make decisions about when and how to safely taper, stop, or switch antihyperglycemic agents in older adults.	Systematic review	GRADE	Recommendations on disease specific medication/ medication classes (Anti-hyperglycaemic medications with or without hypoglycemics risk) on when and how to stopping the medication, dose reduction, or prescription substitution. The cut-off for consensus of the final recommendations wording was based on ≥ 80% of GDT agreement. The GDT comprises of 9 members [7 clinicians (2 family physicians, 3 pharmacists, 1 nurse practitioner, 1 endocrinologist), 1 clinical epidemiologist, 1 not provided]. All clinician members were expert in type 2 diabetes management in older people.	65^{+}years who are receiving at least 1 antihyperglycemic medication to treat type 2 diabetes and who are at risk of hypoglycemia; who are at risk of other antihyperglycemic adverse effects; or for whom benefit is uncertain owing to frailty, dementia, or LLE.	High (98.9%)	Physicians, pharmacists, nurse practitioners, registered nurses, and certified diabetes educators caring for older adults with type 2 diabetes who are receiving the medications.

Mallery LH*, et al.*[47] (canada, 2013)	Develop and disseminate guidelines for the treatment of frail older adults with type 2 diabetes.	Literature (meta-analysis, review of trials)	AGREE reporting approach	Recommendations on disease specific medication/ medication classes (Anti-hyperglycaemic medications) for actions based on glycaemic level. Decrease or discontinue diabetes treatment (HbA1c < 8%); Consider increasing diabetes treatment (HbA1c >12%): unnecessary to alter therapy if an individual with LLE has tolerated at high HbA1c level (not experiencing hyperglycaemic associated symptoms). The guideline committee involves (endocrinologist, a geriatrician, a family physician/ medical director of a long-term care facility, long-term care nurses, nutrition staff, diabetes educators, and a representative from the Department of Health Continuing Care Branch). Each recommendation is accepted based on all agreement of the committees.	Frail older adults (65 years and above) with type 2 diabetes	Moderate (62%)	Nursing home settings. Continuing education needs of health care professionals
Reeve E*, et al*[48](Canada & Australia, 2018).	To develop an evidence-based clinical practice guideline for deprescribing ChEIs and memantine, using robust international guideline development processes	Systematic review and expert opinion and non-systematically reviewed evidence	GRADE	Recommendations on disease specific medication/ medication classes: ChEI (donepezil, rivastigmine, galantamine), Memantine) on discontinuation or Trial deprescribing approach$^{\beta}$. The cut-off for consensus of the final recommendations wording is based on ≥ 80% of GDT agreement. The GDT comprises 12 member's s [(10 clinicians: geriatrician/ clinical pharmacologist, geriatric psychiatrist, GP, GPs with aged care accreditation, registered nurse and pharmacists) and (2 consumer representatives: a person with mild dementia and a career of a person with dementia)]	Adults with Alzheimer's disease or dementia of Parkinson's disease, Lewy body dementia or vascular dementia taking medications for greater than 12 months, who do not have appropriate indication, never benefited or appear to be no longer benefitting, and those who had severe or end-stage dementia	High (100%)	Clinician's involved in the care of adults prescribing a ChEI or memantine, including but not limited to general practitioners, specialist physicians, nurses and pharmacists.
Onder G*, et al*[41](Italy, 2022).	To develop recommendations for the clinical management of persons with multimorbidity and/or polypharmacy and to provide evidence-based	Review of literature (article databases and NICE)	GRADE	Recommendations on managements of multimorbidity and/or polypharmacy including specific medication/ medication classes (Antihypertensive, PPI, Statin and Aspirin including other antiplatelet). No recommendations on discontinuation of anti-hypertensive therapy and antiplatelet including aspirin related to poor quality of	Persons with multimorbidity and/or polypharmacy as well as the prioritization of care through the identification of persons at increased risk of negative health outcomes.	High (92.2%)	persons with multimorbidity and/or polypharmacy and their caregivers, healthcare professionals, and the healthcare system

	guidance to improve their quality of care.	evidence. But provide recommendations on deprescription and possible reintroduction of PPI, discontinuation of statin therapy for all with < 1-year life expectancy and risk benefit analysis for age 80+.The recommendations was developed based on consensus of the expert panels. The guideline development panel involves scientific societies operating in the fields of geriatrics, internal medicine, pharmacology, and general medicine and from multi-displinary fields (epidemiologists, pharmacists, internists, geriatricians, pharmacologists, general practitioners, and nurses and a patient advocate)	

Footnote

©The wording of the final recommendations in the GRADE frameworks of the three guidelines was based on the cut-off ≥ 80% of the Guideline Development Team (GDT) agreement; but the Irish guideline did not specify the cut-off for Guideline Development Group (GDG) consensus. **β** Trial deprescribing (slowly reducing the medication dose (tapering) prior to complete cessation, with monitoring throughout the process).
PIM: Potentially inappropriate medications; **ADRs:** Adverse drug reactions; **PIP:** potentially inappropriate prescription; **NS :** Not specified; **ChEI:** Cholinesterase inhibitors; **AD:** Alzheimer's disease; **GRADE**: Grading of Recommendations, Assessment, Development and Evaluation; **GDT:** Guideline development team; **H2RA:** histamine-2 receptor antagonist; **PPI:** Proton pump inhibitor; **GERD:** gastroesophageal reflux disease; **BZRA:** Benzodiazepine receptor agonists; **CBT:** Cognitive behavioural therapy; GDG: Guideline Development Group

The quality assessment of the included studies revealed that 11 systematic reviews demonstrated a low risk of bias [12, 15, 17-19, 32, 33, 35-38], while the remaining reviews exhibited a moderate [14, 16] or high risk of bias [31, 34]. Among the guidelines, 7 (77.8%) were considered of high quality in terms of their development [39-42, 44, 46, 49], while 2 (22.2%) were rated as moderate quality [47, 50]. Four guidelines fully met all items of the AGREE-II assessment tool, further supporting their high quality [42, 49, 51, 52]. Additional information justifying the assessments of bias can be found in **Supplementary file 2.4**.

Available tools and guidelines for assessing medication appropriateness and aiding in deprescribing PIM

In our study, we initially identified 356 tools and 32 guidelines from the included systematic reviews. After removing duplicate tools and guidelines published in multiple reviews and conducting eligibility evaluations, we narrowed down our selection to 95 unique tools and 9 guidelines that were relevant to our study. The flow diagrams presented in **Figure 2** illustrate the application of each stage of eligibility assessment and the corresponding results throughout the three stages. For detailed characteristics of the identified tools, please refer to **Table 3**, and additional information regarding the exclusion of tools and guidelines at different stages of eligibility assessment can be found in **Supplementary file 2.3**

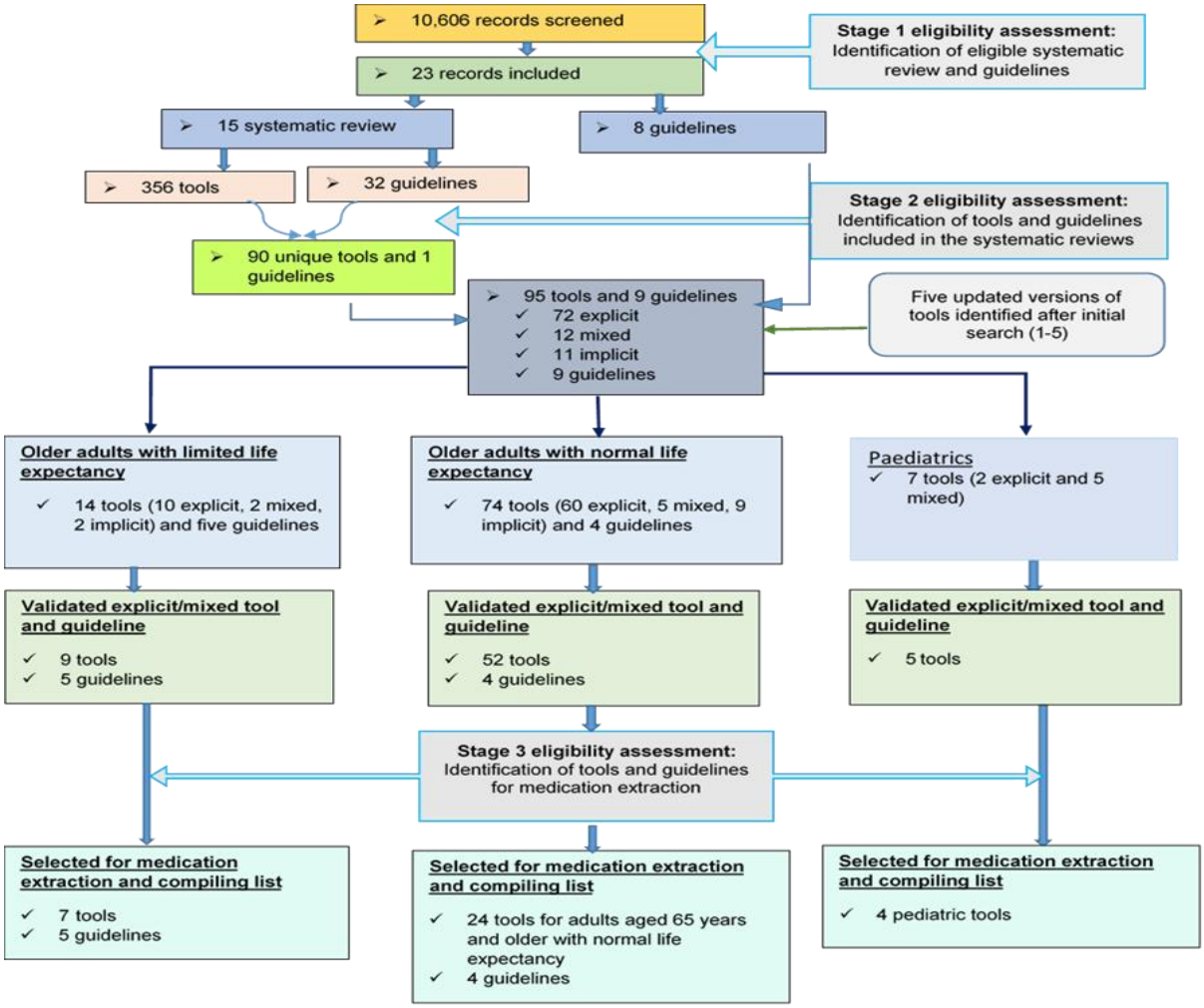


Figure 2: Flow diagram illustrating the progression of eligibility assessment and the application of eligibility criteria for selecting tools and guidelines, along with the key results at each stage of eligibilit

Table 3: Summary of characteristics of tools to appraise appropriateness of medications to uses for different target population

Tool name (ref)	Country	Nature of the criteria	Target age (group)	Setting	Development /base of the criteria	Validation methods (the composition of experts)	Content of the criteria#	Aspects of PIM covered by the lists								
								Independent of diseases	Stopping criteria	Starting criteria	Dosage	Duration	Drug-drug interaction	Drug-disease/ conditions		Alternative medication
Beers, 1991[12, 14, 15, 18, 32]	USA	Explicit	65+	Nursing home	Literature (published 1979–1990 in English)	Two-round written survey based on Delphi method with 13 nationally or internationally recognized experts from the USA and Canada (expertise in psychopharmacology, pharmacoepidemiology, clinical geriatric pharmacology, general clinical geriatrics, long-term care)	30 criteria (19 criteria describing medications or medication classes that generally should be avoided, 11 criteria describing doses, frequencies, or durations that should not be exceeded)	√	√		√	√				
Stuck criteria, 1994[14, 18]	USA and Canada	Explicit	older	Community-residing older persons	Beers, 1991	Modified Delphi method (two-round) by 13 experts (Geriatricians and pharmacists)	27 criteria statements	√	√							
The geriatric medication algorithm 1994[12]	USA	Mixed	65+	Primary care setting	Certified geriatric internists discussed the medications and develop the algorithms	Algorithm was tested in the resident outpatient clinic of a community teaching hospital	Designed to educate physicians in reducing inappropriate prescribing, and divided in to four steps. (provide 10 list of high risk drugs, less toxic alternatives and drug requiring dosage reduction	√			√		√	√		√
Oborne prescribing indicators, 1997[12]	UK	Mixed	65+	hospital setting	Based on the drug charts of 1686 patients (literature review)	Ten algorithms assessed directly from drug chart data and four requiring collection of clinical data	A list of 14 prescribing indicators that were presented in the form of algorithms guiding the user through the process	√	√		√		√			

							of detecting inappropriate prescribing.							
Beers, 1997[12, 14, 15, 18, 32]	USA	Explicit	65+	General ambulatory Elderly population	Beers, 1991 and Literature (published 1990–1995 in English)	Delphi methods with two-round survey (first round, written mail survey; second round, face-to-face full-day meeting) involving 6 nationally recognized expertise in (general geriatrics, clinical pharmacology, pharmacoepidemiology, clinical pharmacy, psycho pharmacology)	43 criteria statements classified as having high severity or not (28 criteria describing potentially inappropriate medications, 15 diseases or conditions and medications to be avoided in these conditions)	√	√	√	√		√	
McLeod, 1997[12, 14, 15, 17-19, 32, 33]	Canada	Explicit	older	not reported	Beers 1991 criteria, Literature (expert review of drug interactions, and Handbook of Adverse Drug Interactions, standard textbooks on therapy provided to elderly people)	Two-round mail survey based on Delphi method with 32 experts (7 clinical pharmacologists, 9 geriatricians, 8 family practitioners, 8 pharmacists)	38 inappropriate high-risk practices in prescribing grouped in to 4 categories with recommendations of alternative therapy (18 criteria generally contraindicated for elderly, 16 practices involving a drug–disease interaction, 4 practices involving a drug–drug interaction)	√	√	√		√	√	√
Zhan criteria, 2001[12, 14, 17-19, 32, 33]	USA	Explicit	65+	General ambulatory Elderly population	33 drugs as a subset from Beers 1997 criteria (PIM irrespective of dose, frequency of administration, or duration of the therapy)	Two-round modified survey involving 7 experts (5 geriatricians, 1 pharmacoepidemiologist, 1 pharmacist)	33 drugs (11 drugs that should always be avoided, 8 drugs that are rarely appropriate, 14 drugs that have some indications for use in an elderly population)	√	√					
Fick-Beers, 2003[12, 14, 15, 18, 19, 32]	USA	Explicit	65+	Ambulatory and nursing facility population	Beers 1997 criteria and Literature (published 1994–2000 in English	Three-round survey (first round, mail survey; second round, face-to-face meeting; third round, mail survey) based on modified Delphi method. Twelve nationally or internationally recognized experts from the USA (expertise in psychopharmacology, pharmacoepidemiology, clinical geriatric pharmacology, and clinical geriatric medicine) was involved.	68 criteria statements classified as having high or low severity (48 criteria describing potentially inappropriate medications, 20 diseases or conditions and medications to be avoided in these conditions)	√	√	√	√		√	

Malon list of drug-drug interactions, 2004	USA	Explicit	Not specified	Community and ambulatory pharmacy settings	Systematic review of drug interaction compendia and published literature	Three round modified Delphi methods involving 5 experts (Physician; clinical pharmacist; and expert in drug-drug interactions)	25 clinically important drug interactions that are likely to occur in the community and ambulatory pharmacy settings were identified	√	√			√			
Rancourt criteria, 2004[12, 14, 17-19, 33]	Canada	Explicit	Older	long-term care facilities	Beers criteria 1991 and 1997, McLeod criteria and additional literatures (four) and excluding the medications unavailable	Two rounds of modified Delphi method by 4 experts	111 criteria and classified in to four categories (PIM; Potentially inappropriate duration; Potentially inappropriate dosage; and Potentially inappropriate drug-drug interaction)	√	√		√	√	√		
Lindblad 2006[12, 14, 15, 17-19]	USA	Explicit	65+	Outpatient	Literature published between 1966 and July 2004 (English-language articles) (E.g. Beers 1997, Fick-Beers, McLeod 1997)	Two-round mail/written survey based on modify Delphi method with 9 experts (2 physicians (geriatricians) and 7 clinical pharmacists)	28 individual drug-disease interactions involving 14 diseases or conditions							√	
Laroche, 2007[12, 14-18, 32, 33]	France	Explicit	75+	Not reported	Beers lists (1991, 1997, 2003), the McLeod 1997, the criteria adapted to French practice and the guidelines of the French Medicine Agency on medication prescribing in the elderly	Two-round mail survey based on Delphi method with 15 experts (5 geriatricians, 5 pharmacologists, 2 pharmacists, 2 general practitioners, 1 pharmacoepidemiologist)	34 inappropriate practices in prescribing with recommendations of alternative therapies (29 medications or medication classes that should be avoided, 5 drug–disease interactions)	√	√		√		√	√	√
Winit-Watjan, 2008 [12, 14-19, 33]	Thailand	Explicit	Older	Not reported	A literature review (databases in Thailand and worldwide) from 1990 to 2006.	Delphi technique with the three-round survey of 17 experts for the first 2 rounds and 16 for the third round). The expert included (geriatricians, geriatric medicine lecturers or physicians working in the geriatrics area)	77 practice statement (33 medications or medication classes with potential adverse reactions, 32 drug–disease interactions, 12 drug–drug interactions)	√	√			√	√		
STOPP/ START version 1, 2008 [12]	Ireland	Explicit	65+	Community-dwelling older adults	Evidence-based literature (not defined exactly in the article) Clinical experience of the investigators	Two-round mail survey based on Delphi method with 18 experts (9 teaching hospital consultants in geriatric medicine, 3 clinical pharmacologists, 1 old age psychiatric, 2 senior academic	**STOPP:** 65 criteria focusing on prevalent problems associated with commonly prescribed medicines in older adults arranged according to	√	√	√	√	√	√	√	

						primary care physicians, 3 senior hospital pharmacists with interest in geriatric pharmacotherapy)	physiological systems (42 criteria concerning avoidance of medications in certain disease states or conditions, 4 criteria concerning specific drug combinations to be avoided, 12 criteria concerning duration of drug therapies, 2 criteria concerning doses, 3 criteria concerning avoidance of prescribing without indication, 2 criteria concerning need for additional therapy) **START:** 22 evidence-based explicit prescribing indicators for common diseases in older adults								
APIT, 2008 [12, 14-16, 19, 32]	Australia	Mixed	65+	Not reported	Australian literature based on; most frequent Australian Pharmaceuticals Benefits Scheme medications prescribed to Australians in 2006, Most common medical conditions for which Australians aged 65 and older consult medical practitioners	Not validated	45 explicit and 3 implicit prescribing indicators (18 concerning avoidance of medications in certain disease states or conditions, 19 concerning recommended treatment in certain disease states or conditions, 4 concerning medication monitoring,3 concerning specific drug interactions, 1 asking about the presence of any drug interactions, 1 asking about any changes in medication in the previous 90 days, 1 concerning smoking status,1 concerning vaccination status	√		√	√	√	√	√	
Portugal Beers criteria, 2008[19]	Portugal	explicit	65+	Not specified	Fick-beers 2003	Not validated but developed based on validated fick-beers 2003	Included 49 drug/drug classes and PIM lists for 10 disease conditions	√		√		√	√		√	√

POM, 2009[12, 15, 33]	Netherland	Mixed	Older	Not reported	Based on evidence from the literature, Dutch guidelines, such as the General Practitioner Guidelines and the National Interdisciplinary Guideline	Not validated Tested in case histories of ten geriatric patients admitted to the geriatric outpatient clinic	POM assists physicians to optimise polypharmacy prescribing in the elderly population. This method is based on six open questions, whereby each question is presented with an overview of the most frequent and clinically relevant problems, together with explicit suggestions to improve prescribing.	√		√	√	√	√	√	√
NORGEP 2009[12, 14-19, 32]	Norway	Explicit	70+	general practice setting (home dwelling elderly)	Beers criteria (1991, 1997,2003), Swedish recommendations, Recent evidence from literature (published 1996-2008), and Clinical experience of the investigators	Three-round mail survey based on Delphi method with 47 experts (14 clinical pharmacologists, 17 geriatricians, 16 general practitioners)	36 criteria for pharmacologically inappropriate prescribing in general practice (21 criteria concerning single drugs and dosages, 15 criteria concerning drug combinations to be avoided)	√		√		√			
FORTA, 2009[12]	Germany	Explicit	65+	Not reported	Reclassification of beers criteria (positively and negatively)	Not validated	It is an expansion of beers criteria by classifying medications in to four groups (A -D). But this versions of FORTA not provide the overview of recommended drugs	√		√					
PRISCUS, 2010[12, 14-19, 33]	German	Explicit	65+	Not reported	Beers criteria 1997, Beers-fick criteria 2003, Mcleod criteria 1997; French/Laroche criteria 2007 and literature review (not specified)	Delphi method (two-round), 25 experts in the first round and 26 experts in the second round having different expertise (geriatric medicine, clinical pharmacology, general practice, internal medicine, pain therapy, neurology, psychiatry, and pharmacy) participated.	83 PIM	√		√		√			√
Kim, 2010 [14-19]	Korea	Explicit	65+	Outpatient setting	Beers criteria , Canadian criteria and Zhan's classification (Adapt to korean	A Delphi evaluation with a two-round survey included 14 geriatric specialists, including 7, family medicine specialists,	57 potentially inappropriate drugs for the elderly, independent of diagnosis 93 potentially	√		√		√	√	√	√

					reimbursed drug list) and classify lists based on fialova etal criteria[53]	3 psychiatrists, 1 neurologist, and 3 clinical pharmacists	inappropriate drugs in 29 diagnoses (48 individual medications or classes of medication to avoid in older adults and their potential concerns and 20 disease/conditions and medication to be avoided in older adults with these conditions)						
New Mexico criteria, 2012[12, 14, 18]	USA	Explicit	65+	Not reported	Fick-beers, 2003	Delphi method (two-round) involving 12 experts (Clinical pharmacists, geriatricians, nurses, managed care specialists, and consumers)	72 drugs to be used with caution in the elderly	√	√	√			√
Matanovic, 2012[14-16, 19, 33]	Croatia	Explicit	65+	Ambulatory and clinical settings as well as in nursing homes"	Explicit screening tools for PIM already published but Adjusted (McLeod, 1997; Fick-Beers, 2003; Lindblad, 2006; Laroche, 2007; Malone 2004, Hanlon 2005)	Not validated	In total list 110 drugs (33 criteria's with unfavourable risk: benefit ratio, 6 questionable efficacy and 71 individual drug–disease interactions involving 28 diseases or conditions	√	√	√	√	√	√
Chang, 2012[14-16, 18, 33]	Twain	Explicit	65+	Not reported	Beers–Fick 2003; McLeod criteria 1997; Rancourt 2004; French criteria 2007, STOPP/ START version 1; NORGEP, 2009 ; and Thailand criteria, 2008 (availability checked)	Delphi method (two-round) involving 21 experts from various specialties (Geriatricians, neurologists, psychiatrists, cardiologists, pulmonologists, gastroenterologist, urologists, and clinical pharmacists)	36 criteria (24 drug or drug classes to be generally avoided in older adults irrespective of comorbidities, 12 chronic conditions with 6 drug or drug classes that patients with these conditions should avoid.)	√	√	√	√	√	√
Mann, 2012[12, 14-19, 33]	Austria	Explicit	65+	Not reported	Beers criteria 1997, Beers-Fick criteria 2003, McLeod criteria 1997, Laroche criteria 2007, STOPP/	Modified two round Delphi method that involves 8 members of experts (A general practitioner, a specialist in neurology, three specialists in internal medicine, a psychiatrist, and two clinical pharmacists working in hospital)	73 drugs to be avoided in older patients because of an unfavourable benefit/risk profile and/or unproven effectiveness.	√	√				√

					START version1 and PRISCUS, 2010											
Beers, 2012[12, 14, 15, 18]	USA	explicit	65+	All ambulatory and institutional care settings	Update of Fick-Beers 2003 criteria; by literature review from December 1, 2001 (the end of the previous panel's search) to March 30, 2011)	Modified Delphi method (a conference call and a 2 day in person meeting) with 11-member interdisciplinary expert panel (expertise in geriatric medicine, nursing, pharmacy practice, research, and quality measures) and representatives from different organization	53 medications or medication classes encompass the final updated Criteria (34 medications or medication classes to avoid in the elderly 14 diseases and conditions and medications to be avoided in these conditions 5 medications to be used with caution in older adults	√		√		√	√		√	√
APIT,2012[1 4, 17, 18, 33]	Australia	Explicit	65+	all settings	Basager, 2008 and literatures in the context of Australia by identifying common problems by obtaining the Healthcare information using the BEACH (Bettering The Evaluation and Care of Health) programme	RAND/UCLA appropriateness method, a two-round modified Delphi method by involving 15 experts in the first and /12 in the second round (Geriatricians/ pharmacologists ,clinical pharmacists, disease management advisors to organizations that produce Australian evidence based therapeutic publications)	41 criteria	√		√	√	√	√	√	√	√	
Clyne criteria, 2013[14, 18, 19]	Ireland	Explicit	65+	Primary care settings	Mcleod 1997, IPET, Beers criteria 2012, Prescription Peer Academic Detailing (Rx-PAD) study, ACOVE-3, and STOPP version 1	Two-round Delphi method and focus group involving 5 experts (2 general practitioners,2 pharmacists, 1 physician)	34 criteria	√		√		√	√	√	√	√	√
PIMHF, 2014[15, 17, 19]	Ireland	Explicit	Older	Ambulatory Heart failure population	literature search (January 1960 to 31 December 2010, English language publication)	Two round modified Delphi method (22 experts with multidisplinary team was involved) with electronical approach (no face to face meeting)	11 disease specific lists (HF)	√		√					√		

RASP list, 2014[14, 17, 33]	Belgium	Explicit	Older	All health care setting	STOPP version 1	Content Validity Index method included 19 experts response in two rounds (5 pharmacists, 4 geriatricians, 5 hospital pharmacists, 5 geriatricians)	76 criteria	√		√		√	√	√	√		
FORTA, 2014[14, 16, 18, 19, 33]	Germany and Austria	Explicit	Older	Not reported	FORTA publication in the second edition of the book "Wehling M, Burkhardt H. Arzneitherapie fu¨r A¨ ltere. 2nd ed. Heidelberg: Springer; 2011 [in German]."	Two-round Delphi procedure was conducted involving 20 experts, 17 geriatric internists and 3 geriatric psychiatrists from Germany (13)and Austria (7)	Classify 190 medications/medication classes in to four category; A (Absolutely; indispensable drug, clear-cut benefit in terms of efficacy /safety ratio proven in elderly patients for a given indication), B(Beneficial, drugs with proven or obvious efficacy in the elderly, but limited extent of effect or safety concerns), C(Careful, drugs with questionable efficacy/safety profiles in the elderly, to be avoided or omitted in the presence of too many drugs, lack of benefits or emerging side effects; review/find alternatives), D (don't; avoid in the elderly, omit first, review/find alternatives)	√		√	√	√					
HRM, 2015[19]	USA	Explicit	Elderly	Not reported	Comprehensive literature review from 2000 to 2015 (3 experts developed the list of alternatives based on the literature)	Not formal validation procedure. But the lists developed by consulting the explicit expert panel consensus criteria and received feedback from National Committee for Quality Assurance (NCQA), the Pharmacy Quality Alliance (PQA), the 2015 American Geriatrics Society (AGS) Beers Criteria panel, and the Executive Committee of the AGS	Provide the list of drug-therapy alternatives with supporting references. Alternatives for high-risk medications organized into 15 therapeutic classes according to the measure specifications for high risk medications (HRM) published in 2015. 10 therapeutic drug classes that are included in the Potentially Harmful Drug-Disease Interactions in the Elderly measure (a prior history of falls,	√						√		√

							dementia, and chronic kidney disease). nonpharmacological alternatives was also provided.							
Beers, 2015[14-16, 18, 33]	USA	Explicit	65+	All ambulatory,acute, and institutionalized settings with the exception of hospice and palliative care.	Beers 2012, literature review (from August 1, 2011 (the end of the previous panel's search) to July 1, 2014) English language	Modified Delphi method (two round) with a 13-member interdisciplinary expert panel Expertise in geriatric medicine, nursing, pharmacy practice, research and quality measures	101 criteria statements classified as having high or low severity (40 medications or medication classes to avoid in the elderly 12 diseases/ conditions and medications to be avoided in these conditions 16 medications/class medications to be used with caution 13 drug–drug interactions 20 medications inappropriate based on kidney function)	√		√		√	√		
Spanish adaptations of beers criteria, 2015[19]	spain	explicit	elderly	Not reported	Beers 2012, STOPP/START 2008, PRISCUS, NORGEP 2009	Not validated but developed based on explicit screening tools for PIM already published	47 (34.3%) active substances were not commercially available in Spain and 40 new ones could be included in the Beers 2012 list. As regards "Disease Dependent Criteria" the figures were 33 (21.3%) and 48, respectively.	√		√		√	√		√
EU (7)-PIM list, 2015[14-16, 18, 19, 33]	7- EU Countries[a]	Explicit	65+	Not reported	PRISCUS 2010, French criteria 2007, Beers criteria 1997, Beers-Fick criteria 2003, McLeod criteria, Beers criteria 2012, and Micromedex	Delphi method (two-round), 26(29)/24 (28) experts (clinical pharmacologist, pharmacist, nursing scientist, geriatrician).brief survey (12 participated/12 invited)	282 drugs/drug class and preparations were classified as medication inappropriate PIM for older people; some PIM are restricted to a certain dose or duration of use, Non-PIM (3 drugs), Questionable PIM (29 drugs)	√		√		√	√		√
STOPP/ START	Ireland (13 EU Countries)[b]	Explicit	65+	All care setting	STOPP/START 2008, and Literature review after 2008	Delphi method (two-round), 19 experts (Expertise in geriatric	Final list of 114 criteria (80 STOPP criteria and 34 START criteria)	√		√	√	√	√	√	√

version 2, 2015[14-19, 38]						medicine and pharmacotherapy in older people)										
STOPP-START Spanish, 2015[19]	spain	Explicit	65+	All care setting	STOPP/START 2015	Language translation	Review of Spanish study on prevalence of inappropriate prescription based on the Spanish STOPP-START 2009 criteria and list the Spanish translations of STOPP-START 2015 criteria. Final list include 114 criteria (80 STOPP and 34 START)	√		√	√	√	√	√	√	√
Kim criteria, 2015[14, 16-19]	Korea	Explicit	65+	long-term care services	Beers 2012 , STOPP version 1, and PRISCUS (intersectional list)	Delphi method (two-round), 20 experts (14 physicians and six pharmacists)	26 ingredients from seven drug classes were selected as PIM candidates	√		√		√		√	√	√
GheOP[3]S, 2016[14, 18, 33]	Europe (Belgium)	Explicit	Older	Community pharmacy setting	Literature review of previously published tools (between January 1990 and December 2012).	RAND/UCLA (two-round), 11 experts (clinical pharmacists, geriatricians, general practitioners, academics, community pharmacist, physician)	Consisting of 83 items for identifying PIP(31 potentially inappropriate drugs, independent of diagnosis; 11 potentially inappropriate drugs, dependent on diagnosis; 6 PPOs; 29 DDIs of specific relevance; 6 general care-related items to be addressed in the community pharmacy)	√		√	√	√	√	√	√	√
FORTA Version 3, 2018[17]	Germany,Austria,Switzerland	Explicit	65+	Not reported	FORTA, 2014	Two round Delphi method involving 22 experts (Geriatric internists; Geriatric psychiatrists)	Contains 296 substances/substance groups aligned to 30 indication groups.	√		√		√			√	
EURO-FORTA, 2018[17, 19]	EU(7)[c]	Explicit	65+	Not reported	Explicit screening tools for PIM already published (FORTA)	Delphi consensus validations (two rounds) involving Geriatric; neurologist; and clinical pharmacist (47)	Seven new country/region-specific FORTA Lists, List containing 264 items in 26 main indication groups	√		√		√				
Korean PIM, 2018[17, 19]	Korea	Explicit	Older	All care setting outside palliative care setting	Beers 2015, STOPP 2, PRISCUS, The PIM List for the Korean Elderly 2010, PIM list for	Four round modified Delphi method (expert panel consisted of 14 geriatric specialists, including 10 geriatricians (7 family medicine doctors and 3 internal medicine	110 drugs and classes (62 drugs were classified as PIMs for older adults irrespective of comorbidities and 48	√		√		√	√	√	√	√

					the Korean Health Insurance Review and Assessment Service, and the PIM list for the Seoul National University Bundang Hospital	doctors), 3 ,geriatric psychiatrists, and 1 clinical pharmacist)	drugs or drug categories were classified as PIMs for 18 specific conditions that older adults encounter frequently)							
The updated PIM-Taiwan criteria, 2019[17, 19]	Taiwan	Explicit	65+	Not reported	Beers 2015, Japan criteria, FORTA and STOPP VERSION 2	Two rounds of modified Delphi methods (24 Geriatricians; Neurologists; Psychiatrists; Cardiologists; Pulmonologists; Gastroenterologists; Urologists; Clinical pharmacists)	131 individual drugs and 9 drugs with combinations that should generally be avoided; and 9 chronic diseases with their corresponding PIMs that have drug–disease interactions	√	√	√	√		√	√
ES-PIA Project (Gonzalez criteria), 2019[17, 19]	Spain	Explicit	65+	Not reported	Previously published criteria, including screening tools product information summaries and pharmaceutical adverse events database	Two round Delphi method involving 25 experts from different backgrounds (Clinical Pharmacology, Geriatrics, Rational Use of Drugs and Pharmacy, Primary Care and Pharmacoepidemiology, and Pharmacovigilance)	138 statements	√	√	√		√	√	√
Beers, 2019 [14, 17, 19, 38]	USA	Explicit	65+	All health care setting except Hospice and palliative care settings	Beers 2015 and literature review from January 1, 2015, to September 30, 2017.	Modified Delphi method; interdisciplinary panel of 13 experts in geriatric care and pharmacotherapy	114 medications/class to be avoided, 37 medication/medication classes interacted with 10 syndromes, 17 drug-drug interactions, 23 medications/medication classes should be avoided or have their dosage reduced with varying Levels of Kidney Function, and 15 medication/ medication classes Drugs To be used With caution	√	√	√	√	√	√	
Angular criteria, 2019[19]	Portugal	explicit	65+	Not reported	24 explicit tools in the literature	Not validated	115 PIM with risk of cardiovascular adverse events to be avoided in elderly patients and 7 drug-disease interactions	√	√				√	

Modified STOPP/START Sri Lanka, 2019[19]	Sri Lanka	Explicit	Older	Not reported (In the context of resource limited healthcare setting)	STOPP START version 2	Two round Delphi consensus methodology involving six experts, including geriatricians, clinical pharmacologists, physicians and a pharmacist, to review and assess each criterion (including the ones flagged by the researchers)	List of 105 criteria, including 70 STOPP and 35 START criteria, indicating an 8% reduction in criteria compared to the original version. Modifications included complete removal (n = 11), re-wording (n = 25), splitting (n = 1) of original criteria and adding a new criterion (n = 1)	√		√	√	√	√	√	√	
Motter Brazilian consensus PIM, 2019[19]	Brazil	Explicit	65+ (pain and inflammation)	Not reported	Beers 2015, STOPP version 2, EU (7) PIM list	Online two round Modified Delphi technique (13 experts who agreed to participate in the study, 10 were geriatricians and 3 were pharmacists; off which 9 was participate in the first round and 7 in the second round). All participants were geriatricians with more than 10 years of experience in geriatric medicine.	33 concerns about drugs that should be avoided in older patients regardless of diagnosis, for 22 concerns about drugs that should be avoided in older patients with specific conditions or diseases, for 11 with special considerations of use, and for 28 of therapeutic alternatives.	√		√		√	√		√	√
TIME, 2020[17, 19]/ TIME 2021 validation study[19]	Turkey	Explicit	Older	All care setting	STOPP/START version2 and CRIME criteria[54]	Three round Delphi method with 11 expert (Academic geriatricians (9); Clinical pharmacologist (1); Community pharmacist academic (1)). Seven countries in Europe (Belgium, Czech Republic, Germany, Italy, Spain, United Kingdom, The Netherlands) and one from Israel	Internationally validated version of the TIME criteria includes 134 criteria (101 TIME-to-STOPP and 33 TIME-to-START criteria).	√		√	√	√	√	√	√	
US-FORTA, 2020[17, 19]	USA	Explicit	65+	Not reported	The EUROFORTA List, validate the FORTA (VALFORTA), Oral Anticoagulants (OAC-FORTA specific lists)	A 2-step Delphi-type approach with 8 experts (Geriatricians; Pharmacists)	contains 273 items aligned to 27 main indication groups	√		√		√				
JAPAN-FORTA, 2020[17, 19]	Japan	Explicit	65+	Not reported	The EUROFORTA List, validate the FORTA (VALFORTA),	2-step Delphi consensus validation by 13 (Geriatricians; Pharmacists; Cardiologists)	Contains 210 items aligned to 24 main indication groups	√		√		√	√			

					Oral Anticoagulants (OAC-FORTA specific lists)										
STOPP Indonesia, 2020 [19]	Indonesia	Explicit	Older	Hospital	STOPP-START version 2 (developed with the Cross-cultural adaptation guidelines from the American Association of Bone Surgeons Committee.	Psychometric test for validation and expert team. 8 expert team consisted of two geriatricians, one pharmacologist, one endocrinologist, one cardiologist, one neurologist, one clinical pharmacist, and one Linguist who was also a translator member.	The expert team was being agreed on 81 criteria (100%) of adaptation of STOPP version 2 criteria. There were 5 criteria that not valid statistically, they could not be removed from the instrument because they can influence content and construct of the instrument.	√		√	√	√	√	√	√	
STOPPFall, 2020 [17]	EU	Explicit	Older	General geriatric setting	Three recently published systematic reviews and meta-analyses and eight national falls prevention guidelines in Europe	A three round modified Delphi technique involving 24 experts (Geriatricians (20); Pharmacists (3); General practitioner (1))	14 medication classes to be included in the STOPPFall	√		√						
The EU(7)-PIM List French, 2020[19]	France	Mixed	elderly	not specified	EU (7)-PIM adaptation and implicit tool: the recommendations of French National Health Authority (HAS) and more specifically the “alerte et maitrise de la iatrogénie” (AMI) tools)	Not validated	From 289 PIM identified in the EU (7) PIM list, 183 drugs were included the list. Three PIM were added to the list of “questionable” PIMs in accordance with the new French recommendations	√		√		√	√	√		√
Hong Kong criteria, 2021	Hong Kong	Explicit	65+	All health care settings	Explicit tools assessing PIM use on the PubMed database from January 1991 to April 2019 internationally (nine sets of explicit criteria were	Two-round of modified Delphi process (8 Geriatricians (6); Pharmacist (2 [1 participant withdrew in round two]); General practitioner (1); Internal medicine (1))	PIM list included a total of 164 statements applicable to older adults aged 65 years or above, among which 77 were under PIMs independent of diagnoses, and 87 were under PIMs considering specific medical	√		√		√	√	√	√	√

					included as reference criteria the McLeod criteria, the Rancourt criteria, the Lindblad criteria, the Laroche criteria, Winit-Watjana criteria, the Norwegian General Practice , the PRISCUS criteria, STOPP version 2, and Beers 2012)		conditions. Eight PIM candidates remained questionable and thus were excluded from the PIM list.											
PIMHF, 2021[17]	Thailand	Explicit	Older	All care settings for patients with heart failure	Heart failure guidelines, heart failure-related explicit criteria and literature review (Beers criteria (2015), STOPP criteria (2015), The St Vincent's list of PIMHF (2014) and AHA scientific statement (2016))	A three round modified Delphi technique involving 17 (Cardiologists (10); Hospital pharmacists (3); Academic pharmacists (4))	47 medication items reached the consensus and agreed as PIMHF		√		√		√					
GheOP3S Version (2), 2021[17, 19]	Belgium	Explicit	65+	Primary Care setting	GheOP3S Version 1 and recent scientific evidence (Beer 2019, STOPP version II and NORGEP-NH)	Two-round modified Delphi process according to the RAND/UCLA appropriateness method with 26 experts (New panel appointed for each round. Round 1: Geriatricians (6); Academics (2); Clinical pharmacists (2); General practitioners (2); Emergency physician (1); Community pharmacists (1); Nurse (1). Round 2: Geriatricians (3); Clinical pharmacists (2); General practitioners (2); Emergency physician (1); Community pharmacist (1); Hospital pharmacist (1); Nurse (1))	64 criteria and can support pharmacists to consolidate their role as medication experts by reducing polypharmacy inappropriateness and/or by optimising patients' medication use in primary care.		√		√	√	√			√	√	
EU(7)PIM criteria—	Portugal	Explicit	Older	Not reported	EU(7)-PIM and Identification of	Not validated	184 potentially inappropriate medicines		√		√		√	√				√

Portugal, 2021[19]					possible PIMs available in the Portuguese market and not included in the EU(7)-PIM list		(from these, 178 are active substances, five are classes of drugs, and one corresponds to the sliding scale therapeutic scheme used in insulin therapy). Of 1089 poly medicated older patients, 83.7% took at least one drug included in the final PIM list or belonging to one of the groups included in the list,								
FORTA List 2021, 2022[55]	Germany, Austria and Switzerland	Explicit	65+	Not specified	Developed based on the existing FORTA version 3, which updated with new evidence and experiences	Delphi technique was conducted online in two rounds. The number of experts involved was 20	Contains 295 items aligned to 30 indications. And the expert propose four new substances/indications suggested by experts	√	√		√			√	
EURO-FORTA, 2023[56]	EU(7)[c]	Explicit	65+	Not specified	Developed based on the existing Euro- FORTA lists, which updated with new evidence and experiences	Delphi technique was conducted online in two rounds. The number of experts involved was 32, with a return rate of 96.9%	Contains 267 items aligned to 27 indications. Three items were added to the EURO-FORTA List, and no drugs were deleted. Eight FORTA items were relabelled from EURO-FORTA version 1.	√	√		√				
Beer, 2023[57]	US	Explicit	65+	all ambulatory, acute, and institutionalized settings of care, except hospice and end-of-life care settings	Beer 2019, and literature search via PubMed from June 1, 2017, to May 31, 2022.	Two rounds of modified Delphi method of expert panel included 12 interprofessional members drawn from medicine, nursing, and pharmacy.	107 medications/class to be avoided, 39 medication/medication classes interacted with 9 disease/ syndromes,18 drug-drug interactions, 18 medication/ medication classes to be used with caution, 24 Medications/medication classes should be avoided or have their dosage reduced with varying Levels of Kidney Function.	√	√		√	√	√	√	√
STOPP-version 3 2023[58]	Ireland (Representing 8	Explicit	Older person	Not reported	Published literature from April 2014 to March 2022	Four rounds of an on-line Delphi validation Panel of 11 academic physicians with	The number of STOPP criteria has increased from 80 to 133 and the number of START criteria	√	√	√	√	√	√	√	√

	European country)					recognized expertise in geriatric pharmacotherapy from 8 European countries participated in a Delphi panel (northern, southern, eastern, and western Europe, i.e., a broad range of European clinical practice and perspective)	has increased from 34 to 57 in version 3 compared to version 2. In total, there are now 190 STOPP/START criteria, representing a 66.7% increase compared to STOPP/START version 2 published in 2015.							
PRISCUS , 2023 [59]	Germany and Austria	Explicit	65+	Not reported	PRISCUS list 2010, and Systematic review for new update and/or revision	Fifty-nine persons took part in a three-round Delphi process, experts from clinical practice and research	187 substances were classed as PIM, 133 of the substances now listed were not in the original PRISCUS lists.	√		√		√		√
Tools used to apply for frail elderly and/LLE/End of life														
Holmes, 2008[14, 19, 33, 37]	USA	Explicit	Elderly with dementia	long-term care facilities	literature review of medication use for palliative care for elderly with dementia ("Reconsidering Medication Appropriateness for Patients Late in Life")	Three-round modified Delphi process with 12 geriatricians. For a medication or medication class was defined according to agreement on Categorization by at least seven of the 12 respondents.	79 medications and medication classes (12 Always appropriate, 30 sometimes appropriate, 14 rarely appropriate, 10 never appropriate and 12 no consensus achieved)	√		√	√			
Patient-centered prescription model in elderly at the end of life, 2015[37]	Spain	Mixed (framework combines both clinical judgment and scientific evidence)	85+ and/cognitive impairment, Individuals with LLE	Acute care elderly unit	Multidisciplinary team made up of geriatricians and a clinical pharmacist develop the model and for appraisal of medication	Not provided (applied to 309 patients admitted in acute care) and detect more in appropriate prescribing	Model for assessing pharmacotherapy, including considerations for discontinuing medications. It is Patient-centered prescription mode involving three step process to develop therapeutic plan (patient centered evaluation, diagnosis centered evaluation, and medication centered assessment)			√		√	√	√

OncPal deprescribing guideline, 2015[19, 38]	Australia	Explicit	palliative cancer patients with an estimated <6-month prognosis	Palliative cancer inpatients	Literature for the de-escalation of medications by systematically reviewing each medication class according to the EphMRA (European Pharmaceutical Market Research Association) anatomical classification list	The guideline was validated by applying it to 61 patients (617 medicines = 10 per patients) and comparing the agreement between the pharmacist applying the guideline and the expert panel decide whether the medications are PIM or not. Finally, agreement happens 94%. Used a single-phase consensus model by sending the draft guideline to three palliative care consultants, three oncology consultants and three senior pharmacists for their feedback.	24 medication/ medication classes	√	√				
NORGEP-NH, 2015[14, 15, 17-19, 33]	Norway	Explicit	70+	Nursing home Residents (frail)	Norwegian General Practice (NORGEP,2009) criteria, literature, and clinical experience	Web based three-round Delphi consensus process (first round (62), second round (52), and third round (49)) with expertise in Geriatrics specialists (15); Clinical pharmacology specialists (5); Pharmacists (5); Nursing home physicians or members of the General Practitioners' Reference Groups for Nursing Home Medicine (24)	34 explicit criteria for PIM (11 single substances criteria/regular use should be avoided, 15 drug–drug combination criteria, 8 criteria where regular consideration of deprescribing)	√	√	√	√	√	
Algorithm of medication review in frail older people, 2016[19]	Australia	Mixed (algorithm +list of criteria)	Older (frail older people)	Residential aged care facilities	Literature review (2012 Beers Criteria, the McLeod criteria, the Laroche list, the PRISCUS list and the Norwegian General Practice criteria)	Not validated	Algorithm comprises several steps leading to individualized prescribing recommendations: (i) identify a high-risk medication; (ii) ascertain the current indications for the medication and assess their validity; (iii) assess if the drug is providing ongoing symptomatic benefit; and (iv) consider withdrawing, altering or continuing medications. Includes PIM lists and Withdrawal regimens for commonly used medications in older people and alternative management strategies for commonly used PIM	√	√	√			√

Futility criteria by Oliveira etal, 2016[38]	Portugal	Explicit	Advanced cancer patients with a life expectancy < 6 month	Oncology setting	fede criteria of unnecessary medication use by advanced cancer patient, 2011[60]	Not validated	Criteria for futility of 7 medication categories, criteria modified from Fede et al [60]. Medication categories included conditions for futility. Medication categories covered gastric protectors, antihypertensive drugs, antidiabetic drugs, statins, anticoagulants, bisphosphonates, and antidementia drugs		√		√
MATCH-D, 2016[17]	Australia	Explicit	65+ (dementia, and comorbidity)	Not reported	Expert opinion	Three round online Delphi methods involving multidisciplinary expert panel consisted of 57 experts with qualifications and experience in relevant fields (Pharmacist n = 33, General practitioner n = 4, Clinical pharmacologist n = 1, Geriatrician n= 9, Physician n = 5, General medicine physician n = 1, Research psychologist n = 1, Registered nurse n = 2,Nurse practitioner n = 1, Patient advocate n=1)	The participants reached consensus on 111 of 128 statements. Of these statements, 67 statements were included in the Medication Appropriateness Tool for Co-morbid Health conditions in Dementia criteria		√		√
LESS-CHRON, 2017[37]	Spain	Explicit	Older persons with multiple comorbiditie s, specifically, frail older persons (criteria are medication specific)	Not reported	literature (Spanish and English, September 2013) and electronic brainstorming	Two online Delphi methods (11 experts included four specialists in hospital pharmacy, three in internal medicine, three general practitioners and one primary care pharmacist)	The final list includes 27 criteria and each of the criteria's contains drug indication for which it is prescribed, clinical situation that offers an opportunity to deprescribe, clinical variable to be monitored and the minimum time to follow up the patient after deprescribing.		√		√
STOPPFrail , 2017[19, 37]	Ireland	Explicit	Frailer older adults with LLE (65+)	all healthcare settings	clinical experience of authors and literature review of the last 20 years	Three Delphi rounds involving 17 expert panels (consultant geriatricians (n = 6), clinical pharmacologists (n = 3), old age	Comprises 27 criteria relating to medications that are potentially inappropriate in frail older patients with LLE	√	√	√	√

						psychiatrists (n = 1), palliative care physicians (n = 3), senior academic primary care physicians (n = 2) and clinical pharmacists with an interest in geriatric pharmacotherapy (n = 2))								
STOPP/ START USA), 2017[14, 18, 19]	USA	Explicit	65+ very frail older adults with less than 1 year to live	Nursing home residents	STOPP/START version 2	E-Delphi panel consisted of three rounds: initial assessment, feedback and discussion, final assessment (17 participated in Round 1, 15 of whom participated in Round 2 and 11 in Round 3). The distribution of experts were 5 pharmacists, 5 nurses, 4 researchers, and 3 physicians	24 criteria (22 PIM, 2 underused medications criteria)	√		√	√	√	√	√	√
Morin European consensus criteria, 2018[19]	10 EU [d]	Explicit	75 years or older (estimated life expectancy of ≤ 3months)	Not specified	Systematic review of the literature updating the findings from Todd et al.	Two round Delphi (40 experts in the first and 39 in the second round), the expert panel included geriatricians (13), palliative care physicians (12), 7 general practitioners, 7 pharmacists or clinical pharmacologists, and 1 palliative care psychiatrist.	Provide a list for **continuation of previously prescribed drug classes** (14 drug classes deemed as **often adequate**, 28 drug classes deemed **questionable**, and 10 drug classes deemed often **inadequate), initiation of new drug treatments (**10 drug classes deemed **often adequate,** 23 drug classes deemed **questionable, and** 23 drug classes deemed often **inadequate)**	√		√	√				
STOPPFrail, 2021[17]	Ireland	Explicit	older adults with limited LLE	All care settings for frail patients with LLE	STOPPFrail version 1, literature and expert opinion	Two round Delphi method (panel comprised eight members with expertise in geriatric medicine (n=3), clinical pharmacology (n=2), psychiatry of older age (n=1), general practice (n=1) and palliative medicine (n=1))	Involves a new method for identifying older people who are likely to be approaching end-of-life is included along with 25 deprescribing criteria that includes general guide, system based drugs and miscellaneous	√		√		√	√		√
Tools developed to use for special target groups														

The List of High-risk Perioperative Medications for Elders in China, 2019[17, 19]	China	Explicit	Older	Perioperative setting	Literature review published before March 2018	Two round Delphi (36 Geriatricians (6); Anaesthesiologists (6); Surgeons (6); Pharmacists (18)	a total of 86 medications of 13 medication classes and 120 screening items were included in the final list, along with perioperative risk profiles and risk aversion recommendations for each drug	√		√		√	√	√	√	√
PIM-Check, 2017[14]	Canada, Belgium, France and Switzerland.	Explicit	Adult	A dults in internal medicine (excluding pregnant women and inpatients with LLE or requiring palliative care)	For each medical domain and subdomains selected during the first step, an extensive literature review of evidence-based optimal and inappropriate medication prescriptions was conducted	Two-round Delphi survey (39 experts participated from 40 invited, both in the first and second round) that involve internist and clinical Pharmacist	160 statements in 17 medical domains and 56 pathologies.	√		√	√	√	√	√	√	√
Explicit /mixed tools developed to apply for uses in children																
POPI 2011[36]	France	mixed	18-	All paediatric practice settings	Internal expert consensus and citing literature for each lists	not validated	9 partial lists (five inappropriate prescription and four omissions of prescription	√		√	√	√	√	√	√	
POPI, 2014[35, 36]	France	Mixed	18-	All paediatrics settings	Literature published after 2000 (including French and international guidelines)	A 2-round-Delphi consensus technique (16 members of experts including pharmacists, 8 paediatricians hospital-based 50% or working in community 50%).	105 (PIM 80, PPO 25)	√		√	√	√	√	√	√	
POPI, 2016	France	Mixed	18-	All paediatrics settings	Literature published after 2000 (including French and international guidelines)	A 2-round-Delphi consensus technique (16 members of experts including pharmacists, 8 paediatricians hospital-based 50% or working in community 50%).	101 criteria were selected (76 inappropriate prescriptions and 25 omissions).	√		√	√	√	√	√	√	
PIPc 2016[35, 36]	Ireland and UK	Explicit	16-	primary care	Literature review, Guidelines produced by different society,	Two-round modified Delphi consensus method (15 experts consisting of GPs, pharmacists and paediatricians from the Republic of Ireland and the UK)	12 (potential prescribing omissions (PPO) 5; PIM 7)	√		√	√			√	√	

					networks and institutions										
Modified POPI (UK) tool, 2017 (short version) [35, 36], Modified POPI (UK) tool, 2019 (full version)	UK	mixed	aged less than or equal to 18 years	all paediatric practice settings	POPI, 2014	Not validated, it is a modification of POPI, 2014	80 (PIM 60, 20 PPO)	√		√	√	√	√	√	√
KIDs List, 2020[35]	USA	Explicit	18-	All care setting	literature review (English language)	Expert consensus panel (7 paediatric pharmacists)through GRADE framework	77 PIM (67 drugs and 10 pharmaceutical excipients)	√		√		√	√		
POPI Int 2020[35]	Multi-national Consensus[e]	Mixed	18-	Primary care	Adapting POPI France (updated POPI, 2016) based on the context of countries	Two-round online Delphi consensus method (20 in the first round (11 pharmacists and 9 physicians) and 14 in the second round)	73 (PIM 58, PPO 15)	√		√	√	√	√	√	√
Implicit tools/tools with scoring system															
MAI,1992[12, 32, 33]	USA	Implicit	Developed among persons in >65, but use not restricted to older adult	Not reported	Literature (Medline and manual search) published 1982–1990 clinical experience of a clinical pharmacist and an internist geriatrician	MAI: convenience sample of 10 academic healthcare professionals judged MAI items to be definitely important or moderately important, providing an independent validation of their suitability	10 criteria (indication, effectiveness, dosage, correct directions, drug–drug interactions, drug–disease interactions, practical directions, costs, duplication, duration) worded as questions to assess the appropriateness of each prescribed drug with instructions for use and operational definitions for each criterion								
Lipton, 1992[12]	USA	Implicit	65+	Outpatient setting	Expert	Not reported	Evaluation of each drug in the patient's regimen in seven categories of potential drug therapy problem. And for each category 0-9 score is given								
Hamdy criteria for medication profile review in extended care, 1995[12]	USA	Implicit	Not specified	Long-term care	literature	Not reported	Aimed to reduce polypharmacy in patients in long-term care. Five open ended questions assess the appropriates of patients medication focusing on patients taking 10 or more medications.								
Robertson's Flow charts 1996[12]	USA	Implicit	Not specified	Hospital settings	Not reported	Not reported	Flow chart encouraging a uniform approach to preventing, identifying, and correcting drug therapy problems								

Cantrill indicators of the appropriateness of long-term prescribing in general practice, 1998[12]	UK	Implicit	not specified	long term care (nursing homes)	expert	Nominal group was used to identify potential indicators of appropriateness of prescribing and two round Delphi exercise used for validation (composed of 100 general practitioners and 100 community pharmacists)	Nine indicators of prescribing appropriateness for assessing the entire drug regimen of patients on long term medications in general practice
Barenholtz Self-administered medication-risk questionnaire in an elderly population, 2003 [12]	USA	Implicit	60-	Not specified	literature	Not reported	10 item questionnaire for use by elderly patients to help in identifying who is at increased risk of medication related problems
Sedative load, 2003[33]	Finland	Implicit(Scoring)	Older	home-dwelling elderly	drugs approved for prescription in Finland in 1998–2001 having sedative effects	Expert panel and the classifications was applied in 1998–99 to a cross-sectional survey of home-dwelling elderly subjects (n¼1197, 43% men) aged 64–97 in Lieto, a semi-rural community in southwestern Finland	List of medicines with a proper or potential sedative effect (Primary sedatives, Drugs with sedation as a prominent side effect or preparations with a sedating component, Drugs with sedation as a potential adverse effect). (Anticholinergic) "
Anticholinergic Risk Scale (ARS), 2008[33]	USA	Implicit (scoring)	65+	Geriatric evaluation and management (GEM) cohort and in a primary care settings	The 500 most prescribed medications within the Veterans Affairs Boston Healthcare System were reviewed independently by 1 geriatrician and by 2 geropharmacists to identify medications with known potential to cause	Medical records of 132 GEM patients were reviewed retrospectively for medications included on the ARS and their resultant possible anticholinergic adverse effects. Prospective 117 patients enrolled , 65 years or older, in primary care clinics; performed medication reconciliation; and asked about anticholinergic adverse effects	Higher ARS scores were associated with increased risk of anticholinergic adverse effects in the GEM (geriatric evaluation and management) cohort.

					anticholinergic adverse effects.		
Comorbidity–polypharmacy score (CPS), 2011[33]	USA	Implicit (Scoring)	45+	trauma setting	A total of 323 patients were examined. Patients were using an average of 4.74 pre-injury medications	Not reported	Comorbidity–polypharmacy score (CPS) was defined as the number of pre-admission medications plus comorbidities.
Implicit tools developed to apply for use in frail elderly/limited life expectancy							
Holmes reconsidering MAI, 2006[37]	USA	Implicit (conceptual model)	65- Individuals with LLE	not specified	not clear (but seems the author them self develops the model)	Not specified (but use three case scenarios to demonstrate how this approach may aid individualized decision making regarding medication discontinuation"	Four components in a model of appropriate prescribing late in life: remaining life expectancy, time until benefit goals of care, and treatment target
Geriatric-palliative algorithm, 2007[37]	Israel	Implicit	Frail older persons (nursing home residents with incurable disease)	Nursing homes and nursing departments .	Not clear (but seems the author them self develops the algorithms)	119 disabled patients in six geriatric nursing departments; the control group included 71 patients of comparable age, gender and co-morbidities in the same wards. After 12 months, they assessed whether any change in medications affected the death rate, referrals to acute care facility, and costs. Application of the geriatric-palliative methodology in the disabled elderly enables simultaneous discontinuation of several medications and yields a number of benefits: reduction in mortality rates and referrals to acute care facilities, lower costs, and improved quality of living.	Algorithm aimed at identifying whether a drug can be deprescribed based on indication, safety, alternative therapies

Footnote

Most of the tools fall in one of the three rating scales included a five-point Likert scale [1-5], a nine-point Likert scale [1-9], and a 1 to 4 rating scale of FORTA-based tools. The decision to include the proposed medications/medication classes in the tools was based on the analysis of the experts'' responses from the Likert scale. These tools used a median or mean score with 95 % CI. The cut-off to classify the drug as PIM slightly varied between tools (e.g. EU (7)-PIM list classifies drugs as PIM (if both the mean value of the score and the upper limit of the 95% CI were lower than 3, whereas updated PIM-Taiwan criteria, 2019 finalized medications/ medication classes list with mean Likert scale scores ⩾3.5). **APIT**: Australian prescribing indicators Tool; **FORTA** Fit fOR The Aged; **POM**, prescribing optimisation method for improving prescribing in elderly, **ACOVE:** Assessing Care of Vulnerable Elders, **PIMHF**: potentially inappropriate medication for heart failure, **PIM**: potentially inappropriate medications, **PPO:** potential prescribing omissions, **PIPc:** Potentially inappropriate prescribing in children , **RAND/UCLA:** University of California at Los Angeles , **DDIs:** Drug-drug interactions **MATCH-D:** Medication Appropriateness Tool for Comorbid Health Conditions in Dementia, **LESS-CHRON**: List of Evidence-Based Deprescribing for Chronic Patients, EU: Europe, **UK:** United Kingdom, **MAI:** medication appropriateness index, **LLE:** Limited life expectancy; [a](Estonia, Finland, France, German, Netherlands, Spain, and sweden); [b] (UK, France, Spain, Italy, Netherlands, Denmark, Czech, Poland, Iceland, Belgium, Switzerland, Austria, Germany), [C](UK/Ireland, France, Poland, Italy, Spain, the Nordic countries and The Netherlands) plus the original FORTA (Germany and Austria),[d](Belgium,France, Germany, Italy, Norway, Portugal, Spain, Sweden, Switzerland, UK), [e](12 countries: England, Belgium, Brazil, Canada, China, Ivory Coast, Ireland, Malaysia, Portugal, Switzerland, Turkey and Vietnam).

Nature of tools: The majority of the tools included in the review were developed in Europe (n = 45/95; 47.37%) and the USA (n = 26/95; 27.37%), while most of the available deprescribing guidelines were developed in Canada (n = 6/9; 66.7%). In terms of the nature of the tools, most were explicit tools (n = 72/95; 75.78%), 11 (11.57%) were implicit tools with scoring systems, and the remaining 12 (12.63%) were mixed tools. Out of the identified tools, we found that only nine (9.5%) explicit tools have been updated at least once [55-59, 61-65]. This includes tools like the Beers criteria, which undergo regular updates, and PRISCUS 2.0 [59], which has been updated once.

Target populations: The target populations for the tools varied in terms of age groups, settings, and applicability for patients with limited life expectancy. The majority of the tools were developed for older adults aged 65 years and older (n = 79/95; 83.16%), recognizing the unique medication management needs of this population. There were also a small number of tools specifically designed for paediatric patients (n = 7/95; 7.37%) [62, 66-72]. Additionally, there were tools intended for other age groups or did not specify a particular age group (n=9/95, 9.47%) [73-81].

The identified tools can also be categorised based on their applicable settings. Firstly, there are tools that can be utilized across all healthcare settings (n = 18/95, 18.94%), [61, 62, 67-70, 82-93] including primary care, long-term care facilities, and secondary care, providing a comprehensive approach to deprescribing. Secondly, some tools are specifically designed for all healthcare settings except hospice and palliative care (n = 5/95, 5.26%), [57, 65, 94-96] making them suitable for primary care and secondary care but not specifically tailored for end-of-life care. Thirdly, there are tools specifically tailored for long-term care facilities or nursing homes (n = 10/95, 10.52%), [76, 78, 97-104] that address the unique medication management needs of older adults residing in these settings. Additionally, there are tools that focus on the community setting (n = 19/95, 20%) [63, 66, 72, 81, 105-117], targeting to aid deprescribing in primary care clinics, ambulatory centres, and outpatient facilities. Lastly, there are tools specifically aimed at secondary care settings (n = 8/95, 8.42%), [73, 74, 77, 79, 80, 118-120] providing guidance for deprescribing in hospital inpatient settings and specialized care delivered by medical specialists. It is worth noting that a subset of tools (n = 35/95, 36.84%) does not specify a particular setting, indicating their potential applicability across various healthcare contexts. [55, 56, 58, 59, 64, 74, 75, 121-148]

Furthermore, a subset of the identified deprescribing tools and guidelines (14 tools and 5 guidelines) has been specifically developed to assess the appropriateness of medication use for older adults with limited life expectancy. These tools cater to the unique needs of older adults facing limited life expectancy, including advanced dementia, [49, 100, 124] advanced cancer, [79, 80] frailty, and/or varying durations of remaining life expectancy. [47, 50, 51, 61, 90, 101-104, 118, 122, 149, 150].

Tools and guidelines development approach

The development process of the tools and guidelines exhibited significant variability in terms of approach, content, and the aspects of medication inappropriateness they addressed, including potentially inappropriate medications (PIM) both independent of and dependent on specific diseases/syndromes, as well as drug-drug interactions **(Table 3)**. The contents of these tools were also influenced by the availability of medications in the countries where they were developed, and in some instances, they were tailored based on the prevalence of certain diseases in the country [58, 61, 62]. Notably, a majority of the guidelines (8 out of 9, which accounts for 88.9%) focused on providing recommendations specifically for certain drug classes. These classes included antihyperglycemic medications[47, 51], proton pump inhibitors (PPI) [52, 149], psychotropic drugs [44, 49, 151], benzodiazepine

receptor agonists (BZRA) [42], statins, and medications for anti-hypertensive therapy and antiplatelet use [149] **(Table 2)**.

The development follows a diverse approach, categorized into six distinct methodologies, reflecting the various techniques used by researchers and healthcare experts.

1. **Systematic (literature) Review based tool development**: The review was utilized in four ways. Firstly, they employed a systematic review to develop tools solely based on existing tools, using them as the primary foundation for creating new tools. Approximately 42.8% (36/84) of explicit/mixed tools were developed based on existing tools. Secondly, they conducted systematic literature reviews to gather insights from existing tools and guidelines, and then enriched these tools with new evidence or knowledge. Thirdly, they engaged in comprehensive literature reviews to establish a solid foundation for tools, refining them with the incorporation of new evidence and clinical experience. Lastly, they conducted systematic literature reviews of original articles to create entirely new tools[15, 47, 49-51, 55-59, 62-70, 72, 80-82, 84, 88, 89, 91, 93-98, 107, 109, 110, 112-114, 118, 121-123, 125, 129, 132, 135, 136, 138, 139, 141, 143, 145-149, 152, 153].

2. **Adaptation from existing tools:** We found 13 tools and guidelines following this approach [79, 83, 87, 99, 101, 102, 105, 108, 126, 130, 140, 144, 154].This approach involves tailoring existing tools to specific contexts and patient groups. For instance, tools were adapted from criteria like Beers criteria [105, 108, 140, 144], STOPP-START [83, 87, 130], and EU (7)-criteria [126, 154], for use in different countries, to suit frail elderly in nursing home settings or study purposes.

3. **Reclassification of Existing Tools:** This approach involves rearranging or redefining criteria in pre-existing tools to address medication appropriateness issues more effectively. For instance, FORTA (Fit fOR The Aged) list was originally proposed as a reclassification of Beers criteria, providing both positive and negative lists based on the indications to better suit the target population. Additionally, FORTA lists assessed for possible reclassification based on updated evidence from the precedent versions, ensuring their relevance and accuracy over time. We found 8 tools that followed this approach [53, 127, 128, 133, 134, 137, 142, 148].

4. **Language Translation of Existing Tools:** Tools mainly utilised the translating approach when prescribing practises that were consistent across linguistic contexts, increasing accessibility and applicability in diverse regions. However, they employed adaptation approaches when substantial differences existed. We identified 2 tools developed by direct translation [85, 119].

5. **Expert-led Tool Development Approaches:** We identified three expert-led tool development approaches. The first approach, "Development of Lists and/or Algorithms Based on Expertise," involves creating tools by leveraging the knowledge and experience of certified healthcare experts. This approach aims to develop comprehensive lists and algorithms tailored to ensure medication appropriateness. The second approach is the expert-led consensus approach, where authors with different expertise collaboratively developed the initial lists and further refined it through a consensus process [124]. Additionally, the "Expert-led Literature Review Approach" centres on experts leading literature reviews to combine evidence and expert knowledge (i.e., an initial draft list created by the authors based on their clinical experience followed by evidence generated from the literature review). This collaborative process leads to the development of

robust tools that draw from both research findings and expert insights. In total, this approach was evident in 5 tools for patients with limited life expectancy and paediatrics, where guidelines and tools were developed through expert-led literature reviews [61, 90, 104, 106, 124].

6. **Concept-to-list Approach:** This approach involves creating tools based on a conceptual model to guide medication appropriateness decisions, ensuring a structured and conceptually sound tool development process. We found one example in tools for patients with limited life expectancy, where a disease-specific explicit tool (advanced dementia) was developed using this approach [100]. The conceptual model considered patient-related factors, such as remaining life expectancy and goals of care, as well as medication-related factors like time until benefit and treatment target.

Tool development for paediatric and older persons with limited life expectancy heavily relies on expert-led methods, integrating clinical insights to address unique needs and complement evidence-driven strategies.

Tools and guidelines Validation approach

The explicit/mixed tools and guidelines included in our review underwent validation using various techniques. Out of the included guidelines, all 9 (100%) and a substantial majority of explicit/mixed tools, 66 out of 84 (78.57%), underwent validation. In total, 75 tools and guidelines were validated. The detailed validation process for each specific guideline and tool is presented in **Table 2** and **Table 3,** respectively.

***Consensus-Based Validation Methods*:** This category encompasses validation techniques that involve reaching a consensus among experts or a guideline development team. It includes the following approaches:

1. (Modified) Delphi technique (n = 58/75, 77.3%): Involved iterative rounds of expert input and feedback to reach a consensus on medication appropriateness criteria; they used two to four rounds for more comprehensive input and convergence of opinions.

2. GRADE Framework with Consensus Approach (n = 5/75, 6.7%): The GRADE framework was integrated with the Delphi technique or expert panel consensus approach to combine evidence-based decision-making and expert consensus. The GRADE approach facilitated a transparent and systematic evaluation of evidence and expert opinion and ensured a rigorous evaluation of evidence and expert input. [57, 69, 91, 94, 95]

3. GRADE framework combined with consensus validation by the guideline development team (n = 8/75, 10.7%): The GRADE framework was utilised along with consensus validation by the guideline development team. This combination allowed for evidence-based guidelines supported by a consensus of experts involved in the development process. [40, 42, 44, 49, 50, 52, 149, 151]

4. Consensus of guideline development team (GDT) without GRADE framework (n= 1): In this approach, the guideline development team reached a consensus without utilising the GRADE framework for evidence evaluation. The team's expertise and consensus were the basis for the validation of the guidelines.[47]

Metric-Based Validation Techniques (n = 3): This category involves validation methods that rely on metrics and measurements to assess the reliability and relevance of tools and guidelines, such as psychometric test (n = 1) [119], Content Validity Index method (n = 1) [83], and testing the tool in the field and comparing with expert panel decisions (n = 1) [80]. The adaptation and translation of tools mainly employed the metrics approach, which focused on ensuring the reliability and relevance of the adapted or translated screening tools for identifying potentially inappropriate prescribing in older individuals.

The consensus-based validation processes of the tools and guidelines showed variations in panel size, rating scales, and consensus thresholds. The panel sizes involved in the validation of tools ranged from 4 [98] to 57 [124] with the variation mainly influenced by whether multicounty or international experts were part of the process. On the other hand, the guideline development team consisted of 9 -12 members, which were responsible for developing the deprescribing guidelines.

In terms of rating scales, the review highlights the incorporation of different Likert rating scales such as [1–5], [1–9], and [1–10]. These diverse scales were utilised to assess the appropriateness of proposed medications or medication classes. Furthermore, the predefined percentage of agreement used to decide which medications or medication classes should be included in the tools or guidelines is varied. For tools, a minimum agreement threshold of 60% was identified [100], meaning that at least 60% of the experts needed to agree on the appropriateness of a medication or class for it to be included based on the median or mean scores. On the other hand, for guidelines, a minimum agreement threshold of 80% was set, requiring a substantial level of consensus among experts for a medication or class to be recommended in the guidelines.

Medication lists developed by target populations

Applying the genealogy of tools **(Figure 3)** and conducting eligibility assessment stage 3, we extracted medication data from 57.4% (35/66) of validated explicit or mixed tools and all guidelines. Specifically, we selected 22 tools for adults aged 65 years and older with normal life expectancy [55-59, 63-65, 82, 87, 88, 92, 110, 112, 113, 125, 127, 128, 130, 132, 146, 147], 2 tools for very specific target groups (e.g., perioperative patients) [73, 120], 4 paediatric tools for patients under 18 years of age [62, 66, 69, 72], and 7 tools tailored to patients with limited life expectancy [61, 80, 100-102, 122, 123] **(Figure 2)**.

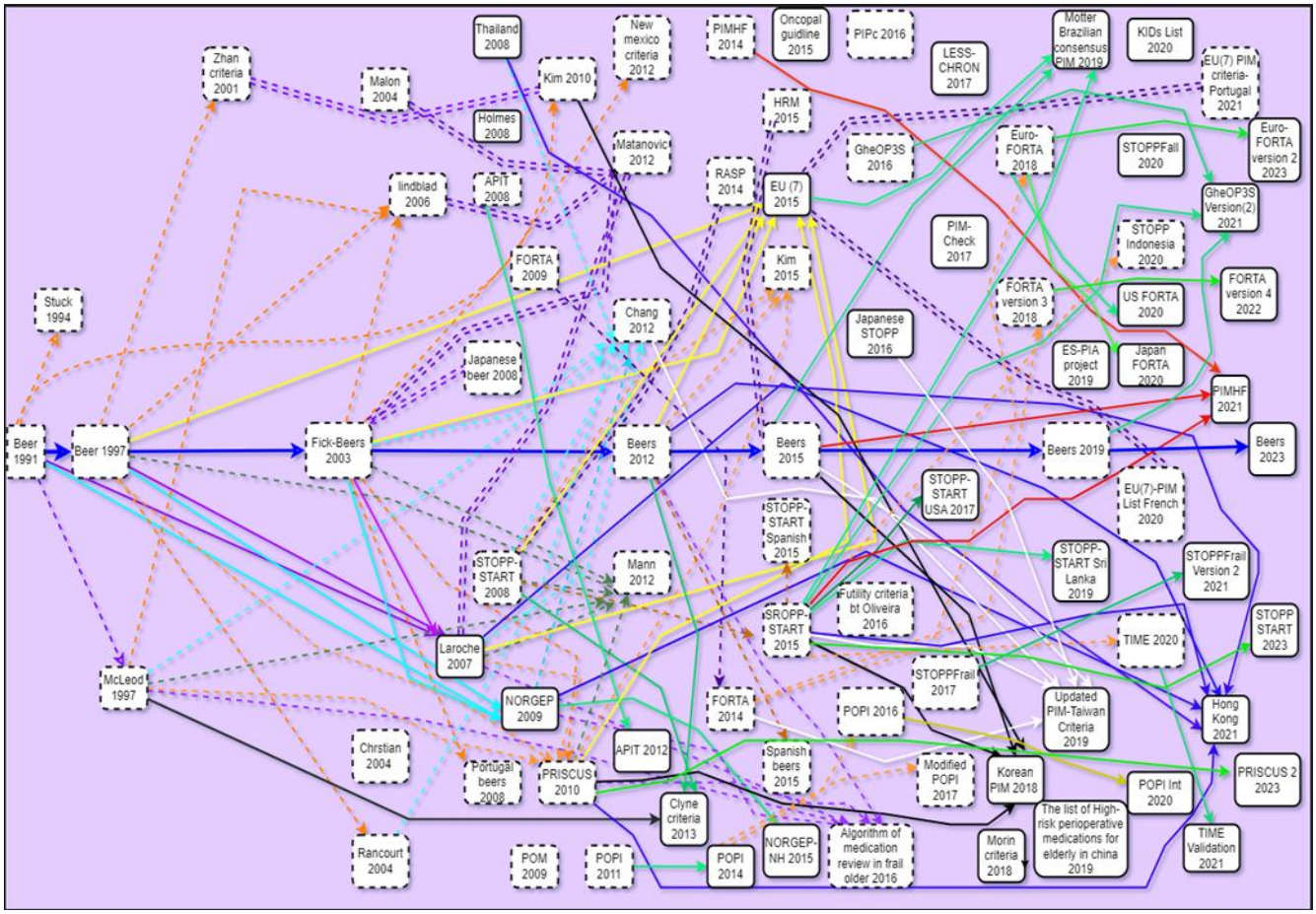


Figure 3: Genealogy-based selection of Tools and Guidelines for Medication Extractions. The identical version of the figure is available in the electronic supplement accompanying the manuscript. This version allows the option to enlarge the figure, enhancing its clarity and visibility (**Supplementary file 2.2**).

Key: Lines

- ✓ **Solid lines**- arrow directed to selected tool included for medication extractions
- ✓ **Dote lines**- arrow directed to tools not included for medication extraction because no additional medications are provided
- ✓ **Double dote line**- arrow directed to tools having additional medication listed but due to different reasons not selected for medication extraction (e.g. not validated)
- ✓ **Centre blue line**- link the Beers criteria

Rectangle

- ✓ Dote line of the rectangle tools not included in medication extraction
- ✓ Solid line rectangle tools included for medication extraction

The list of PIMs for older persons aged 65 years and older with normal life expectancy and list of medications for frail older persons with limited life expectancy is provided in **Table 4 and 5,** respectively. However, to provide a more comprehensive resource for interested researchers and clinicians, we have thoughtfully developed supplementary files **(Supplementary file 2.5)**.These supplementary files contain a comprehensive list of medications for each target populations organized according to different aspects of appropriateness, ensuring that readers have access to detailed information for further exploration. Furthermore, the supplementary files include a separate methodology outlining how we developed the medication lists **(Supplementary file 2.2)**, offering valuable insights into the process. In the following section, we provide a comprehensive overview of the identified medications for each target population, highlighting key findings and essential details.

For older persons aged 65 years and older with normal life expectancy, our analysis revealed 484 PIMs (437 medications and 47 medication classes) independent of diseases or conditions **(Table 4)**, along with PIM lists for 54 diseases or conditions, 117 inappropriate omissions of medications,128 drug-drug interactions, and 14 fall risking medication classes. Moreover, 96 medications/medication classes were classified as having questionable benefits due to a lack of consensus among experts.

However, in our analysis, we found variations in the assignments of medications as PIM, questionable benefit, or not PIM across different tools. These variations were evident in the following ways:

1. PIM in one tool is not PIM in another tool; for instance, Rivaroxaban is considered a PIM in Beers 2023[57] but not classified as PIM in PRISCUS 2023[59].
2. Some medications listed as PIM in one tool were considered as having questionable benefits (no consensus) in another tool. For example, Phenylbutazone was reported as PIM by EU(7)-PIM list[125] and PRISCUS 2023[59], but in Motter Brazilian consensus PIM 2019 [129], consensus was not reached.
3. In some cases, a drug classified as PIM in one tool was listed as an alternative medication in another tool. For instance, Trazodone was categorized as PIM by the Spanish tool (ES-PIA) [132], whereas on the EU(7)-PIM list[125], it was considered as an alternative treatment for Dosulepin (classified as PIM by the EU(7)-PIM).
4. Daily Dosage Inconsistencies: The assignment of medications as PIM was influenced by inconsistencies in the daily dosage criteria across different tools. For instance, Lorazepam was classified as PIM by Beers 2023[57] regardless of the dosage, whereas other tools specified specific dosages to consider it as PIM, but the dosages were not standardized [112, 125, 147].

Table 4: Potentially inappropriate medication for older persons aged 65 years and older with normal life expectancy

Organ system	ATC code[A]	Quality of evidence[B]	Strength of recommendation[C]	Organ system	ATC code[A]	Quality of evidence[B]	Strength of recommendation[C]
Alimentary tract and metabolism				**Antigout preparations**			
Drugs for acid- related disorders				Allopurinol for asymptomatic hyperuricemia (those without gout or nephrolithiasis)[87]	M04AA01		
Antacids				Colchicine[125]	M04AC01		
Magnesium hydroxide/ Antacids containing magnesium (> 4 weeks)[59, 125]	A02AA, A02AA04			**Drugs affecting bone structure and mineralization**			
Aluminium-containing antacids[59, 125]	A02AB, A02AD			Bisphosphonates for > 5 years[63]	M05BA		
Drugs for peptic ulcer and gastro-oesophageal reflux disease (GORD)				Zoledronate[87]	M05BA08		
H2-receptor antagonists[45, 64, 125]	A02BA	Moderate	Strong	Strontium ranelate[125]	M05BX03		
Cimetidine[59, 64, 65, 125, 147]	A02BA01			Denosumab[87]	M05BX04		
Ranitidine[64, 125]	A02BA02			**Other drugs for disorders of the musculo-skeletal system**			
Famotidine[59, 64, 125]	A02BA03			Quinine and derivatives [59, 125]	M09AA		
Nizatidine[64]	A02BA04			**Nervous system**			
Proton-pump inhibitors (> 8 weeks)[57-59, 63, 87, 112, 125, 130]	A02BC	**High:** C. difficile, bone loss, and fractures **Moderate:** Pneumonia and GI malignancies	Strong	**Anesthetics**			
Omeprazole[57, 59]	A02BC01	High/moderate	Strong	Propofol[132]	N01AX10		
Pantoprazole[57, 59]	A02BC02	High/moderate	Strong	Benzocaine[132]	N01BA05		
Lansoprazole[57, 59]	A02BC03	High/moderate	Strong	Topical lidocaine (lignocaine) patch for treatment of chronic osteoarthritis pain[58]	N01BB02		
Rabeprazole[57, 59]	A02BC04	High/moderate	Strong	**Analgesics**			
Esomeprazole[57, 59]	A02BC05	High/moderate	Strong	Opioids[63, 65]			
Dexlansoprazole[57, 59]	A02BC06	High/moderate	Strong	Pethidine (Meperidine) [57, 59, 63, 65, 87, 125, 129, 132, 146]	N02AB02	Moderate	Strong
Drugs for functional bowel disorder				Pentazocine[63, 65, 125]	N02AD01		
Mebeverine[59, 125]	A03AA04			Tramadol (sustained- / non-sustained-release)[59, 125, 129]	N02AX02		
Trimebutine[125]	A03AA05			Tapentadol[59]	N02AX06		
Dicyclomine[57]	A03AA07	Moderate	Strong	Morphine [132]	N02AA01		
Dihexyverine[125]	A03AA08			Dihydrocodeine[59]	N02AA08		
Propantheline[88]	A03AB05			Codeine[59]	R05DA04		
Otilonium bromide[125]	A03AB06			Polyethylene glycol electrolyte powder[88]	N02AA59		
Tiemonium[125]	A03AB17			Dextropropoxyphene[110]	N02AC04		
Pinaveriumc[125]	A03AX04			Oral or transdermal strong opioids as first line therapy for mild pain [58, 130]			
Atropine (excludes ophthalmic)[57, 88]	A03BA01	Moderate	Strong	**Other analgesics and antipyretics**			
Hyoscyamine[57, 87, 125]	A03BA03	Moderate	Strong	Acetylsalicylic acid (>325 mg) [57, 59, 63, 65, 112, 125, 129, 132]	N02BA01	Moderate	Strong
Belladonna alkaloids[125, 146, 147]	A03BA04			Diflunisal[57]	N02BA11	Moderate	Strong

Homatropine(excludes ophthalmic) [57]	A03BB06	Moderate	Strong	Phenazone[59]	N02BB01		
Clidinium-chlordiazepoxide[57, 64, 65, 125, 147]	A03CA02	Moderate	Strong	Propyphenazone[59]	N02BB04		
Pitofenone[125]	A03DA02			Long-term opioids for osteoarthritis[58]			
Metoclopramide[45, 57, 59, 63, 65, 87, 88, 125, 146]	A03FA01	Moderate	Strong	Gabapentinoids for non-neuropathic pain[58]	N02BF		
Domperidone (>30 mg/d)[59, 125]	A03FA03			Gabapentin[58]	N02BF01		
Alizapride	A03FA05			Gregabalin[58]	N02BF02		
Antiemetics and antinauseants				**Antimigraine preparations**			
Scopolamine[125]	A04AD01			Ergotamine[59, 125]	N02CA02		
Metopimazine[125, 147]	A04AD05			Triptanes [125]	N02CC		
Drugs for constipation				Sumatriptan[125]	N02CC01		
Viscous paraffin (Liquid paraffin) Mineral oil, given orally[57, 59, 63, 125]	A06AA01	Moderate	Strong	Naratriptan[125]	N02CC02		
Docusate sodium[125, 147]	A06AA02			Zolmitriptan[125]	N02CC03		
Contact/stimulant laxatives[63, 147]	A06AB			Eletriptan[125]	N02CC06		
Bisacodyl (>3 days)[63, 125]	A06AB02			**Antiepileptics**			
Castor oil (=Ricinus communis, =Neoloid)[125, 147]	A06AB05			Phenobarbital[57, 59, 87, 125, 146]	N03AA02	High	Strong
Senna glycosides (sennoside > 1 week)[59, 63, 125]	A06AB06			Primidone[57, 59]	N03AA03	High	Strong
Cascara sagrada[125, 147]	A06AB07			Phenytoin [59, 87, 125]	N03AB02		
Sodium picosulfate > 1 week[59, 63, 125]	A06AB08			Clonazepam[57, 64, 65, 125]	N03AE01	Moderate	Strong
Aloe[125, 147]	A06AB13			Carbamazepine[59, 87, 125, 132]	N03AF01		
Prucalopride[125]	A06AX05			oxcarbazepine[132]	N03AF02		
Osmotically acting laxatives				Topiramate[125]	N03AX11		
Magnesium oxide[45]	A06AD02	low	strong	Gabapentin[132]	N03AX12		
Enema				Valproate[87]	N03AG01		
Sodium phosphate enema[88]	A06AG01			**Anti-parkinson drugs**			
Antidiarrheal, intestinal anti-inflammatory/anti-infective agents				Anticholinergic agents to treat extra-pyramidal side-effects of neuroleptic medications			
Diphenoxylate-Atropine[125]	A07DA01			Trihexyphenidyl[45, 57-59, 64, 65, 125]	N04AA01	Moderate	Strong
Loperamide (>3 day, > 12 mg/d) [59, 125]	A07DA03			Biperiden[45, 58, 59, 64, 125]	N04AA02	Moderate	Strong
Racecadotril [125]	A07XA04			Procyclidine[58, 59]	N04AA04		
Drugs used in diabetes				Bornaprine[59]	N04AA11		
Insulins and analogues				Tropatepin[125]	N04AA12		
Insulin, sliding scale (insulin regimens containing only short- or rapid-acting insulin dosed according to current blood glucose levels without concurrent use of basal or long-acting insulin)[45, 57, 65, 125]		Moderate	strong	Orphenadrine[58]	N04AB02		
Blood glucose lowering drugs, excl. insulins				Benztropine (oral)[57, 65, 125]	N04AC01	Moderate	Strong
Biguanides				Dopaminergic agents	N04B		
Buformin[45]	A10BA03	low	weak	Amantadine[59, 125]	N04BB01		
metformin[45]	A10BA02	low	weak	Bromocriptine[125]	N04BC01		
Sulfonylureas, long acting (Type II DM)[45, 57, 58, 63, 64, 87, 88, 112, 130, 147]	A10BB	**High:**Hypoglycemia **Moderate:** CV events and all-cause mortality **Low:** CV death and ischemic stroke	Strong	Pergolide[59, 125]	N04BC02		
Glyburide (glibenclamide)[45, 57-59, 64, 65, 112, 125]	A10BB01	High/moderate/low	Strong	Dihydroergocryptine [59, 125]	N04BC03		
Chlorpropamide[45, 58, 64, 112, 125, 146]	A10BB02			Ropinirole[125]	N04BC04		
Carbutamide[125, 147]	A10BB06			Pramipexole[59, 125]	N04BC05		

Glipizide[57, 88, 125, 147]	A10BB07	High/moderate/low	Strong	Cabergoline[125]	N04BC06		
				Piribedil[59, 125]	N04BC08		
Gliquidone[59]	A10BB08			Rotigotine[125]	N04BC09		
Gliclazide[57, 59]	A10BB09	High/moderate/low	Strong	Selegiline[59, 125]	N04BD01		
Glimepiride [57-59, 125]	A10BB12	High/moderate/low	Strong	Tolcapone[59, 125]	N04BX01		
Thiazolidinediones	A10BG			Levodopa or dopamine agonists for **benign essential tremor** or for treatment of extrapyramidal side-effects of antipsychotics or other forms of drug-induced Parkinsonism[58, 87, 130]	N04BA01/ N04BC		
Pioglitazone[45, 59, 64, 125]	A10BG03	High	strong	**Psycholeptics**			
α-glucosidase inhibitors[45]	A10BF	Moderate	Weak	Antipsychotics[57, 63-65, 88, 110, 125, 132, 146, 147]		Moderate	Strong
Acarbose[45, 59, 125]	A10BF01	Moderate	Weak	Chlorpromazine[57, 65, 88, 110, 125, 146, 147]	N05AA01	Moderate	Strong
miglitol[45]	A10BF02	Moderate	Weak	Levomepromazine[59, 64, 110, 125, 147]	N05AA02		
voglibose[45]	A10BF03	Moderate	Weak	cyamemazine[125, 147]	N05AA06		
Dipeptidyl peptidase 4 (DPP-4) inhibitors	A10BH			Fluphenazine[57, 59, 64, 125, 132, 147]	N05AB02	Moderate	Strong
Sitagliptine[125]	A10BH01			Perphenazine [57, 59, 64, 125, 147]	N05AB03	Moderate	Strong
Vildagliptine[125]	A10BH02			Prochlorperazine [45, 88, 110, 125]	N05AB04	Moderate	Strong
Sodium-glucose co-transporter 2 (SGLT2) inhibitors (All)[45]	A10BK	Low	Strong	Trifluoperazine[64, 88, 125]	N05AB06		
Blood and blood forming organs				perazine[59]	N05AB10		
Antithrombotic agents				Propericiazine/ Periciazine/ pericyazine[125, 147]	N05AC01		
Vitamin Kantagonists as first-line anticoagulant for atrial fibrillation[58]	B01AA			Thioridazine[59, 64, 125]	N05AC02		
Warfarin[57, 146]	B01AA03	High	Strong	pipotiazine[125, 147]	N05AC04		
Acenocoumarol[125]	B01AA07			Haloperidol (>2 mg single dose; >5mg/d)[57, 59, 64, 65, 88]	N05AD01	Moderate	Strong
Heparins and derivatives[132]	B01AB			Melperone > 100 mg/d, > 6 weeks[59]	N05AD03		
Platelet aggregation inhibitors excl. heparin[132]	B01AC			Pipamperone > 120 mg/d, > 6 weeks[59]	N05AD05		
Ticlopidine[58, 59, 65, 87, 125, 146, 147]	B01AC05			bromperidol[59]	N05AD06		
Aspirin (long-term use at doses > 100mg/day)[58, 87, 130]	B01AC06			Benperidol[59]	N05AD07		
Dipyridamole[63, 87, 125, 147]	B01AC07	Moderate	Strong	Droperidol[125]	N05AD08		
Prasugrel [59, 125]	B01AC22			Sertindole[59, 125]	N05AE03		
Cilostazol [59]	B01AC23			Ziprasidone[57, 59, 64, 88, 125]	N05AE04	Moderate	Strong
Enzymes				Lurasidone[57, 64]	N05AE05	Moderate	Strong
Alteplase[132]	B01AD02			Flupentixole[59, 64, 125]	N05AF01		
Direct thrombin inhibitors				Chlorprothixene[59, 64, 110, 125]	N05AF03		
Dabigatran[58, 125]	B01AE07			Zuclopenthixol[59, 125]	N05AF05		
Direct factor Xa inhibitors				fluspirilene[59]	N05AG01		
Rivaroxaban[57, 125]	B01AF01	Moderate	Strong	Pimozide[59, 64, 88, 125, 132]	N05AG02		
Apixaban[58, 125]	B01AF02			Loxapine[64]	N05AH01		
Antianemic preparations				Clozapine[57, 59, 64, 65, 88, 125, 146]	N05AH02	Moderate	Strong
Iron preparation (elemental iron doses >200 mg daily)[58, 63, 130]	B03A			Olanzapine (>10 mg/d)[57, 59, 64, 65, 88, 125, 146]	N05AH03	Moderate	Strong
Ferrous Fumarate [58, 63, 130]	B03AA02			Quetiapine (> 100 mg/d, > 6 weeks)[57, 59, 65, 88]	N05AH04	Moderate	Strong
Ferrous Gluconate[58, 63, 130]	B03AA03			Sulpiride[45, 59, 64]	N05AL01	low	Strong
Ferrous Sulphate[58, 63, 125, 130]	B03AA07			tiapride[59]	N05AL03		
Cardiovascular system				Amisulpride[59, 64]	N05AL05		
Cardiac therapy				lithium[125, 132]	N05AN01		
Cardiac glycosides				prothipendyl[59]	N05AX07		
Acetyldigoxin[59, 125]	C01AA02			Risperidone > 6 weeks[57, 59]	N05AX08	Moderate	Strong
Digitoxin[125]	C01AA04			Zotepine[64]	N05AX11		
Digoxin [45, 59, 63-65, 87, 88, 112, 125, 130, 132, 146, 147]	C01AA05	**Low:** atrial fibrillation,	Strong	Aripiprazole[57, 59, 64, 88, 125]	N05AX12	Moderate	Strong

• First-line treatment of atrial fibrillation or heart failure[57] • Long-term (> 3months) use as a ventricular rate control[58]		heart failure **Moderate:** dosage>0.125 mg/day					
Metildigoxin[125]	C01AA08			Paliperidone[57, 59, 64, 88]	N05AX13	Moderate	Strong
Antiarrhythmics, Class I and III				cariprazine[57, 59]	N05AX15	Moderate	Strong
Antiarrhythmics, class Ia				brexpiprazole[57]	N05AX16	Moderate	Strong
Quinidine[125]	C01BA01			pimavanserin[57]	N05AX17	Moderate	Strong
Procainamide[125]	C01BA02			**Benzodiazepines**[45, 57-59, 63, 65, 82, 87, 112, 130, 132, 146]	N05BA/ N05CD	Moderate[57] High[45]	Strong
Disopyramide[88, 125, 132, 147]	C01BA03			**Short and intermediate acting:**			
Quinidine in combinaton with verapamil [125]	C01BA51			Oxazepam[57, 59, 64, 112, 125, 147]	N05BA04	Moderate	Strong
Antiarrhythmics, class Ib				Lorazepam[57, 59, 64, 65, 88, 112, 125, 146, 147]	N05BA06	Moderate	Strong
lidocaine [59]	C01BB01			Alprazolam[57, 59, 64, 65, 88, 112, 125, 146, 147]	N05BA12	Moderate	Strong
Antiarrhythmics, class Ic				Clotiazepam>5 mg/d[125, 147]	N05BA21		
Propafenone[59, 125]	C01BC03			Estazolam[57, 64, 125]	N05CD04	Moderate	Strong
Flecainide[59, 65, 125]	C01BC04			Triazolam[45, 57, 59, 64, 65, 88, 112, 125, 146, 147]	N05CD05	Moderate	Strong
Antiarrhythmics, class III				Lormetazepam [59, 125, 147]	N05CD06		
Amiodarone[57, 64, 65, 88, 125]	C01BD01	High	Strong	Temazepam[57, 59, 65, 112, 125, 147]	N05CD07	Moderate	Strong
Dronedarone[57, 59, 65, 125]	C01BD07	High	Strong	Midazolam[57, 64, 88, 125]	N05CD08	Moderate	Strong
Other cardiac preparations				Brotizolam [59, 64, 125]	N05CD09		
Trimetazidine [87, 125]	C01EB15			loprazolam >0.5 mg[125, 147]	N05CD11		
Ivabradine[125]	C01EB17			**Long acting:**			
Antihypertensive				Diazepam[45, 57, 59, 64, 65, 88, 110, 112, 125, 146, 147]	N05BA01	Moderate[57] High[45]	Strong
Antiadrenergic agents, centrally acting/Central alpha-agonists[57, 58, 63, 87, 88, 130]	C02A	Low	Strong	Chlordiazepoxide[57, 59, 65, 88, 112, 125, 146, 147]	N05BA02	Moderate	Strong
Reserpine [63, 87, 125, 130, 147]	C02AA02			Chlordiazepoxide combined with amitriptyline[57]	N05BA02	Moderate	Strong
Methyldopa[58, 59, 63, 87, 88, 125, 130, 146]	C02AB01			Chlordiazepoxide combined with clidinium[57]	N05BA02	Moderate	Strong
Clonidine [57-59, 63, 64, 88, 125, 130, 146, 147]	C02AC01	Low	Strong	Medazepam[59, 64, 125]	N05BA03		
Guanfacine[57, 58, 63, 125, 130, 147]	C02AC02	Low	Strong	Clorazepate (Dipotassium clorazepate)[57, 59, 112, 125, 147]	N05BA05	Moderate	Strong
Moxonidine[58, 59, 125, 147]	C02AC05			lorazepate-acepromazine[125, 147]	N05BA05		
Rilmenidine[58, 87, 125, 147]	C02AC06			Aceprometazine[125, 147]			
Guanabenz[63, 130]		Low	Strong	Bromazepam[64, 65, 88, 125, 147]	N05BA08		
Antiadrenergic agents, peripherally acting[45, 57, 64, 65, 88, 146]	C02C	Moderate	Strong	Clobazam[57, 64, 65, 88, 125, 147]	N05BA09	Moderate	Strong
Prazosin[57, 64, 65, 88, 125, 146]	C02CA01	Moderate	Strong	Prazepam[64, 125, 147]	N05BA11		
Terazosin as antihypertensive [57, 59, 64, 65, 88, 125]	G04CA03	Moderate	Strong	Halazepam[125]	N05BA13		
Doxazosin[57, 59, 64, 65, 88, 125, 146]	C02CA04	Moderate	Strong	Nordazepam[64, 125, 147]	N05BA16		
Urapidil[45, 125]	C02CA06	Moderate	Strong	Fludiazepam[64]	N05BA17		
Guanethidine[125]	C02CC02			(Ethyl-) loflazepate[125, 147]	N05BA18		
Agents acting on Arteriolar Smooth muscle				Etizolam[45, 147]	N05BA19	High	Strong
Dihydralazine[59]	C02DB01			Flurazepam[45, 57, 64, 65, 112, 125, 146]	N05CD01	High	Strong
Hydralazine[59, 125]	C02DB02			Nitrazepam[64, 88, 110, 125, 147]	N05CD02		
Minoxidil [59]	C02DC01			Flunitrazepam [64, 65, 88, 110, 125, 147]	N05CD03		
Diuretics				Quazepam[125]	N05CD10		
Loop diuretics [45]		Moderate	Strong	loprazolam[125, 132]	N05CD11		
Loop diuretic as: • First-line treatment for hypertension[58, 130]	C03C			Oxazolam[64, 110]			

• For dependent ankle oedema[58, 87, 130]							
Potassium-sparing agent[64]	C03D	Moderate	Strong	**Nonbenzodiazepine, benzodiazepine receptor agonist hypnotics (ie, "Z-drugs")**[45, 57, 58, 63, 64, 87, 88, 130]	N05CF	Moderate	Strong
Spironolactone (>25 mg/d)[64]	C03DA01	Moderate	Strong	Zopiclone[45, 59, 64, 87, 88, 110, 125, 147]	N05CF01	Moderate	Strong
Eplerenone[45]	C03DA04	Moderate	Strong	Zolpidem[45, 57, 59, 64, 65, 87, 88, 125, 147]	N05CF02	Moderate	Strong
Peripheral vasodilators				Zaleplon[57, 64, 87, 125]	N05CF03	Moderate	Strong
Pentoxifylline [59, 125, 147]	C04AD03			Eszopiclone[45, 57, 64]	N05CF04	Moderate	Strong
Ergoloid mesylates[57, 125, 146, 147]	C04AE01	High	Strong	Hydroxyzine[57, 59, 64, 65, 88, 110, 132, 147]	N05BB01	Moderate	Strong
Nicergoline [59, 125, 147]	C04AE02			**carbamate**[87]	N05BC		
Dihydroergocristine [125, 147]	C04AE04			Meprobamate[57, 125]	N05BC01	Moderate	Strong
Raubasine-Dihydroergocristine[125, 147]	C04AE54			**Barbiturates**[63]	N05CA		
Cyclandelate(Cyclospasmol)[125]	C04AX01			Butalbital[57]	N05CB01	High	Strong
Vincamine[125, 147]	C04AX07			chloral hydrate[59, 125]	N05CC01		
Moxisylyte[125, 147]	C04AX10			**Other hypnotics and sedatives**			
Vinburnine[125, 147]	C04AX17			clomethiazole[59, 125]	N05CM02		
Buflomedil[125]	C04AX20			Propiomazine[125]	N05CM06		
Naftidrofuryl[59, 125, 147]	C04AX21			**Psychoanaleptics**			
Vasoprotectives				**Antidepressants, alone or in combination**[57, 63, 65, 146, 147]	N06A		
Hidrosmin[125]	C05CA05			Non-selective monoamine reuptake inhibitors (TCA)[45, 57-59, 87, 146]	N06AA	High	strong
Escin (=Aescin)[125]	C05CA07			Desipramine [57, 125]	N06AA01	High	strong
Vincamine-Rutoside [125, 147]	C05CA51			Imipramine[45, 57, 59, 64, 88, 125, 132, 146, 147]	N06AA02	High	strong
Troxerutin-Vincamine [125, 147]	C05CA54			Clomipramine[45, 57, 59, 64, 88, 110, 125, 132, 147]	N06AA04	High	strong
Beta-blocking agents				Opipramol[59]	N06AA05		
Oxprenolol [125]	C07AA02			Trimipramine[59, 88, 110, 125, 147]	N06AA06		
Pindolol[59, 125]	C07AA03			Amitriptyline[57, 59, 64, 88, 110, 125]	N06AA09	High	strong
Propranolol[59, 125]	C07AA05			Nortriptyline[57, 59, 88, 125]	N06AA10	High	strong
Sotalol[59, 110, 125, 132]	C07AA07			Doxepin (>6 mg/day)[57, 59, 64, 88, 110, 125, 146, 147]	N06AA12	High	strong
Nadolol [125]	C07AA12			dosulepin[125, 147]	N06AA16		
Labetalol[125]	C07AG01			Amoxapine[57, 125]	N06AA17	High	strong
Calcium channel blockers Selective calcium channel blockers with mainly vascular effects[57, 64, 65, 88, 125, 146]	C08C	Moderate	Strong	Maprotiline[59, 64, 125, 147]	N06AA21		
Nicardipine[125, 147]	C08CA04			**Selective serotonin reuptake inhibitors**[57, 87]	**N06AB**	High	strong
Nifedipine [88, 146] • non-sustained/immediate release [57, 59, 125, 147] sustained/Extended-release [125]	C08CA05	Moderate	Strong	fluoxetine[59, 87, 125]	N06AB03		
• Nimodipine[59]	C08CA06			escitalopram >10 mg / day [87]	N06AB04		
Selective calcium channel blockers with direct cardiac effects				Paroxetine[57, 59, 64, 87, 125]	N06AB05	High	strong
Verapamil[125, 146]	C08DA01			Sertraline > 100 mg/d[59]	N06AB06		
Diltiazem[125]	C08DB01			fluvoxamine[59, 87, 125]	N06AB08		
Agents acting on the renin-angiotensin system				Citalopram >20 mg / day[87]	N06AB10		
aliskiren [59]	C09XA02			**Monoamine oxidase inhibitors**			
Lipid modifying agents				tranylcypromine[59, 125]	N06AF04		
Niacin (=Nicotinic acid) [125]	C10AD02			moclobemide[59]	N06AG02		
Genito-urinary system and sex hormones				St John's wort[59]			
Sex hormones and modulators of the genital system				**Other antidepressant**			
Androgens [57, 64, 88, 130]	G03B	Moderate	Weak	Mianserin [59]	N06AX03		
Methyltestosterone[57, 64, 130]	G03BA02	Moderate	Weak	Trazodone[132]	N06AX05		

Testosterone[57, 59, 64, 88, 130, 146]	G03BA03	Moderate	Weak	Mirtazapine[132]	N06AX11		
Estrogens (including combination)[57, 59, 64, 65, 146]	G03C	**High:** Oral and patch **Moderate:** vaginal cream or vaginal tablet	**Strong:** Oral and patch strong **Weak:** Topical vaginal cream or tablets	Bupropion[59, 125]	N06AX12		
Estradiol [64, 88]	G03CA03			Tianeptine[59]	N06AX14		
Estriol[64]	G03CA04			Venlafaxine[125]	N06AX16		
Tibolone [64, 88]	G03CX01			Reboxetine[125]	N06AX18		
Estrone[64]	G03CA07			Agomelatine[59]	N06AX22		
Estradiol, combinations[64]	G03CA53			**Psychostimulants, agents used for ADHD and nootropics**			
Conjugated estrogens[64]	G03CA57			Methylphenidate[59, 125, 132]	N06BA04		
Progesterone and estrogen[64]	G03FA04			Pyritinol [59]	N06BX02		
Norethisterone and estrogen[64]	G03FA01			Piracetam[59, 87, 125, 147]	N06BX03		
Hydroxyprogesterone and estrogen[64]	G03FA02			**Antidepressants in combination with psycholeptics**			
Norgestrel and estrogen[64]	G03FA10			Melitracen and psycholeptics[64]	N06CA02		
Medroxyprogesterone and estrogen[64]	G03FA12			**Anti-dementia drugs**			
Urologicals				Ginkgo biloba/Ginkgo folium[59, 125, 147]	N06DX02		
Drugs for urinary frequency and incontinence[45]	G04BD	High	Strong	**Parasympathomimetics**			
Flavoxate[59]	G04BD02			Bethanechol[125]	N07AB02		
Transdermal Oxybutynin[45]	G04BD04	High	Strong	**Drugs Used In Addictive Disorders**			
Oxybutynin[45, 57, 59, 64, 65, 125, 146, 147]	G04BD04	High	Strong	Methadone[59, 125]	N07BC02		
Propiverine Hydrochloride[45, 59]	G04BD06	High	Strong	levomethadone[59]	N07BC05		
Tolterodine[45, 59, 64, 125, 147]	G04BD07	High	Strong	**Antivertigo**			
Solifenacin[45, 59, 125, 147]	G04BD08	High	Strong	Betahistine[59, 87]	N07CA01		
Trospium[59, 125]	G04BD09			Cinnarizine[59, 146]	N07CA02		
Darifenacin[59, 125]	G04BD10			Flunarizine[59, 146]	N07CA03		
Fesoterodine[45, 59, 125]	G04BD11	High	Strong	**Respiratory system**			
Desfesoterodine[59]	G04BD13			Intranasal decongestants > 10 days (Decongestants and other nasal preparations for topical use)[63]	R01A		
Imidafenacin[45]	G04BD14	High	Strong	Nasal decongestants for systemic use (Sympathomimetics) [63, 125, 132]			
Mirabegron[59]	G04BD12			Norephedrine (Phenylpropanolamine)[125]	R01BA01		
Duloxetine with urinary urgency or urge incontinence [58]	N06AX21			Pseudoephedrine[125]	R01BA02		
Systemic hormonal preparations, excl. sex hormones and insulins				Phenylephrine[63, 132]	R01BA03		
Growth hormone[57, 65]	H01AC01	High	Strong	**Drugs for obstructive airway diseases**	R03		
Vasopressin[58]	H01BA01			Systemic corticosteroids instead of inhaled corticosteroids for maintenance therapy in moderate-severe COPD[58, 87, 112, 130]			
Desmopressin[57-59, 63, 65]	H01BA02	Moderate	Strong	Sympathomimetics for systemic use, no inhalation [59, 125]	R03CC		
Levothyroxine[146]	H03AA01			Salbumatol[59]	R03CC02		
Teriparatide[87]	H05AA02			Terbutaline[59, 125]	R03CC03		
Desiccated thyroid[57]		Low	Strong	Bambuterol [59]	R03CC12		

Anti-infective for systematic use				Clenbuterol [59]	R03CC13		
Fluoroquinolones [59]	J01MA			Reproterol [59]	R03CC14		
Ofloxacin[59, 125]	J01MA01			Other systemic drugs for airway diseases			
Ciprofloxacin [59]	J01MA02			Theophylline [58, 59, 63, 87, 110, 112, 125, 130, 146]	R03DA04		
Norfloxacin [59]	J01MA06			Aminophylline[59]	R03DA05		
Levofloxacin [59]	J01MA12			**Cough and cold preparation**	**R05**		
Moxifloxacin [59]	J01MA14			Opium alkaloids and derivatives[63]	R05D		
Aminoglycosides [146]	J01G			Ethylmorphine[125]	R05DA01		
Nitrofurantoin[57, 63, 82, 88, 125, 147]	J01XE01			Codeine[59, 125]	R05DA04		
Hexamine (methenamine)[82]	J01XX05			dihydrocodeine[59]	N02AA08		
Antineoplastic and immunomodulating agents				Dextrometorphan[125]	R05DA09		
Medroxyprogesterone[59]	L02AB02			**Antihistamines, systemic use**			
Megestrol acetate [57, 58, 87]	L02AB01			**First generation** [45, 57, 58, 63-65, 88, 112, 130, 132]		Moderate	strong
Musculo-skeletal system				Brompheniramine[57, 147]	R06AB01	Moderate	strong
Anti-inflammatory and anti-rheumatic products				Brompheniramine, combinations[64]	R06AB51		
Anti-inflammatory and anti-rheumatic products, non-steroid (NSAID)[63]				Triprolidine, combinations[64, 147]	R06AX07		
Non-COX-2-selective NSAIDs, oral[45, 57, 59, 65, 88, 125, 129, 146]		Moderate[57] High[45]	Strong	Promethazine, combinations[64]	R06AD52		
Phenylbutazone[59, 88, 125, 146, 147]	M01AA01			Promethazine[45, 59, 64, 88, 110, 112, 125, 147]	R06AD02	Moderate	strong
Indomethacin[57, 59, 64, 65, 88, 125, 129, 147]	M01AB01	Moderate	strong	Dexchlorpheniramine, combinations (Dexchlorpheniramine-Betamethason)[64, 125, 147]	R06AB52		
Sulindac [57, 64, 88]	M01AB02	Moderate	strong	Dexchlorpheniramine[64, 88, 110, 125, 147]	R06AB02		
Tolmetin [64, 65]	M01AB03			Diphenhydramine[45, 57, 59, 64, 65, 88, 112, 147]	R06AA02	Moderate	strong
Diclofenac [57, 59, 64, 65, 88, 125, 129]	M01AB05	Moderate	strong	Dimenhydrinate[57, 59, 64, 65, 125, 147]	R06AA11	Moderate	strong
Alclofenac[88]	M01AB06			Clemastine[59, 64, 125]	R06AA04		
Etodolac[57, 64, 129]	M01AB08	Moderate	strong	Diphenylpyraline[64]	R06AA07		
Acemetacin[59, 64]	M01AB11			Carbinoxamine[64, 125, 147]	R06AA08		
Proglumetacin[59]	M01AB14			Doxylamine[57, 59, 64, 125, 147]	R06AA09	Moderate	strong
Ketorolac, includes oral and parenteral [57, 64, 65, 88, 125, 129]	M01AB15	Moderate	strong	Trimethobenzamide[87]	R06AA10		
Aceclofenac[57, 59, 64, 88, 129]	M01AB16	Moderate	strong	Diphenhydramine, combinations[64]	R06AA52		
Piroxicam[57, 59, 64, 65, 88, 125, 129, 146]	M01AC01	Moderate	strong	Diphenylpyraline,combinations [64]	R06AA57		
Tenoxicam[57, 64, 88, 129]	M01AC02	Moderate	strong	Brompheniramine[64, 125]	R06AB01		
Lornoxicam[57, 88, 125, 129]	M01AC05	Moderate	strong	Chlorpheniramine (Chlorphenamine) [45, 57, 64, 65, 88, 112, 125, 147]	R06AB04	Moderate	strong
Meloxicam[57, 59, 64, 88, 125, 129]	M01AC06	Moderate	strong	Mequitazine[64, 125, 147]	R06AD07		
Ibuprofen[57, 59, 64, 65, 88, 125, 129]	M01AE01	Moderate	strong	Oxomemazine[125, 147]	R06AD08		
Naproxen[57, 59, 65, 88, 125, 129, 146]	M01AE02	Moderate	strong	Buclizine[64, 125, 147]	R06AE01		
Ketoprofen[59, 64, 125, 129]	M01AE03			Cyclizine[64, 112, 125]	R06AE03		
Fenoprofen[64]	M01AE04			Chlorcyclizine[64]	R06AE04		
Fenbufen[64]	M01AE05			Meclizine (meclozine)[57, 64, 125, 147]	R06AE05	Moderate	strong
Flurbiprofen[57, 64, 88, 125, 129]	M01AE09	Moderate	strong	Oxatomide[64]	R06AE06		
Tiaprofenic acid[64]	M01AE11			Buclizine, combinations [64]	R06AE51		
Oxaprozin[57]	M01AE12	Moderate	strong	Meclizine, combinations [64]	R06AE55		
Dexibuprofen[65]	M01AE14			Homochlorcyclizine HCl (homoginin)[64]	R06AE91		
Dexketoprofen[59, 125]	M01AE17			Cyproheptadine[57, 59, 64, 88, 125, 147]	R06AX02	Moderate	strong
Mefenamic acid[64, 65, 88, 125, 129]	M01AG01			Phenindamine[64]	R06AX04		
Flufenamic acid[64]	M01AG03			Triprolidine[45, 57, 64, 65, 125, 147]	R06AX07	Moderate	strong

Nabumetone[57, 59, 64, 125]	M01AX01	Moderate	strong	Mebhydrolin[64]	R06AX15		
Niflumic acid[64]	M01AX02			Pimethixene[125, 147]	R06AX23		
Benzydamine[64]	M01AX07			Ketotifen[59, 64]	R06AX17		
Nimesulide[57, 64, 88, 129]	M01AX17			Pheniramine[147 125]	R06AB05		
COX II inhibitors (coxibs)[59, 88, 125, 129, 146]				Trimeprazine(Alimemazine)[125, 147]	R06AD01		
Celecoxib[45, 59, 88, 125, 129, 146]	M01AH01	High	Strong	Dimetindene[59, 125]	R06AB03		
Etoricoxib[59, 88, 125, 129, 146]	M01AH05			Tripelennamine[125]	R06AC04		
Anti-inflammatory preparations non-steroids for topical use	M02A			**Second generation anti-histamine**			
Etofenamate[59]	M02AA06			Terfenadine [125]	R06AX12		
Loxoprofen (topical use)[88, 129]	M02AA31			Ebastine[59, 125]	R06AX22		
Muscle relaxants	M03			Rupatadine[59]	R06AX28		
Muscle relaxants, centrally acting agents[57, 65, 87, 88, 125, 129]	M03B	Moderate	Strong				
Carisoprodol[57, 87, 110, 125, 129, 146]	M03BA02	Moderate	Strong				
Chlorzoxazone[57, 87]	M03BB03	Moderate	Strong				
Cyclobenzaprine[57, 87, 125, 129]	M03BX08	Moderate	Strong				
Metaxalone[57, 87]		Moderate	Strong				
Methocarbamol[57, 59, 65, 87, 125, 146, 147]	M03BA03	Moderate	Strong				
Orphenadrine[57, 59, 65, 87, 88, 125, 129, 146]	M03BC01	Moderate	Strong				
Tolperisone[59]	M03BX04						
Thiocolchicoside[87, 129]	M03BX05						
Tizanidine[59, 87, 125]	M03BX02						
Baclofen[59, 88, 125, 129, 147]	M03BX01						
Pridinol[59]	M03BX03						
Tolperisone[59, 88]	M03BX04						
Tetrazepam[125, 147]	M03BX07						
chlorfenese[87]							

[A.] If the medications had no Anatomical Therapeutic Chemical (ATC) code, the field was left blank.

[B.] The quality of evidence was not graded by us; rather, it was directly assigned based on information taken from the original articles, specifically the Beer 2023 criteria and the Screening Tool for Older Persons' Appropriate Prescriptions for Japanese (STOPP Japanese 2016). In case any discrepancies were identified, they were specified. If the quality of evidence was not filled in, it indicated that the medications were not included in the two tools.

[C.] Similar to the quality of evidence, the strength of evidence was also based on the reports from the articles.

For patients with limited life expectancy, the development of an integrated list of medications from different tools was challenging due to variations in frailty criteria, expected remaining life expectancy, and the clinical components addressed (e.g., the Holmes list was developed for advanced dementia, whereas STOPPFrail was developed generally for frail older persons with limited life expectancy). However, we identified a total of 202 (117 medication classes and 85 specific medications), which were classified as either appropriate, inappropriate, or questionable, depending on the clinical component addressed by the tools **(Table 5)**.

The content of the tools primarily included a combination of appropriate/adequate medication lists and inappropriate/inadequate medications [100, 122], or they provided PIM lists/deprescribing criteria alone [61, 80, 101, 102, 123]. Medications listed in these tools can be categorized as follows:

1. Adequate/appropriate medications prescribed for symptom management and comfort [122], including analgesics (including opioids), antinauseants, and drugs for constipation.
2. Inappropriate/inadequate drug treatments used for long-term prevention of chronic diseases, such as vitamin D and lipid-lowering medications (statins), which are targeted for deprescribing[61, 80, 100, 101, 122, 123].
3. Drugs with a questionable nature of the decision to continue or initiate treatments, such as digital glycosides, or those for which there is no consensus on use, like fast-acting insulin, may require patient-specific evaluation [122].

Table 5: Overview of potentially inappropriate medications in frail patients with limited life expectancy eligible for deprescribing

Medication/ medication class	ATC code	STOPPFrail 2021[61]	Morin 2018[122]		Holmes 2008[100]	Oncopal Deprescribing guidelines 2015[80]	List of Evidence-baSed depreScribing for CHRONic patients[123]	STOPP NH(US)[102]	NORGEP_NH[101]
Definition of frailty with limited life expectancy		Frail older adults with less than one 1 year remaining life	Estimated life expectancy of ≤ 3months (75 years or older): Initiation and discontinuation		Palliative care patients with advanced dementia: Functional Assessment Stage test (FAST) score of 6E,7A, 7B, or 7C	Palliative cancer patients: Validated on patients < 6 months of remaining life	Patients with multimorbidity (PMM)	Nursing home setting (assuming the life expectancy is low) but not specified the progression	Frail patients in nursing home
			Initiation	Continuation					
Alimentary tract and metabolism									
Drugs for acid-related disorders, excluding PPI			Questionable	Questionable					
H2 receptor antagonist	A02BA	PIM			Sometimes appropriate	PIM			
Proton pump Inhibitors	A02BC	PIM	No consensus	No consensus	Sometimes appropriate	PIM		PIM	
Antispasmodics	A03				Rarely appropriate				
Butylscopolamine	A03BB01		Often adequate	Often adequate					
Metoclopramide	A03FA01		Often adequate	No consensus					
Antiemetics and antinauseants	A04A		Often adequate	Often adequate	Always appropriate				
Drugs for constipation/ laxatives	A06A		Often adequate	Often adequate	Always appropriate				
Antidiarrheal	A07DA				Always appropriate				
Anti-diabetic drugs	A10	PIM							
Insulin	A10A				Sometimes appropriate				
Fast-acting insulin	A10AB		No consensus	No consensus					
Intermediate-acting	A10AC		Questionable	No consensus					
combined insulin	A10AD		Questionable	No consensus					
Long-acting insulin	A10AE		No consensus	No consensus					
Oral diabetic agents	A10B		Questionable		Sometimes appropriate	PIM			
Other oral antidiabetics, excluding metformin				Questionable			Eligible to deprescribe		
Metformin	A10BA02			No consensus		PIM	Eligible to deprescribe		
Sulfonylureas	A10BB			Questionable		PIM		PIM	
Acarbose	A10BF01					PIM			
Thiazolidinediones	A10BG					PIM			
DPP-4 inhibitors	A10BH					PIM			
GLP-1 analogues	A10BJ					PIM			
Vitamins	A11				No consensus	PIM			
Multi-vitamin combination supplements	A11A	PIM							

Vitamin D	A11CC		Often inadequate	Often inadequate			Eligible to deprescribe		
Minerals	A12				No consensus	PIM			
Calcium supplement	A12A		Often inadequate	Often inadequate			Eligible to deprescribe		
Nutritional supplements (other than vitamins)		PIM			Sometimes appropriate				
Complementary—alternative medicines						PIM			
Appetite stimulants					Rarely appropriate				
Blood and blood-forming organs									
Vitamin K antagonists	B01AA		Often inadequate	Questionable					
Warfarin	B01AA03				Rarely appropriate				
Unfractionated heparin	B01AB01		Questionable	Questionable	Rarely appropriate				
Low molecular weight heparin	(B01AB04 - B01AB11)		Questionable	No consensus	Rarely appropriate				
Platelet aggregation inhibitors	B01AC	PIM	Questionable						
Antiplatelet agents, excluding aspirin	B01AC			Questionable	Never appropriate				
Aspirin	B01AC06	PIM		Questionable	No consensus	PIM	Eligible to deprescribe		
Oral anticoagulants							Eligible to deprescribe		
Novel oral anticoagulants	B01AE, B01AF		Often inadequate	Questionable					
Other anticoagulants	B01AD, B01AX		Often inadequate	Questionable					
Antianemic preparations	B03			Questionable					
Iron	B03AA				No consensus				
Oral elemental iron doses >200 mg/d								PIM	
Iron preparations and erythropoietin	B03A, B03XA01		Often inadequate						
Vitamin B12 and folic acid	B03B		Often inadequate						
Folic acid	B03BB01	PIM							
Red blood cell colony stimulating factors	B03XA				No consensus				
Blood products	B05A		Questionable	Questionable					
Electrolytes	B05XA				Sometimes appropriate				
Cardiovascular system									
Digitalis glycosides	C01AA		Questionable	Questionable					
Digoxin	C01AA05				Rarely appropriate			PIM (>0.125 mg/day)	
Cardiac glycosides, excluding digoxin	C01A		Often inadequate	Questionable					
Antiarrhythmic	C01B				Rarely appropriate				
Cardiac stimulants excluding cardiac glycoside	C01C		Often inadequate	Often inadequate					

Nitroglycerin	C01DA02				Sometimes appropriate				
Antihypertensives	C02	PIM	Often inadequate			PIM	Eligible to deprescribe		Eligible to deprescribe
Antihypertensive, excluding α-blockers	C02			Often inadequate					
Clonidine	C02AC01				Rarely appropriate				
Alpha-blocker antihypertensives	C02CA, C02LE			Questionable	Rarely appropriate				
Hydralazine	C02DB02				Rarely appropriate				
Diuretics	C03				Sometimes appropriate				
Low-ceiling diuretics, thiazides	C03A		Questionable	Questionable		PIM			
Low-ceiling diuretics, non-thiazides	C03B		Questionable	Questionable					
High-ceiling diuretics, excluding furosemide and torasemide	C03C		Questionable						
Other high-ceiling diuretics	C03C			No consensus					
Furosemide	C03CA01		No consensus	No consensus					
Torasemide	C03CA04		No consensus	No consensus					
Potassium-sparing agents	C03D		Questionable						
Potassium-sparing agents, excluding spironolactone	C03D			Questionable					
Spironolactone	C03DA01			No consensus					
Peripheral vasodilators	C04		Often inadequate	Often inadequate					
Beta-blocking agents	C07		Questionable		Sometimes appropriate	PIM			
Non-selective beta-blockers	C07AA			Questionable					
Selective beta-blockers	C07AB			No consensus					
Alpha and beta blocking agents	C07AG			No consensus					
Calcium channel blockers	C08			Questionable	Sometimes appropriate	PIM			
Calcium channel blockers, excluding verapamil	C08		Questionable						
Nimodipine	C08CA06						Eligible to deprescribe		
Verapamil	C08DA01		Often inadequate						
Angiotensin-converting-enzyme inhibitors	C09A, C09B		Often inadequate	Questionable	Sometimes appropriate	PIM			
Angiotensin II antagonists (Sartans)	C09C, C09D		Often inadequate	Questionable	Sometimes appropriate	PIM			
Lipid-modifying agents	C10		Often inadequate	Often inadequate	Never appropriate				
Statins	C10AA	PIM				PIM	Eligible to deprescribe		Eligible to deprescribe
Ezetimibe	C10AX09	PIM				PIM			
Bile acid Bequestrants	C10AC	PIM							
Fibrates	C10AB	PIM				PIM			
Nicotinic acid	C10AD02	PIM							
Acipimox	C10AD06	PIM							
Lomitapide	C10AX12	PIM							

Dermatologicals									
Antifungal creams	D01				Sometimes appropriate				
Genitourinary system and sex hormones									
Sex hormones	G03				Never appropriate				
Systemic oestrogens for menopausal symptoms	G03C	PIM							
Raloxifene	G03XC01					PIM			
Urinary muscarinic antagonists /Urologic spasmolytic/ Bladder relaxant/Drugs for urinary incontinence	G04BD	PIM	Often inadequate (except oxybutynin)	No consensus	Rarely appropriate		Eligible to deprescribe		Eligible to deprescribe
Oxybutynin	G04BD04		Questionable	No consensus					
Mirabegron	G04BD12	PIM							
Drugs for prostatic hypertrophy, excluding finasteride	G04C		Questionable	No consensus					
Finasteride	G04CB01, G04CA51		Often inadequate	Questionable	No consensus				
Alpha-adrenergic blockers	G04CA	PIM			Rarely appropriate		Eligible to deprescribe		
Tamsulosin	G04CA02				Rarely appropriate				
5-Alpha reductase inhibitors in catheterised male patients	G04CB	PIM							
Systemic hormonal preparations, excl. sex hormones and insulins									
Systemic corticosteroids	H02	PIM (long term use)			Sometimes appropriate			PIM (instead of inhaled corticosteroid)	
Mineralocorticoids	H02AA		No consensus	No consensus	Rarely appropriate				
Glucocorticoids for systemic use	H02AB		Often adequate	Often adequate					
Thyroid hormones	H03AA		No consensus	Often adequate	Sometimes appropriate				
Anti-thyroid drugs	H03B		Questionable	No consensus	Sometimes appropriate				
Iodine therapy	H03C		Questionable	Questionable					
Teriparatide	H05AA02	PIM							
Calcitonin	H05BA				No consensus				
Anti-infective for systemic use									
Antibacterial	J01				Sometimes appropriate				
Antivirals	J05				Sometimes appropriate				
Antineoplastic and immunomodulating agents									
Antineoplastic drugs	L01		Often inadequate	Questionable	Never appropriate				
Endocrine therapies	L02		Often inadequate	Questionable					
Hormone antagonists	L02B				Never appropriate				
Antiestrogens	L02BA				Never appropriate				
Antiandrogens	L02BB				Rarely appropriate				
Immunostimulant	L03A		Often inadequate	Often inadequate	Never appropriate				

Immunosuppressant	L04A		Often inadequate	Questionable	Never appropriate				
Musculo-skeletal system									
Long-term oral NSAIDs	M01A	PIM							PIM
Acetic acid derivatives	M01AB		No consensus	No consensus					
Propionic acid derivatives	M01AE		No consensus	No consensus					
Coxibs	M01AH		No consensus	No consensus					
Capsaicin	M02AB01				Sometimes appropriate				
Muscle relaxant	M03		No consensus	No consensus	No consensus				
Baclofen	M03BX01		No consensus	No consensus					
Anti-gout medications, excluding colchicine	M04		Questionable						
Anti-gout drugs, excluding allopurinol and colchicine	M04			Questionable					
Allopurinol	M04AA01			No consensus	Sometimes appropriate		Eligible to deprescribe		
Colchicine	M04AC01		No consensus	No consensus	Sometimes appropriate				
Bisphosphonates	M05BA	PIM	Often inadequate	Often inadequate	Rarely appropriate	PIM	Eligible to deprescribe		Eligible to deprescribe
Other osteoporosis drugs	M05B		Often inadequate	Often inadequate					
strontium	M05BX03	PIM				PIM			
denosumab	M05BX04	PIM				PIM			
Pressure ulcer products					Always appropriate				
Nervous system									
Anesthesia									
Ketamine	N01AX03		No consensus	No consensus					
Nitrous oxide	N01AX13		No consensus	No consensus					
Lidoderm	N01BB20				Always appropriate				
Analgesics									
Opioid analgesics	N02A		Often adequate	Often adequate	Always appropriate				
Non-opioid analgesics	N02B		Often adequate	Often adequate	Always appropriate				
Antiepileptic's	N03		Often adequate Excluding drugs (e.g.,gabapentin, pregabalin, amitriptyline) prescribed for the management of neuropathic pain	Often adequate Excluding drugs (e.g.,gabapentin, pregabalin, amitriptyline) prescribed for the management of neuropathic pain	Always appropriate				
Clonazepam	N03AE01		Often adequate						
Gabapentin for neuropathic pain	N03AX12		No consensus	No consensus					
Levetiracetam	N03AX14		Often adequate						
Pregabalin for neuropathic pain	N03AX16		No consensus	No consensus					
Anti-parkinson drugs									
Levodopa	N04BA		No consensus	Often adequate					
Dopamine agonists	N04BC			No consensus					
Other anti-Parkinson drugs	N04			No consensus					
Psycholeptics									

Antipsychotics	N05A	PIM	No consensus	No consensus	Sometimes appropriate			PIM (first generation)	Eligible to deprescribe
Phenothiazine	N05AA, N05AB, N05AC							PIM	
Levomepromazine	N05AA02		No consensus	No consensus					
Haloperidol	N05AD01		No consensus	No consensus			Eligible to deprescribe		
Olanzapine	N05AH03		No consensus	No consensus					
Quetiapine	N05AH04						Eligible to deprescribe		
Risperidone	N05AX08						Eligible to deprescribe		
Anxiolytics	N05B				Always appropriate				
Benzodiazepines: Anxiolytics	N05BA		Often adequate	Often adequate			Eligible to deprescribe	PIM (>4 week)	
Other anxiolytics	N05B		No consensus	No consensus					
Diazepam	N05BA01								PIM
Oxazepam	N05BA04								PIM (> 30 mg/day)
hydroxyzine	N05BB01								PIM
Hypnotics and sedatives	N05C				No consensus				PIM (regular use)
Hypnotics and sedatives, excluding benzodiazepines	N05C		Questionable	No consensus					
Benzodiazepines: Hypnotics and sedatives	N05CD		No consensus	Often adequate			Eligible to deprescribe	PIM (>4 week)	
Benzodiazepines Z drugs	N05CF						Eligible to deprescribe		
Zopiclone	N05CF01		No consensus	No consensus			Eligible to deprescribe		PIM (> 5 mg/day)
Zolpidem	N05CF02		No consensus	No consensus			Eligible to deprescribe		
Zaleplone	N05CF03						Eligible to deprescribe		
Eszopiclone	N05CF04		No consensus	No consensus					
Nitrazepam	N05CD02								PIM
Flunitrazepam	N05CD03								PIM
Melatonin	N05CH01		No consensus	No consensus					
Clomethiazole	N05CM02								PIM
Psychoanaleptics									
Anti-depressants	N06A				Sometimes appropriate		Eligible to deprescribe		Eligible to deprescribe
Tricyclic antidepressants	N06AA		Questionable Excluding drugs (e.g.,gabapentin, pregabalin, amitriptyline) prescribed for the management of neuropathic pain		Sometimes appropriate			PIM	PIM
Tricyclic antidepressants for neuropathic pain	N06AA		No consensus	No consensus					
Tricyclic antidepressants for depression	N06AA			No consensus					

Amitriptyline	N06AA09								PIM
doxepine	N06AA12								PIM
Clomipramine	N06AA04								PIM
trimipramine	N06AA06								PIM
nortryptiline	N06AA10								PIM
Selective serotonin reuptake inhibitors	N06AB		No consensus	No consensus					
Monoamine oxidase inhibitors	N06AF, N06AG		Questionable	No consensus					
Trazodone	N06AX05		No consensus	No consensus					
Mirtazapine	N06AX11		No consensus	No consensus					
Venlafaxine for neuropathic pain	N06AX16		No consensus	No consensus					
Duloxetine for neuropathic pain	N06AX21		No consensus	No consensus					
Central nervous system stimulants	N06B				No consensus				
Citicoline	N06BX06						Eligible to deprescribe		
Antidementia drugs	N06D		Often inadequate	Often inadequate					
Memantine	N06DX01	PIM			Never appropriate				
Other nervous system drugs									
Anticholinesterase inhibitors	N07AA				Never appropriate		Eligible to deprescribe		Eligible to deprescribe
Methadone	N07BC02		No consensus	No consensus					
Antiparasitic products, insecticides and repellents									
Antiparasitic agents	P				Sometimes appropriate				
Respiratory system									
Decongestants	R01A,R01B				Sometimes appropriate				
Inhaled bronchodilators	R03A				Always appropriate				
Salbutamol, inhalant	R03AC02		No consensus	Often adequate					
Inhaled corticosteroids	R03BA		No consensus	Often adequate	Sometimes appropriate				
Ipratropium, inhalant	R03BB01		No consensus	Often adequate					
Other inhalants for COPD	R03B		No consensus	No consensus					
Systemic drugs for obstructive airway diseases	R03C, R03D		Questionable	Questionable					
Theophylline	R03DA04	PIM							
Aminophylline	R03DA05	PIM							
Leukotriene antagonists	R03DC	PIM			Never appropriate				
Zafirlukast	R03DC01	PIM							
Montelukast	R03DC03	PIM							
Expectorants	R05CA				Always appropriate		Eligible to deprescribe		
Mucolytics	R05CB				Sometimes appropriate		Eligible to deprescribe		
Antihistamine	R06				Sometimes appropriate				PIM (first generation)
dexchlorpheniramine	R06AB02								PIM

trimeprazine(Alimemazine)	R06AD01								PIM
promethazine	R06AD02								PIM
Cyclizine	R06AE03		No consensus	No consensus					
Meclizine: Antivertigo agents	R06AE05				No consensus				
Sensory organs									
Antiglaucoma drops	S01E				Sometimes appropriate				
Antiinflammatory eye drops	S01B				Sometimes appropriate				
Lubricating eye					Always appropriate				
drops					Always appropriate				
Any preventive medicine									Eligible to deprescribe
General criteria									
Any drug that the patient persistently fails to take or tolerate despite adequate education and consideration of all appropriate formulations		PIM							
Any drug without clear clinical indication		PIM							
Any drug for symptoms which have now resolved (e.g. pain, nausea, vertigo,pruritus)		PIM							

Holmes 2008: Categorized medications for use in advanced dementia into five groups based on the consensus of 12 experts. The classification aimed to guide appropriate medication management in palliative care for patients with advanced dementia. The categories include medications that are "Never appropriate," having no use in palliative care and should be stopped or not started; "Rarely appropriate," seldom used in palliative care and likely to be discontinued; "Sometimes appropriate," with uses depending on palliative care indications and potential continuation despite risks; "Always appropriate," useful in palliative care and suitable for continuation or initiation without reservations; and "No consensus (<7/12) agreement," indicating uncertainty among experts, requiring further evaluation and discussion.

The Morin 2018 criteria provide a comprehensive classification for medication appropriateness at the end of life, encompassing both new medication initiation and continuation for patients already on treatment. **Often adequate** drug prescribing involves medications that are appropriate and beneficial for symptom management and comfort during the end-of-life period, essential for improving the patient's quality of life and addressing palliative care needs. **Questionable** drug prescribing includes medications for which appropriateness is uncertain, necessitating careful evaluation of potential benefits and risks based on the patient's condition and goals of care. **Often inadequate** drug prescribing refers to medications unsuitable for end-of-life care, often used for long-term chronic disease prevention or treatment, not aligned with the main focus of palliative care. "Not consensus" is applied when there is limited agreement among experts regarding medication appropriateness (If llevel of agreement was < 75%).

Eligible to deprescribe: Medications eligible for deprescribing are those with limited benefits that are suitable targets for discontinuation, and their need for continued use should be reassessed.

PIM: potentially inappropriate medications; **SSRI:** selective serotonin reuptake inhibitors; **SNRI:** selective norepinephrine reuptake inhibitors; **Coxibs:** cyclooxygenase-2-selective inhibitors; **ACE:** angiotensin-converting enzyme

STOPPFrail 2021 criteria applied for patients with End-stage irreversible pathology, Poor one-year survival prognosis, severe functional impairment or severe cognitive impairment or both, and Symptom control is the priority rather than prevention of disease progression.

For paediatric patients, we identified 152 potentially inappropriate prescriptions (PIPs), consisting of 78 that require clinical information and 74 criteria that could be applied in the absence of clinical information. Additionally, we found 29 potentially inappropriate omissions (PIOs) for the treatment of commonly encountered health problems in all or subgroups of paediatric patients **(Supplementary file 2.5)**.

Medication evidence levels included in tools and guidelines

Among the 35 tools and 9 guidelines selected for medication extractions, only two tools (1 for older persons with normal life expectancy and 1 for paediatric patients) and eight guidelines following the GRADE framework provided information on the level of evidence for reported medications **(Figure 2)**. For older persons with limited life expectancy, none of the tools offered a level of evidence. For older adults aged 65 years and above, Beers 2023 tools [57] and Japanese STOPP 2016 guidelines [45] provided information on the level of evidence and strength of recommendations for medications in their lists. Approximately 7.4% of medications in Beers 2023 tools (n = 242) were supported by low-quality evidence, 71.5% by moderate-quality evidence, and 21.1% by high-quality evidence. The Japanese STOPP 2016 guidelines (n = 37) also had 10.8% recommendations backed by low-quality evidence, 40.5% by intermediate-quality evidence, and 48.6% by high-quality evidence. Notably, there was a discrepancy observed, particularly concerning medications like benzodiazepam and NSAIDs, both listed as PIM but with different levels of quality evidence for avoiding their use in older persons **(Table 4).** Compiling the two tools for older persons, approximately a quarter (24.7% or n = 69/279) of medications were included based on the high quality of evidence. The evidence available for paediatric patients was also limited, with only the KIDs list providing information on the quality of evidence. About 47.9% of the list's contents were supported by low and very low-quality evidence, while 19.7% and 32.4% were backed by moderate and high-quality evidence, respectively (n = 71). Detailed information on the level of evidence for medications can be found in **Supplementary file 2.5**.

Discussion

In this umbrella review, including 15 systematic reviews, we identified 72 explicit and 12 mixed tools for medication appropriateness assessment, along with 9 guidelines for deprescribing. A significant proportion of explicit/mixed tools (n=66/84, 78.57%) and all guidelines were validated, with the (Modified) Delphi technique being the most common validation approach (n = 58/75, 77.3%). We developed a comprehensive list of medications, including 484 PIMs for older adults with a normal life expectancy, along with lists for 54 diseases/conditions, 128 drug-drug interactions, and 96 drugs with questionable benefits. Additionally, we identified 117 medication classes and 85 specific medications for older persons with limited life expectancy, categorized based on their appropriateness with different clinical components and remaining life expectancy. For paediatric patients, we found 152 potentially inappropriate prescriptions (PIPs) and 29 potentially inappropriate omissions (PIOs). Notably, only 2 tools and 8 guidelines following the GRADE framework provided information on the level of evidence for the medications/medication classes included. In older persons, we observed that only a quarter (24.7% or n = 69/279) of the medications were included in the list based on high quality of evidence.

To our knowledge and search, there is only one systematic review of systematic review that reported 49 explicit tools to use for older adults. [14] In comparison with this review, we identified more explicit tools for the similar target population (n = 72) and looked at additional tools supporting the deprescribing process (i.e., deprescribing guidelines). The higher numbers of tools identified in our review is justified by the fact that we included more years and used five databases, as opposed to the one database searched in the previous review.

During our review, we identified that in almost one-third of the tools, the settings where the tool could be applied were not specified. Additionally, we found that some tools had been adapted from existing non-specific settings to focus on a specific setting, such as nursing home residents, but made little to no changes in their list of medications, disregarding the differences in the characteristics of the target population, such as frailty aspects not being considered [18, 99]. This lack of clear differentiation between the health care settings in which the tools should be implemented and the specific target groups for whom they are intended can potentially confuse users when they have to choose which tools to use for particular settings. In addition, although the majority of PIM lists have been validated using the Delphi consensus technique, there was variation in panel size, panel composition, the rating scale, and the cut-off to determine whether the medication was PIM or not. This variation could be a potential source of bias in consensus studies where the choice of rating scale had a substantial influence on the final consensus results (9).

A (systematic) literature review of existing tools was the most common approach to tool development used by authors. Although the use of medications should be based on recommendations from well-established clinical trials, many drugs for children and older persons are used based on the experience of clinicians because, for ethical and practical reasons, generating evidence from clinical trials is difficult and evidence is mostly lacking for this population [66, 155-157]. Therefore, the development of PIM lists based on high-quality evidence is a challenging process, and his challenge might contribute to the prevalent trend of tools being developed based on existing PIM lists. In our study, 42.8% (36/84) of explicit/mixed tools were developed based on existing tools. Fully relying on the content of existing tools for the development of new tools and adapting to other countries drug availability (i.e., including drugs as PIM if the original tools classify the medication classes as PIM) may introduce bias or lead to the missing of new medication or recent evidence [32]. Therefore, to improve the quality and impact of the tool, combining the prior lists, considering clinical experience, and adding new evidence are required, and this can be achieved by regularly updating existing tools.

The initial aim of our review was to distinguish three groups of medications in different specific populations: appropriate medications, PIMs, and medications for which a consensus has not been achieved. However, when scrutinising the content of the existing tools, we had to slightly deviate from the protocol [CRD42021235348]. For instance, medications classified as not PIMs are not always the same as those considered appropriate (e.g., if a medication carries a known risk but the risk does not differ between younger and older adults, it was classified as not a PIM). Additionally, for tools developed for use in patients with limited life expectancy, the varied clinical components they addressed, along with the unspecified or varied duration of remaining life expectancy, added complexity. As a result of these complexities, we decided not to pool the medications from these tools into the pre-specified three categories. Instead, we chose to classify them into broader categories. Consequently, we opted to provide a comprehensive overview of medications based on their various

components. This approach facilitates the comparison of the appropriateness of medications for different clinical conditions and remaining life expectancy. Notably, medications primarily prescribed for symptom management, comfort, or those beneficial for palliative care were generally classified as adequate or appropriate. In contrast, medications intended for the long-term prevention or treatment of chronic diseases tended to be labelled as inappropriate or inadequate. Shrestha S. et al. [158] also suggested categorising medications into preventive, symptom-control, and dual-purpose categories for patients with limited life expectancy. However, due to these complexities, developing the pooled list of medications based on existing tools without expert input and clearly defining limited life expectancy seems challenging. Unclear definitions and the availability of tools for different time points in separate tools might be barriers for clinicians attempting to use the tools. Therefore, it may be crucial to develop a unified list of PIMs for different time points of remaining life expectancy (e.g., the last 3 months, 6 months, 1 year, and 2 years) within a single tool.

Only a few tools reported the level of evidence used for their development. Even these tools and guidelines were mostly developed based on low- and moderate-quality evidence as opposed to high-quality evidence. This indicates the currently available tools and guidelines were developed based on low-quality evidence and justifies the need to develop tools based on high-quality evidence. Developing tools based on high-quality evidence might not be achieved overnight, but regularly updating tools in line with new medication and newly generated evidence could improve the quality of evidence. For example, 21.1% of the criteria in Beers 2023 were developed based on high-quality evidence[57]. whereas in Beers 2015, a lower number of criteria (18.5%) were developed based on high-quality evidence [94]. Notwithstanding, in our review, we have only identified nine (9.5%) tools that have been updated at least once. Regularly updating the tools might not be a good solution in cases where evidence from individual-level studies is not continually generated. For instance, in patients with limited life expectancy, mostly evidence is lacking to formulate recommendations. Therefore, in addition to the development and updating of the tools based on expert consensus, generating evidence based on individual-level data is required to strengthen the level of evidence. The list of medications and the level of evidence included in our Excel files will help the researchers in the selection of the medications for generating evidence and then facilitate the strengthening of the level of evidence.

Overall, the low level of evidence and consensus methodology with different approaches might be the reason for variations in the classification of medications across tools. For instance, Rivaroxaban is considered PIM in Beers 2023 [57] but not classified as a PIM in PRISCUS 2023 [59]. One could expect heterogeneity in the list of medications between tools depending on the marketing and variation in the availability of drugs in the country developing the tool, but assigning the same medications to different categories (PIM or not PIM) for similar target groups is difficult to explain. In fact, for some tools and guidelines, the varying levels of stringency applied during the validation process for the inclusions of medications in the list might be the reason for the discrepancy. This could consequently be a barrier to using tools in clinical practice or lead to a selection of different treatments depending on which tools are selected by clinicians. Therefore, clinical judgement remains important when using the tools; consider the tools as an instrument to aid in the prescribing or deprescribing process without replacing the clinician's judgement. For future development of deprescribing tools and guidelines, a transparent approach that includes grading of evidence and sufficient information in their publications would greatly benefit clinicians and researchers. This approach enhances the credibility and reliability

of the tools, empowering healthcare professionals to make more informed decisions about medication appropriateness and deprescribing. Training clinicians about the pros and cons of using the tools is relevant, not to encourage indiscriminate use, but to equip them with the necessary skills and knowledge to critically evaluate evidence and make informed decisions.

Although this umbrella review provides a comprehensive and structured overview of existing tools and guidelines along with the level of evidence for the included medications, it also has some limitations. Firstly, a limitation of the study is that, despite conducting an extensive search of research and guideline databases, there is a possibility of missing some tools that were published after the date of the initial search, particularly new tools released in 2023 and tools that were not included in the systematic reviews. However, to limit this particular limitation, we checked for updates and identified five tools that were updated in late 2022 and 2023 (until July 7, 2023) [55-59]. Secondly, although the tools and guidelines were organised based on the target populations, we considered tools targeted for limited life expectancy as an umbrella term representing frailty, advanced diseases, end-of-life care situations, and tools that are not providing frailty criteria but noted that the tools are intended for frail individuals (e.g., nursing home residents). However, the estimated life expectancy for these components is not well defined in most of the literature and can vary. Thirdly, we included validated and most recent versions of the tools for medication extraction, using genealogy as a tool to describe a link between the tools. Therefore, the medications of some earlier tools that are not linked with recent tools are extracted and included in the list, but some of the medications could be rarely used or no longer available on the market.

Conclusion: Implications for clinical practice and further research

Our structured overview of existing tools and guidelines, along with the level of evidence for the included medications, enables clinicians and researchers to evaluate the strengths and weaknesses of different tools and guidelines for various purposes. This can help clinicians choose appropriate tools for specific settings/target populations and use them for shared decision-making. Our review offers extensive lists; distinguishing PIMs, appropriate medications, drugs where consensus is not reached, and therapeutic alternatives for PIMs for different target populations. This can provide a wider overview of medication appropriateness for clinicians while prescribing medications, and deprescribing PIMs for patients.

These compiled medication lists can serve as a database (starting point) for researchers developing new medication appropriateness assessment tools, aid in medication selection for evidence generation, and provide hypotheses to validate consensus-based classifications using real-world data. Overall, it will facilitate the efforts to be made in strengthening the level of evidence. However, compiling lists from tools targeting older adults with limited life expectancy proved challenging due to varying definitions of the target population across tools and guidelines. Thus, it is crucial to develop a list of appropriate, questionable medications, and PIM for different time points of remaining life expectancy in a single tool and should involve international experts. In addition to the development of the tools based on a clear definition of limited life expectancy, individual-level data is required to strengthen the level of evidence, as the evidence is generally low or lacking.

The discrepancies in distinguishing the appropriateness of medications across tools could stem from the low level of evidence and variations in methodological development and validation. To address

this, it is recommended that tools be transparent about their methodology, provide sufficient information for users, and be regularly updated in line with new evidence. An international consensus on tool and guideline development might narrow the discrepancy between lists attributed to the difference in rating scales and consensus criteria. This approach could also provide a broader context as well as the possibility of capturing the current available evidence and accounting for the prescribing behaviours of physicians in different countries. Therefore, in the future, the development and validation processes of medication lists should be clearer, more transparent, and more adaptable to the intended settings, taking into account the unique characteristics of the target population.

References

1. Scott IA, Hilmer SN, Reeve E*, et al.* Reducing inappropriate polypharmacy: the process of deprescribing. JAMA internal medicine. 2015;175(5):827-34.
2. World Health Organization. Medication safety in polypharmacy: technical report. World Health Organization; 2019.
3. Spinewine A, Schmader KE, Barber N*, et al.* Appropriate prescribing in elderly people: how well can it be measured and optimised? The Lancet. 2007;370(9582):173-84.
4. Commonwealth of Australia. What is palliative care? 2019; https://www.health.gov.au/health-topics/palliative-care/about-palliative-care/what-is-palliative-care. Accessed 20/01/2023.
5. Xing XX, Zhu C, Liang HY*, et al.* Associations Between Potentially Inappropriate Medications and Adverse Health Outcomes in the Elderly: A Systematic Review and Meta-analysis. Ann Pharmacother. 2019;53(10):1005-19.
6. Cardwell K, Kerse N, Hughes CM*, et al.* Does potentially inappropriate prescribing predict an increased risk of admission to hospital and mortality? A longitudinal study of the 'oldest old'. BMC Geriatr. 2020;20(1):28.
7. Hyttinen V, Jyrkkä J, Valtonen H. A Systematic Review of the Impact of Potentially Inappropriate Medication on Health Care Utilization and Costs Among Older Adults. Med Care. 2016;54(10):950-64.
8. Bartelink IH, Rademaker CMA, Schobben AFAM*, et al.* Guidelines on Paediatric Dosing on the Basis of Developmental Physiology and Pharmacokinetic Considerations. Clin Pharmacokinet. 2006;45(11):1077-97.
9. Corsonello A, Pedone C, Incalzi RA. Age-related pharmacokinetic and pharmacodynamic changes and related risk of adverse drug reactions. Curr Med Chem. 2010;17(6):571-84.
10. Paque K, Vander Stichele R, Elseviers M*, et al.* Barriers and enablers to deprescribing in people with a life-limiting disease: a systematic review. Palliat Med. 2019;33(1):37-48.
11. Reeve E. Deprescribing tools: a review of the types of tools available to aid deprescribing in clinical practice. Journal of Pharmacy Practice and Research. 2020;50(1):98-107.
12. Kaufmann CP, Tremp R, Hersberger KE*, et al.* Inappropriate prescribing: a systematic overview of published assessment tools. Eur J Clin Pharmacol. 2014;70(1):1-11.
13. Farrell B, Richardson L, Raman-Wilms L*, et al.* Self-efficacy for deprescribing: A survey for health care professionals using evidence-based deprescribing guidelines. Res Social Adm Pharm. 2018;14(1):18-25.
14. Farhat A, Al-Hajje A, Csajka C*, et al.* Clinical and economic impacts of explicit tools detecting prescribing errors: A systematic review. J Clin Pharm Ther. 2021;46(4):877-86.
15. Aguiar JP, Brito AM, Martins AP*, et al.* Potentially inappropriate medications with risk of cardiovascular adverse events in the elderly: A systematic review of tools addressing inappropriate prescribing. J Clin Pharm Ther. 2019;44(3):349-60.
16. Lucchetti G, Lucchetti A, G. rL. Inappropriate prescribing in older persons: A systematic review of medications available in different criteria. Arch Gerontol Geriatr. 2017;68:55-61.
17. Lee G, Lim J-F, Page AT*, et al.* Applicability of explicit potentially inappropriate medication lists to the Australian context: A systematic review. Australas J Ageing. 2022;41(2):200-21.
18. Motter FR, Fritzen JS, Hilmer SN*, et al.* Potentially inappropriate medication in the elderly: a systematic review of validated explicit criteria. Eur J Clin Pharmacol. 2018;74(6):679-700.
19. Schiavo G, Forgerini M, Lucchetta RC*, et al.* A comprehensive look at explicit screening tools for potentially inappropriate medication: A systematic scoping review. Australas J Ageing. 2022.
20. Rethlefsen ML, Kirtley S, Waffenschmidt S*, et al.* PRISMA-S: an extension to the PRISMA Statement for Reporting Literature Searches in Systematic Reviews. Systematic Reviews. 2021;10(1):39.
21. Page MJ, McKenzie JE, Bossuyt PM*, et al.* The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. PLoS Med. 2021;18(3):e1003583.
22. Shamseer L, Moher D, Clarke M*, et al.* Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ. 2015;350:g7647.
23. Brouwers MC, Kerkvliet K, Spithoff K. The AGREE Reporting Checklist: a tool to improve reporting of clinical practice guidelines. BMJ. 2016;352:i1152.
24. GRADE working group. Criteria for applying or using GRADE 2009 [updated March 24, 2016 Available from: https://www.gradeworkinggroup.org/.
25. Ivanova I, Elseviers M, Wauters M*, et al.* European repository of explicit criteria of potentially inappropriate medications in old age. Geriatrics & gerontology international. 2018;18(8):1293-7.
26. Deprescribing Guidelines and Algorithms. https://deprescribing.org/resources/deprescribing-guidelines-algorithms/ [cited 2022 /06/12].
27. Ouzzani M, Hammady H, Fedorowicz Z*, et al.* Rayyan—a web and mobile app for systematic reviews. Systematic Reviews. 2016;5(1):210.
28. Aromataris E, Fernandez R, Godfrey C, Holly C, Khalil H, Tungpunkom P. Chapter 10: Umbrella Reviews. In: Aromataris E, Munn Z (Editors). JBI Manual for Evidence Synthesis. JBI, 2020. Available from https://synthesismanual.jbi.global. https://doi.org/10.46658/JBIMES-20-11.
29. Brouwers MC, Kho ME, Browman GP*, et al.* AGREE II: advancing guideline development, reporting and evaluation in health care. CMAJ. 2010;182(18):E839-E42.

30. WHO Collaborating centre for Drug Statistics Methodology. ATC/DDD Index 2023 [cited 2023 27/01/]. Available from: https://www.whocc.no/atc_ddd_index/.
31. Darr-Foit S, Elsner P, Tittelbach J. Deprescribing in dermatology: a systematic review of current dermatological guidelines. Journal der Deutschen Dermatologischen Gesellschaft = Journal of the German Society of Dermatology : JDDG. 2019;17(3):261-5.
32. Dimitrow MS, Airaksinen MSA, Kivela S-L, *et al.* Comparison of prescribing criteria to evaluate the appropriateness of drug treatment in individuals aged 65 and older: a systematic review. J Am Geriatr Soc. 2011;59(8):1521-30.
33. Masnoon N, Shakib S, Kalisch-Ellett L, *et al.* Tools for Assessment of the Appropriateness of Prescribing and Association with Patient-Related Outcomes: A Systematic Review. Drugs Aging. 2018;35(1):43-60.
34. Renn BN, Asghar-Ali AA, Thielke S, *et al.* A Systematic Review of Practice Guidelines and Recommendations for Discontinuation of Cholinesterase Inhibitors in Dementia. The American journal of geriatric psychiatry : official journal of the American Association for Geriatric Psychiatry. 2018;26(2):134-47.
35. Li S, Huang L, Chen Z, *et al.* Tools for Identifying Potentially Inappropriate Prescriptions for Children and Their Applicability in Clinical Practices: A Systematic Review. Front Pharmacol. 2022;13:787113.
36. Corrick F, Conroy S, Sammons H, *et al.* Paediatric Rational Prescribing: A Systematic Review of Assessment Tools. Int J Environ Res Public Health. 2020;17(5).
37. Thompson W, Lundby C, Graabaek T, *et al.* Tools for Deprescribing in Frail Older Persons and Those with Limited Life Expectancy: A Systematic Review. J Am Geriatr Soc. 2019;67(1):172-80.
38. van Merendonk LN, Crul M. Deprescribing in palliative patients with cancer: a concise review of tools and guidelines. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer. 2022;30(4):2933-43.
39. Bjerre LM, Farrell B, Hogel M, *et al.* Deprescribing antipsychotics for behavioural and psychological symptoms of dementia and insomnia: Evidence-based clinical practice guideline. Canadian family physician Medecin de famille canadien. 2018;64(1):17-27.
40. Farrell B, Black C, Thompson W, *et al.* Deprescribing antihyperglycemic agents in older persons: Evidence-based clinical practice guideline. Canadian family physician Medecin de famille canadien. 2017;63(11):832-43.
41. Onder G, Vetrano DL, Palmer K, *et al.* Italian guidelines on management of persons with multimorbidity and polypharmacy. Aging Clin Exp Res. 2022;34(5):989-96.
42. Pottie K, Thompson W, Davies S, *et al.* Deprescription of Benzodiazepine agonists Evidence-based Clinical practice Guidelines. Can Fam Physician. 2018;64(5):E209-E24.
43. Reeve E, Farrell B, Thompson W, *et al.* Deprescribing cholinesterase inhibitors and memantine in dementia: guideline summary. The Medical journal of Australia. 2019;210(4):174-9.
44. Department of Health (2019). Appropriate prescribing of psychotropic medication for non-cognitive symptoms in people with dementia (NCEC National Clinical Guideline No. 21). Available at: https://www.gov.ie/en/collection/c9fa9a-national-clinical-guidelines.
45. Kojima T, Mizukami K, Tomita N, *et al.* Screening Tool for Older Persons' Appropriate Prescriptions for Japanese: Report of the Japan Geriatrics Society Working Group on "Guidelines for medical treatment and its safety in the elderly". Geriatrics & gerontology international. 2016;16(9):983-1001.
46. Farrell B, Pottie K, Thompson W, *et al.* Deprescribing proton pump inhibitors: Evidence-based clinical practice guideline. Canadian family physician Medecin de famille canadien. 2017;63(5):354-64.
47. Mallery LH, Ransom T, Steeves B, *et al.* Evidence-Informed Guidelines for Treating Frail Older Adults With Type 2 Diabetes: From the Diabetes Care Program of Nova Scotia (DCPNS) and the Palliative and Therapeutic Harmonization (PATH) Program. J Am Med Dir Assoc. 2013;14(11):801-8.
48. Reeve E, Farrell B, Rockwood K, *et al.* Development of an evidence-based clinical practice guideline for deprescribing cholinesterase inhibitors and memantine. Australas J Ageing. 2018;37:41-.
49. Reeve E, Farrell B, Thompson W, *et al.* Deprescribing cholinesterase inhibitors and memantine in dementia: guideline summary. Med J Aust. 2019;210(4):174-9.
50. Kojima T, Mizukami K, Tomita N, *et al.* Screening Tool for Older Persons' Appropriate Prescriptions for Japanese: Report of the Japan Geriatrics Society Working Group on "Guidelines for medical treatment and its safety in the elderly". Geriatrics & gerontology international. 2016;16(9):983-1001.
51. Farrell B, Black C, Thompson W, *et al.* Deprescribing antihyperglycemic agents in older persons: evidence-based clinical practice guideline. Can Fam Physician. 2017;63(11):832-43.
52. Farrell B, Pottie K, Thompson W, *et al.* Deprescribing proton pump inhibitors: evidence-based clinical practice guideline. Can Fam Physician. 2017;63(5):354-64.
53. Fialová D, Topinková E, Gambassi G, *et al.* Potentially inappropriate medication use among elderly home care patients in Europe. JAMA. 2005;293(11):1348-58.
54. Onder G, Landi F, Fusco D, *et al.* Recommendations to Prescribe in Complex Older Adults: Results of the CRIteria to Assess Appropriate Medication Use Among Elderly Complex Patients (CRIME) Project. Drugs Aging. 2014;31(1):33-45.
55. Pazan F, Weiss C, Wehling M. The FORTA (fit for the aged) list 2021: fourth version of a validated clinical aid for improved pharmacotherapy in older adults. Drugs Aging. 2022;39(3):245-7.
56. Pazan F, Weiss C, Wehling M. The EURO-FORTA (Fit fOR The Aged) List Version 2: Consensus Validation of a Clinical Tool for Improved Pharmacotherapy in Older Adults. Drugs Aging. 2023:1-10.

57. Panel AGSBCUE. American Geriatrics Society 2023 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2023.
58. O'Mahony D, Cherubini A, Guiteras AR*, et al.* STOPP/START criteria for potentially inappropriate prescribing in older people: version 3. Eur Geriatr Med. 2023:1-8.
59. Mann N-K, Mathes T, Sönnichsen A*, et al.* Potentially Inadequate Medications in the Elderly: PRISCUS 2.0: First Update of the PRISCUS List. Deutsches Ärzteblatt International. 2023;120(1-2):3.
60. Fede A, Miranda M, Antonangelo D*, et al.* Use of unnecessary medications by patients with advanced cancer: cross-sectional survey. Support Care Cancer. 2011;19(9):1313-8.
61. Curtin D, Gallagher P, O'Mahony D. Deprescribing in older people approaching end-of-life: development and validation of STOPPFrail version 2. Age Ageing. 2021;50(2):465-71.
62. Prot-Labarthe S, Weil T, Angoulvant F*, et al.* POPI (Pediatrics: Omission of Prescriptions and Inappropriate prescriptions): development of a tool to identify inappropriate prescribing. PLoS One. 2014;9(6):e101171.
63. Foubert K, Capiau A, Mehuys E*, et al.* Ghent Older People's Prescriptions Community Pharmacy Screening (GheOP3S)-Tool Version 2: Update of a Tool to Detect Drug-Related Problems in Older People in Primary Care. Drugs Aging. 2021;38(6):523-33.
64. Chang C-B, Lai H-Y, Hwang S-J*, et al.* The updated PIM-Taiwan criteria: a list of potentially inappropriate medications in older people. Ther Adv Chronic Dis. 2019;10:2040622319879602.
65. Kim M-Y, Etherton-Beer C, Kim C-B*, et al.* Development of a consensus list of potentially inappropriate medications for Korean older adults. Annals of geriatric medicine and research. 2018;22(3):121.
66. Sadozai L, Sable S, Le Roux E*, et al.* International consensus validation of the POPI tool (Pediatrics: Omission of Prescriptions and Inappropriate prescriptions) to identify inappropriate prescribing in pediatrics. PLoS One. 2020;15(10):e0240105.
67. Prot-Labarthe S, Weil T, Nguyen N*, et al.* Validation par consensus d'un outil d'identification de prescriptions inappropriées en pédiatrie (POPI). Arch Pediatr. 2016;23(5):481-90.
68. Prot-Labarthe S, Vercheval C, Angoulvant F*, et al.* « POPI ; pédiatrie : omissions et prescriptions inappropriées ». Outil d'identification des prescriptions inappropriées chez l'enfant. Arch Pediatr. 2011;18(11):1231-2.
69. Meyers RS, Thackray J, Matson KL*, et al.* K ey Potentially I nappropriate D rugs in Pediatrics: The KIDs List. The Journal of Pediatric Pharmacology and Therapeutics. 2020;25(3):175-91.
70. Corrick F, Conroy S, Choonara I*, et al.* Developing Paediatric Rational Prescribing Criteria. BMJ Publishing Group Ltd; 2017.
71. Corrick F, Choonara I, Conroy S*, et al.* Modifying a Paediatric Rational Prescribing Tool (POPI) for Use in the UK. Healthcare. 2019;7(1):33.
72. Barry E, O'Brien K, Moriarty F*, et al.* PIPc study: development of indicators of potentially inappropriate prescribing in children (PIPc) in primary care using a modified Delphi technique. BMJ open. 2016;6(9):e012079.
73. Desnoyer A, Blanc AL, Pourcher V*, et al.* PIM-Check: development of an international prescription-screening checklist designed by a Delphi method for internal medicine patients. BMJ Open. 2017;7(7):e016070.
74. Evans DC, Gerlach AT, Christy JM*, et al.* Pre-injury polypharmacy as a predictor of outcomes in trauma patients. Int J Crit Illn Inj Sci. 2011;1(2):104.
75. Levy HB. Self-administered medication-risk questionnaire in an elderly population. Ann Pharmacother. 2003;37(7-8):982-7.
76. Cantrill JA, Sibbald B, Buetow S. Indicators of the appropriateness of long-term prescribing in general practice in the United Kingdom: consensus development, face and content validity, feasibility, and reliability. BMJ Quality & Safety. 1998;7(3):130-5.
77. Robertson KE. Process for preventing or identifying and resolving problems in drug therapy. Am J Health Syst Pharm. 1996;53(6):639-50.
78. Hamdy RC, Moore SW, Whalen K*, et al.* Reducing polypharmacy in extended care. South Med J. 1995;88(5):534-8.
79. Oliveira L, Ferreira MO, Rola A*, et al.* Deprescription in advanced cancer patients referred to palliative care. J Pain Palliat Care Pharmacother. 2016;30(3):201-5.
80. Lindsay J, Dooley M, Martin J*, et al.* The development and evaluation of an oncological palliative care deprescribing guideline: the 'OncPal deprescribing guideline'. Support Care Cancer. 2015;23(1):71-8.
81. Malone DC, Armstrong EP, Abarca J*, et al.* Identification of serious drug–drug interactions: results of the partnership to prevent drug–drug interactions. J Am Pharm Assoc (2003). 2004;44(2):142-51.
82. Basger B, Chen T, Moles R. Validation of prescribing appropriateness criteria for older Australians using the RAND/UCLA appropriateness method. BMJ Open. 2012; 2: e001431.
83. Van der Linden L, Decoutere L, Flamaing J*, et al.* Development and validation of the RASP list (Rationalization of Home Medication by an Adjusted STOPP list in Older Patients): A novel tool in the management of geriatric polypharmacy. Eur Geriatr Med. 2014;5(3):175-80.
84. O'Mahony D, O'Sullivan D, Byrne S*, et al.* STOPP/START criteria for potentially inappropriate prescribing in older people: version 2. Age Ageing. 2014;44(2):213-8.
85. Silveira ED, Errasquín BM, García MM*, et al.* Mejorando la prescripción de medicamentos en las personas mayores: una nueva edición de los criterios STOPP-START. Revista Española de Geriatría y Gerontología. 2015;50(2):89-96.
86. Bahat G, Ilhan B, Erdogan T*, et al.* Turkish inappropriate medication use in the elderly (TIME) criteria to improve prescribing in older adults: TIME-to-STOP/TIME-to-START. Eur Geriatr Med. 2020;11(3):491-8.

87. Bahat G, Ilhan B, Erdogan T*, et al.* International validation of the Turkish Inappropriate Medication Use in the Elderly (TIME) criteria set: a Delphi panel study. Drugs Aging. 2021;38(6):513-21.
88. Zhang H, Wong EL, Yeoh E-k*, et al.* Development of an explicit tool assessing potentially inappropriate medication use in Hong Kong elder patients. BMC Geriatr. 2021;21(1):1-12.
89. Jenghua K, Chinwong S, Chinwong D*, et al.* Development of a list of potentially inappropriate medications for patients with heart failure (PIMHF). Research in Social and Administrative Pharmacy. 2021;17(5):894-903.
90. Lavan AH, Gallagher P, Parsons C*, et al.* STOPPFrail (Screening Tool of Older Persons Prescriptions in Frail adults with limited life expectancy): consensus validation. Age Ageing. 2017;46(4):600-7.
91. Campanelli CM. American Geriatrics Society updated beers criteria for potentially inappropriate medication use in older adults: the American Geriatrics Society 2012 Beers Criteria Update Expert Panel. J Am Geriatr Soc. 2012;60(4):616.
92. Seppala LJ, Petrovic M, Ryg J*, et al.* STOPPFall (screening tool of older persons prescriptions in older adults with high fall risk): a Delphi study by the EuGMS task and finish group on fall-risk-increasing drugs. Age Ageing. 2021;50(4):1189-99.
93. Mimica Matanović S, Vlahovic-Palcevski V. Potentially inappropriate medications in the elderly: a comprehensive protocol. Eur J Clin Pharmacol. 2012;68(8):1123-38.
94. American Geriatrics Society Beers Criteria Update Expert Panel, Fick DM, Semla TP*, et al.* American Geriatrics Society 2015 updated beers criteria for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2015;63(11):2227-46.
95. American Geriatrics Society Beers Criteria® Update Expert Panel, Fick DM, Semla TP*, et al.* American Geriatrics Society 2019 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2019;67(4):674-94.
96. Fick DM, Cooper JW, Wade WE*, et al.* Updating the Beers criteria for potentially inappropriate medication use in older adults: results of a US consensus panel of experts. Arch Intern Med. 2003;163(22):2716-24.
97. Beers MH, Ouslander JG, Rollingher I*, et al.* Explicit criteria for determining inappropriate medication use in nursing home residents. Arch Intern Med. 1991;151(9):1825-32.
98. Rancourt C, Moisan J, Baillargeon L*, et al.* Potentially inappropriate prescriptions for older patients in long-term care. BMC Geriatr. 2004;4(1):9.
99. Kim S-O, Jang S, Kim C-M*, et al.* Consensus Validated List of Potentially Inappropriate Medication for the Elderly and Their Prevalence in South Korea. International Journal of Gerontology. 2015;9(3):136-41.
100. Holmes HM, Sachs GA, Shega JW*, et al.* Integrating palliative medicine into the care of persons with advanced dementia: identifying appropriate medication use. J Am Geriatr Soc. 2008;56(7):1306-11.
101. Nyborg G, Straand J, Klovning A*, et al.* The Norwegian general practice–nursing home criteria (NORGEP-NH) for potentially inappropriate medication use: a web-based Delphi study. Scand J Prim Health Care. 2015;33(2):134-41.
102. Khodyakov D, Ochoa A, Olivieri-Mui BL*, et al.* Screening tool of older person's prescriptions/screening tools to alert doctors to right treatment medication criteria modified for US nursing home setting. J Am Geriatr Soc. 2017;65(3):586-91.
103. Garfinkel D, Zur-Gil S, Ben-Israel H. The war against polypharmacy: a new cost-effective geriatric-palliative approach for improving drug therapy in disabled elderly people. IMAJ-RAMAT GAN-. 2007;9(6):430.
104. Poudel A, Ballokova A, Hubbard RE*, et al.* Algorithm of medication review in frail older people: focus on minimizing the use of high-risk medications. Geriatrics & Gerontology International. 2016;16(9):1002-13.
105. Stuck AE, Beers MH, Steiner A*, et al.* Inappropriate medication use in community-residing older persons. Arch Intern Med. 1994;154(19):2195-200.
106. Newton PF, Levinson W, Maslen D. The geriatric medication algorithm. J Gen Intern Med. 1994;9(3):164-7.
107. Beers MH. Explicit criteria for determining potentially inappropriate medication use by the elderly: an update. Arch Intern Med. 1997;157(14):1531-6.
108. Zhan C, Sangl J, Bierman AS*, et al.* Potentially inappropriate medication use in the community-dwelling elderly: findings from the 1996 Medical Expenditure Panel Survey. JAMA. 2001;286(22):2823-9.
109. Gallagher P, O'Mahony D. STOPP (Screening Tool of Older Persons' potentially inappropriate Prescriptions): application to acutely ill elderly patients and comparison with Beers' criteria. Age Ageing. 2008;37(6):673-9.
110. Rognstad S, Brekke M, Fetveit A*, et al.* The Norwegian General Practice (NORGEP) criteria for assessing potentially inappropriate prescriptions to elderly patients: a modified Delphi study. Scand J Prim Health Care. 2009;27(3):153-9.
111. Kim DS, Im Heo S, Lee SH. Development of a list of potentially inappropriate drugs for the korean elderly using the delphi method. Healthcare informatics research. 2010;16(4):231-52.
112. Clyne B, Bradley MC, Hughes CM*, et al.* Addressing potentially inappropriate prescribing in older patients: development and pilot study of an intervention in primary care (the OPTI-SCRIPT study). BMC Health Serv Res. 2013;13:307.
113. Bermingham M, Ryder M, Travers B*, et al.* The St Vincent's potentially inappropriate medicines study: development of a disease-specific consensus list and its evaluation in ambulatory heart failure care. Eur J Heart Fail. 2014;16(8):915-22.
114. Tommelein E, Petrovic M, Somers A*, et al.* Older patients' prescriptions screening in the community pharmacy: development of the Ghent Older People's Prescriptions community Pharmacy Screening (GheOP^{3}S) tool. Journal of Public Health. 2015;38(2):e158-e70.

115. Lipton HL, Bero LA, Bird JA*, et al.* The impact of clinical pharmacists' consultations on physicians' geriatric drug prescribing: a randomized controlled trial. Med Care. 1992:646-58.
116. Linjakumpu T, Hartikainen S, Klaukka T*, et al.* A model to classify the sedative load of drugs. Int J Geriatr Psychiatry. 2003;18(6):542-4.
117. Rudolph JL, Salow MJ, Angelini MC*, et al.* The anticholinergic risk scale and anticholinergic adverse effects in older persons. Arch Intern Med. 2008;168(5):508-13.
118. Brunet NM, Panicot JE, Sevilla-Sánchez D*, et al.* A patient-centered prescription model assessing the appropriateness of chronic drug therapy in older patients at the end of life. Eur Geriatr Med. 2015;6(6):565-9.
119. Fauziyah S, Andrajati R, Sartika RAD*, et al.* Adaptation and validation of the Screening Tool of Older People's Prescriptions Instrument for the Indonesian population. Journal of Research in Pharmacy Practice. 2020;9(1):24.
120. Wang K, Shen J, Jiang D*, et al.* Development of a list of high-risk perioperative medications for the elderly: a Delphi method. Expert Opin Drug Saf. 2019;18(9):853-9.
121. Hanlon JT, Schmader KE, Samsa GP*, et al.* A method for assessing drug therapy appropriateness. J Clin Epidemiol. 1992;45(10):1045-51.
122. Morin L, Laroche M-L, Vetrano DL*, et al.* Adequate, questionable, and inadequate drug prescribing for older adults at the end of life: a European expert consensus. Eur J Clin Pharmacol. 2018;74(10):1333-42.
123. Rodríguez-Pérez A, Alfaro-Lara ER, Albiñana-Perez S*, et al.* Novel tool for deprescribing in chronic patients with multimorbidity: List of Evidence-Based Deprescribing for Chronic Patients criteria. Geriatrics & gerontology international. 2017;17(11):2200-7.
124. Page A, Potter K, Clifford R*, et al.* Medication appropriateness tool for co-morbid health conditions in dementia: consensus recommendations from a multidisciplinary expert panel. Intern Med J. 2016;46(10):1189-97.
125. Renom-Guiteras A, Meyer G, Thürmann PA. The EU (7)-PIM list: a list of potentially inappropriate medications for older people consented by experts from seven European countries. Eur J Clin Pharmacol. 2015;71(7):861-75.
126. Zacarin A, Strumia M, Piau A*, et al.* Les médicaments potentiellement inappropriés: adaptation de la liste EU (7) PIM à la pratique médicale française. Therapies. 2020;75(6):663-73.
127. Pazan F, Gercke Y, Weiss C*, et al.* The JAPAN-FORTA (Fit fOR The Aged) list: Consensus validation of a clinical tool to improve drug therapy in older adults. Arch Gerontol Geriatr. 2020;91:104217.
128. Pazan F, Gercke Y, Weiss C*, et al.* The US-FORTA (Fit fOR The Aged) list: consensus validation of a clinical tool to improve drug therapy in older adults. J Am Med Dir Assoc. 2020;21(3):439. e9-. e13.
129. Motter FR, Hilmer SN, Paniz VMV. Pain and inflammation management in older adults: a Brazilian consensus of potentially inappropriate medication and their alternative therapies. Front Pharmacol. 2019;10:1408.
130. Samaranayake N, Balasuriya A, Fernando G*, et al.* 'Modified STOPP-START criteria for Sri Lanka'; translating to a resource limited healthcare setting by Delphi consensus. BMC Geriatr. 2019;19(1):1-5.
131. Aguiar JP, Costa LH, da Costa FA*, et al.* Identification of potentially inappropriate medications with risk of major adverse cardiac and cerebrovascular events among elderly patients in ambulatory setting and long-term care facilities. Clin Interv Aging. 2019;14:535.
132. Gonzalez-Colaço Harmand M, Aldea-Perona AM, Boada-Fernández del Campo C*, et al.* Spanish list of potentially inappropriate drugs in the elderly (ES-PIA project). Eur J Clin Pharmacol. 2019;75(8):1161-76.
133. Pazan F, Weiss C, Wehling M. The EURO-FORTA (Fit fOR The Aged) list: international consensus validation of a clinical tool for improved drug treatment in older people. Drugs Aging. 2018;35(1):61-71.
134. Pazan F, Weiss C, Wehling M. The FORTA (Fit fOR The Aged) list 2018: third version of a validated clinical tool for improved drug treatment in older people. Drugs Aging. 2019;36(5):481-4.
135. Cano JP, Garcia AA, Cánovas JG*, et al.*, editors. Spanish adaptation of Beers criteria. Anales del sistema sanitario de Navarra; 2015.
136. Hanlon JT, Semla TP, Schmader KE. Alternative medications for medications in the use of high-risk medications in the elderly and potentially harmful drug–disease interactions in the elderly quality measures. J Am Geriatr Soc. 2015;63(12):e8-e18.
137. Kuhn-Thiel AM, Weiß C, Wehling M*, et al.* Consensus Validation of the FORTA (Fit fOR The Aged) List: A Clinical Tool for Increasing the Appropriateness of Pharmacotherapy in the Elderly. Drugs Aging. 2014;31(2):131-40.
138. Mann E, Böhmdorfer B, Frühwald T*, et al.* Potentially inappropriate medication in geriatric patients: the Austrian consensus panel list. Wien Klin Wochenschr. 2012;124(5):160-9.
139. Chang CB, Yang SY, Lai HY*, et al.* Using published criteria to develop a list of potentially inappropriate medications for elderly patients in Taiwan. Pharmacoepidemiol Drug Saf. 2012;21(12):1269-79.
140. Bachyrycz A, Dodd MA, Priloutskaya G. Development and Dissemination of a Statewide System to Minimize Use of Potentially Inappropriate Medications (PIMs). Med Care. 2012;50(11):993-6.
141. Holt S, Schmiedl S, Thürmann PA. Potentially inappropriate medications in the elderly: the PRISCUS list. Deutsches Ärzteblatt International. 2010;107(31-32):543.
142. Wehling M. Multimorbidity and polypharmacy: how to reduce the harmful drug load and yet add needed drugs in the elderly? Proposal of a new drug classification: fit for the aged. J Am Geriatr Soc. 2009;57(3):560-1.
143. Drenth-Van Maanen A, Van Marum RJ, Knol W*, et al.* Prescribing optimization method for improving prescribing in elderly patients receiving polypharmacy. Drugs Aging. 2009;26(8):687-701.
144. Soares MA, Fernandez-LlimóS F, Lança C*, et al.* Operationalization to Portugal: Beers criteria of inappropriate medication use in the elderly. Acta Med Port. 2008;21(5):441-52.

145. Basger BJ, Chen TF, Moles RJ. Inappropriate medication use and prescribing indicators in elderly Australians. Drugs Aging. 2008;25(9):777-93.
146. Winit-Watjana W, Sakulrat P, Kespichayawattana J. Criteria for high-risk medication use in Thai older patients. Arch Gerontol Geriatr. 2008;47(1):35-51.
147. Laroche M-L, Charmes J-P, Merle L. Potentially inappropriate medications in the elderly: a French consensus panel list. Eur J Clin Pharmacol. 2007;63(8):725-31.
148. McLeod PJ, Huang AR, Tamblyn RM*, et al.* Defining inappropriate practices in prescribing for elderly people: a national consensus panel. CMAJ. 1997;156(3):385-91.
149. Onder G, Vetrano DL, Palmer K*, et al.* Italian guidelines on management of persons with multimorbidity and polypharmacy. Aging Clin Exp Res. 2022:1-8.
150. Holmes HM, Hayley DC, Alexander GC*, et al.* Reconsidering medication appropriateness for patients late in life. Arch Intern Med. 2006;166(6):605-9.
151. Bjerre LM, Farrell B, Hogel M*, et al.* Deprescribing antipsychotics for behavioural and psychological symptoms of dementia and insomnia: evidence-based clinical practice guideline. Can Fam Physician. 2018;64(1):17-27.
152. Oborne CA, Batty GM, Maskrey V*, et al.* Development of prescribing indicators for elderly medical inpatients. Br J Clin Pharmacol. 1997;43(1):91-7.
153. Lindblad CI, Hanlon JT, Gross CR*, et al.* Clinically important drug-disease interactions and their prevalence in older adults. Clin Ther. 2006;28(8):1133-43.
154. Rodrigues DA, Herdeiro MT, Thürmann PA*, et al.* Operationalisation for Portugal of the EU (7)-PIM List for Identification of Potentially Inappropriate Medicines in Older Adults. Acta Med Port. 2021;34(3):194-200.
155. Shah SS, Hall M, Goodman DM*, et al.* Off-label Drug Use in Hospitalized Children. Arch Pediatr Adolesc Med. 2007;161(3):282-90.
156. Cherubini A, Oristrell J, Pla X*, et al.* The Persistent Exclusion of Older Patients From Ongoing Clinical Trials Regarding Heart Failure. Arch Intern Med. 2011;171(6):550-6.
157. Crome P, Lally F, Cherubini A*, et al.* Exclusion of Older People from Clinical Trials. Drugs Aging. 2011;28(8):667-77.
158. Shrestha S, Poudel A, Forough AS*, et al.* A systematic review on methods for developing and validating deprescribing tools for older adults with limited life expectancy. Int J Pharm Pract. 2022.

PART III

REAL-WORLD IMPLEMENTATION OF DEPRESCRIBING IN NURSING HOME RESIDENTS WITH LIMITED LIFE EXPECTANCY

Chapter 3

International deprescribing guidelines did not impact actual practice in deprescribing of potentially inappropriate medications for nursing home residents: an interrupted time series analysis

Published:
Anlay DZ, Paque K, Van den Eynden B, Dilles T, Cohen J. International deprescribing guidelines did not impact actual practice in deprescribing of potentially inappropriate medications for nursing home residents: an interrupted time series analysis.
Drugs Aging 42, 485–499 (2025). DOI: https://doi.org/10.1007/s40266-025-01197-2

ABSTRACT

Background

Deprescribing guidelines reduce the use of potentially inappropriate medications (PIMs) in trial settings; however, their real-world impact remains unclear. Therefore, this study assesses deprescribing trends and the impact of guideline publications (STOPPFrail, proton pump inhibitors [PPIs], and antipsychotics) on these trends among nursing home residents with limited life expectancy in Belgium.

Methods

Deprescribing was assessed using linked healthcare reimbursement data for all residents aged 65 and older who died between 2014 and 2019. Fifteen PIMs from STOPPFrail version 1 were selected. Deprescribing was operationalized as discontinuing at least one PIM in the last four months of life among those who had been prescribed these medications chronically between 6-12 months prior to death. To identify changes in the trend of deprescribing we employed a Joinpoint linear regression model. We calculated the average quarterly percent change (AQPC) and 95% CIs. Additionally, we used Autoregressive Integrated Moving Average (ARIMA) modelling to explore the impact of publication of these guidelines on four commonly used PIMs: PPIs, antipsychotics, lipid modifying agents, and calcium.

Results

Among 244,865 residents, 169,782 (69.3%) were chronically prescribed at least one PIM, and 50,487 (29.7%) had at least one discontinued. The prevalence of deprescribing declined from 31.7% to 27.66% between the first quarter of 2014 and the fourth quarter of 2019, with an average quarterly percent change decline of -0.47% (95% CI: -0.85, -0.10). No joinpoints were identified, indicating a consistent linear trend with no interruptions or statistically significant shifts in the rate of change in deprescribing prevalence. ARIMA modeling found that the publication of deprescribing guidelines had no impact on deprescribing trends.

Conclusion

Despite the high use of PIMs, and the publication of the STOPPFrail, PPI, and antipsychotics deprescribing guidelines, deprescribing rates remained low and even decreased. These findings emphasize the importance of implementation efforts that go well beyond guideline publications to effectively change deprescribing practices.

1. Introduction

Polypharmacy (the concurrent use of five or more chronic medications) [1] and multimorbidity are prevalent among nursing home (NH) residents with limited life expectancy (LLE). Both are significant risk factors for the use of potentially inappropriate medications (PIMs),[2] for which the risk outweigh the benefits.[3] Most NH residents receive multiple medications to manage their multimorbid conditions and symptoms, often leading to drug-drug and drug-disease interactions.[4] Up to 88% of residents have been reported to use at least one PIM.[5, 6] The prescription of PIMs has been linked to poor outcomes, including adverse drug events (ADEs),[7] hospitalizations,[8, 9] reduced quality of life,[7] and death.[10] Moreover, it incurs avoidable health care costs in a context of scarce resources.[11, 12] Reducing the prescription of PIMs in NH is particularly relevant, as the use of PIMs is high; [2] residents are often frail with limited life expectancy and vulnerable to adverse drug events, which can negatively affect their quality of life, while the primary treatment goal is to enhance quality of life.[13] Additionally, the share of the aging population requiring long-term care in NHs is rising globally. [14, 15]

The desire to reduce the use of PIMs, in NH residents as well as other patient populations, has led to the development and publications of multiple and diverse tools to assist healthcare professionals in identifying PIMs and then supporting them for their deprescription.[16] Most of the developed tools have been validated for older persons aged 65 and above in general populations, with only a limited number of tools validated for use in NHs.[17-19] In recent years, explicit tools with lists of PIMs have been developed to assist clinicians in identifying and discontinuing PIMs for patients with life limiting illnesses or for those at the end of life.[19-21] In 2017, researchers developed the Screening Tool of Older Persons Prescriptions in Frail adults with limited life expectancy (STOPPFrail) criteria[20] and updated it in 2021 for use in the last years of life. [22] Additionally, guidelines developed by the Bruyère Research Institute specifically support the deprescribing process for individual medications and are published on their website, "Deprescribing.org." These guidelines cover medications that are also relevant in the nursing home context, such as antipsychotics [23, 24] and proton pump inhibitors (PPIs). [25]

The purpose of guidelines is actual change of clinical practice and the effectiveness of STOPPFrail-guided deprescribing interventions in reducing PIMs has indeed been demonstrated in a small-scale pre-post study in NH and in a randomized control trials in two hospital settings in Ireland.[12, 26] Both studies demonstrated that the use of STOPPFrail is feasible and substantially reduces both the number of medications and the associated costs, suggesting its utilization is beneficial. [12, 26] However, these studies provide insights into the causal effects of deprescribing guidelines in controlled interventional settings only. Hitherto, there has been little to no evidence about how the publication of guidelines has impacted deprescribing practices in the real world, where implementation of guidelines may happen much 'messier' and the road from guideline distribution to actual practice less linear than in the context of an interventional study.

Despite promising results of deprescribing guidelines, and despite contributions of international experts in developing and promoting deprescribing guidelines, research has indicated that their adoption in clinical practice remains limited in many countries.[27] Even among guidelines that include deprescribing recommendations, they often lack clear and actionable steps, making their implementation dependent on healthcare professionals' awareness and willingness to use these guidelines. [28] Compared to in other healthcare settings, residents typically stay for longer periods in a NH, allowing more time for medication reviews. Nevertheless, in practice, guideline implementation

is challenging due to the complex organization of care in NHs. A mix of permanent and temporary staff provides daily care, residents are treated by different family physicians of their choice, who visit only as needed and have limited time for each consultation. Additionally, pharmacists primarily focus on medication supply rather than comprehensive reviews, as medication review activities are generally not funded and require coordinated multidisciplinary efforts.[29] This highlights a critical knowledge gap: did the publication of STOPPFrail and other deprescribing guidelines have an impact on the trend of deprescribing PIMs outside of trial contexts or pilot intervention programs? Moreover, there is a scarcity of studies examining the underlying trends in the deprescription of PIMs in this population. Assessing these trends is crucial for understanding the current state of PIM management in NHs and for providing evidence-based insights that can inform deprescribing efforts. Such insights can help various stakeholders develop targeted interventions and policies to enhance deprescribing, ultimately improving safety and care quality for residents with limited life expectancy. Therefore, this study assesses deprescribing trends and the impact of publications of international deprescribing guidelines (STOPPFrail, PPIs, and antipsychotics) on these trends among NH residents with limited life expectancy in Belgium between 2014 and 2019 using real world data.

2. Methods

2.1. Study design and settings

A decedent cohort study was conducted using Belgian healthcare reimbursement data to assess deprescribing trends over six years (2014-2019) among NH residents with limited life expectancy. The cohort included individuals aged 65 years or older at the time of death, who had received at least one reimbursed healthcare service in a NH within 0-365 days prior to death and/or were legally registered as NH residents, with their month and year of death recorded. Data were aggregated by grouping individuals who died in the same months and years, resulting in a total of 72 months of follow-up data, with different decedents each month. The trend of deprescribing at least one PIM was assessed quarterly, yielding 24 quarterly data points. Inaddition, to evaluate the impact of deprescribing guideline publications, we applied an interrupted time series design using the same monthly aggregated data. This study was reported in accordance with the reporting of studies conducted using observational routinely-collected health Data (RECORD) Statement. [30]

2.2. Data sources and handling

Administratively collected population-level databases were linked into one database for analysis using Structured Query Language (SQL) in SAS. The linked dataset contains data from five sources managed by the InterMutualist Agency (IMA-AIM): (1) a socio-demographic database of all individuals with healthcare insurance (legally mandatory in Belgium), covering more than 99% of the population; (2) a national dataset of healthcare claims data from seven healthcare insurers, containing all reimbursed healthcare use data from home, NH and hospital care, and reimbursed medication data dispensed in hospital pharmacies; (3) a Katz-scale database, containing all mandatory evaluations of independence in activities of daily living of patients who need outpatient nursing care or are staying in a NH; (4) Pharmanet, containing all reimbursed medication data dispensed in community pharmacies; and (5) a hospitalization database, containing all hospital admissions. These data were deterministically linked at the individual level using multiple encrypted social security numbers to data from Statistics Belgium on three additional sources: (6) a death certificate database with causes and place of death; (7) a census database, including educational level; and (8) a fiscal database, including net taxable income.

More information on the different databases, the linking procedure, and the data protection approvals is published elsewhere. [31]

All medication data in this study were dispensing data from all hospital and community pharmacies. The medications in the database were classified and recorded based on the World Health Organization's Anatomical Therapeutic Chemical (ATC) system, which classifies drugs into different groups according to the organ or system on which they act and their chemical, pharmacological, and therapeutic properties. [32] ATC codes at all levels—from one (anatomical main group) to five (chemical substance)—of every medication were traceable in the database. For each selected PIM, the corresponding ATC code was selected from the IMA database and used to evaluate outcomes and deprescribing trends at the aggregate level.

2.2.1. PIM Identification

The specific medications analyzed were selected on the basis of the list of PIMs included in the first versions of the STOPPFrail guidelines. The guidelines consist of 27 criteria related to medications that may be inappropriate for frail individuals with limited life expectancy. [20] Since we used linked healthcare reimbursement data, which lack detailed clinical information for individual patients, we only selected medications for which inappropriateness does not require high-level patient-specific clinical data. This selection was based on categorization by experts from Ghent University, as published by Paque et al. [33] Inaddition, we considered whether these PIMs were available on the Belgian market and reimbursed by insurers.

Deprescribing trends were assessed for medications 1) used for long-term prevention, 2) for which safer alternatives are available, and 3) for which chronic use is inappropriate. This led to the selection of 15 medications for trend analysis. For the interrupted time series analysis, in view of statistical power, we included only those medications that had been deprescribed for at least 50 residents at each of the 72 time points, resulting in four medications being analyzed for guideline impact. Of these, two (antipsychotics and PPIs) have published guidelines on Bruyère's Deprescribing.org, [34] allowing for the assessment of both STOPPFrail and Bruyère guidelines, while for the other two (lipid-modifying agents and calcium), only the impact of STOPPFrail was assessed, as specific deprescribing guidelines had not yet been published for the observation period (**Table 1**).

Table 1: Potentially inappropriate medications according to STOPPFrail categorized by *Paque etal* and selected for this study

Categorization	Medications	ATC code[a]	Selected for trend analysis[b]	Drug-Specific Guideline		Selected for impact analysis[C]
				Published on deprescribing.org	Publication Month and Year	
Medications for long-term prevention	Lipid modifying agents	C10%	✓	✗		✓
	Calcium supplements	A12AX%	✓	✗		✓
	Osteoporosis drugs[d]	M05B%, H05AA02	✓	✗		✗
	Selective Estrogen Receptor Modulators (SERMS)	G03XC%	✓	✗		✗

Medications for which chronic use is inappropriate	Memantine	N06DX01	✓	✓	February, 2018	✗
	Sex hormones	G03% excl. G03XC%	✓	✗		✗
	Neuroleptic antipsychotics	N05A%	✓	✓	January, 2018	✓
	Proton pump inhibitors (PPIs)	A02BC%	✓	✓	May,2017	✓
	H2-receptor antagonists	A02BA%	✓	✗		✗
	Gastrointestinal antispasmodics	A03%	✓	✗		✗
	Long-term oral steroids ≥ 2 months	H02%	✓	✗		✗
(Outdated) Medications for which a safer alternative exists	Theophylline	R03D%	✓	✗		✗
	Long-term oral NSAIDs ≥ 2 months	M01A%	✓	✗		✗
	5-alpha reductase inhibitors	G04CA%, G04CB%	✓	✗		✗
	Alpha-blockers	C02CA%, C02LE%	✓	✗		✗
Medications not selected because clinical information is needed to determine their appropriateness	Anti-platelets	B01AC%	✗	✗		✗
	Leukotriene antagonists	R03DC%	✗	✗		✗
	Muscarinic antagonists	G04BD%	✗	✗		✗
	Diabetic oral agents	A10B%	✗	✓	November, 2017	✗
	ACE inhibitors for diabetes	C09A%, C09B%	✗	✗		✗
	Angiotensin receptor blockers	C09C%, C09D%	✗	✗		✗
	Prophylactic antibiotics		✗	✗		✗
	Systemic oestrogens for menopausal symptoms	G03C%	✗	✗		✗
	Multi-vitamin combination supplements	A11A%	✗	✗		✗
Not medications (and thus not on the medication chart)	Nutritional supplements (other than vitamins)		✗	✗		✗

[a] In our dataset, we have the ATC code at the fifth level. For our analysis in SAS, we used different levels of the ATC code (2nd to 5th) depending on the criteria included in the STOPPFrail guideline. For example, a lipid-modifying agent is a second-level ATC medication class, so we selected medications with the code C10%, which includes all medications starting with C10. For other cases, for example, Theophylline is classified under the third-level ATC code R03D%, proton pump inhibitors (PPIs) are categorized under the fourth-level ATC code A02BC%, and Memantine is specifically identified by the fifth-level ATC code N06DX01.

[b] Medications selected for trend of at least one PIM deprescribed (15 medications)

[c] The impact of guidelines was assessed for individual medications. In view of statistical power to detect whether the ARIMA modeling fitted, we only selected medications for which at least 50 residents with deprescription could be identified at each of the 72 time points/months.

[d] Anti-resorptive/bone anabolic drugs (bisphosphonates, strontium, teriparatide, denosumab

2.3. Measures

2.3.1. Outcome

The main outcome measure was a deprescription of a PIM. To identify a deprescription towards the end of life, we divided the last year of life into two periods: T1 (12 to 6 months prior to death) and T2

(the last 4 months) (**Fig. 1**). A deprescription was defined as any of the 15 selected PIMs that was dispensed at least twice during T1 (i.e. chronic prescription) [33] and no dispension of the drug in T2. To calculate the percentage of deprescriptions we used the cases of chronic prescription as denominator. The reason for our operationalisation is that deprescribing generally targets medications used chronically, [28] defined here as requiring at least two prescriptions to account for use extending beyond 3 months, given that each prescription in Belgium is valid for 3 months.

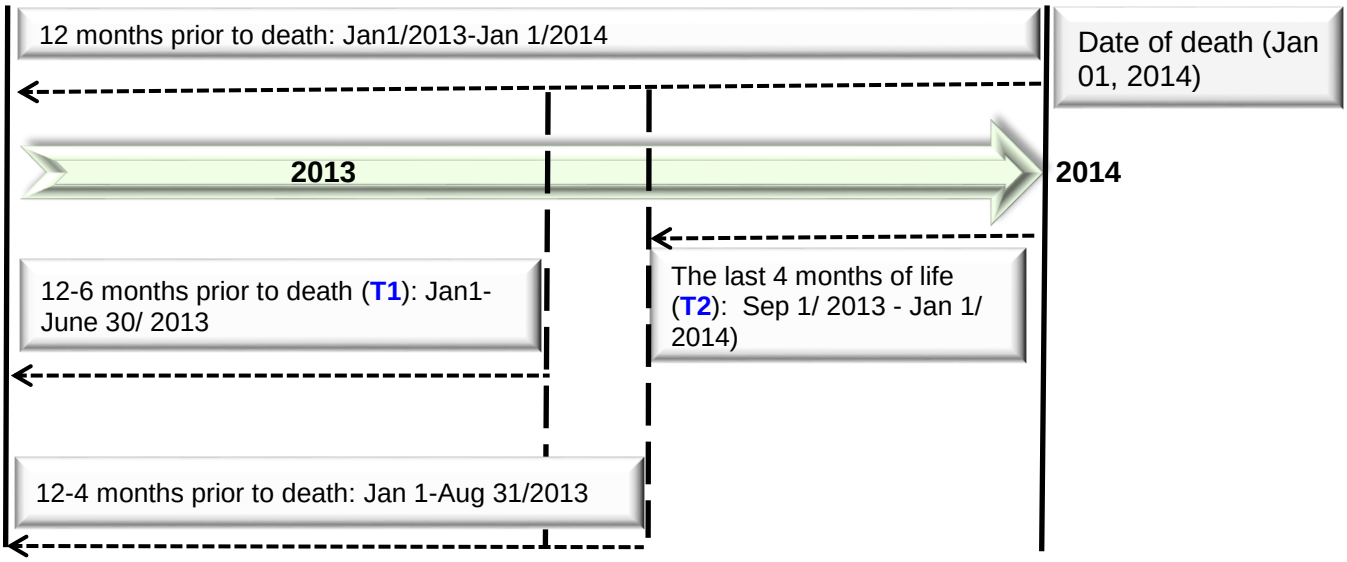


Fig.1: A retrospective timeline showing the time periods for defining chronic prescribing and deprescribing of PIMs at individual decedent level, using the example case of someone who died on January 1, 2014. Deprescribing is defined as at least two prescriptions (chronic continued use) in **T1** (12 to 6 months prior to death) and no prescriptions in **T2** (the last 4 months of life). The period between 6 and 4 months prior to death serves as "a validation window", during which medication use was not considered. In Belgium, prescriptions are typically valid for 3 months. To confirm actual discontinuation, we included data from the last 4 months of life. This is because if a resident had a dispension exactly 3 months prior to death, it would last until death. The final month before death is particularly informative, as it confirms whether a maximum 3-month prescription was renewed, indicating discontinuation. If a patient took the medication 12 months before death but restarted it at 5 months prior, this indicates intermittent use. However, our study does not focus on intermittent use when defining deprescribing. Rather, we define deprescribing by using chronic use as the denominator—specifically, patients with continuous medication use at T1, who then have no prescriptions during T2. Therefore, selected medication use between 6 and 4 months before death was not included in the study setup. However, other healthcare utilization data (hospitalization, intensive care unit, and emergency admission, and chronic medication use) were assessed from 12 to 4 months for descriptive and predictive analyses, whereas demographic variables were assessed at the time of death.

2.3.2. Interventions

We selected three guidelines—STOPPFrail, and the subsequent drug-specific guidelines on Antipsychotics, and PPI—to assess their impact on the deprescribing trend. We defined 2 consecutive interventions: intervention 1 was the publication of STOPPFrail (published on January 24, 2017) from February 2017 onwards (i.e. month 38 of the total 72-month observation period) and intervention 2 was the conduct of an international symposium on evidence-based deprescribing guidelines (held at the end of March 2018, hosted by the Bruyère Deprescribing Research team, which gathered over 130 participants from 10 countries, including Belgium, and focused on implementing and developing deprescribing guidelines) [27] from April 2018 onwards (i.e. month 52). This symposium preceded by

the uploading of guidelines, algorithms, and supportive documents to the deprescribing.org website for antipsychotics [23] and PPIs guidelines. [25]

2.3.3. Demographic and health care utilization of the decendents

The socio-demographic characteristics of the decedents at the time of death were provided in the dataset, including age, sex, highest attainable educational status, place of death, and causes of death.

- *Age was provided in 5-year categories starting from 65 years owing to data protection regulations, and we recategorized it into three groups: 65–74, 75–84, and ≥85 years.*
- *Educational status was recorded in the database based on the International Standard Classification of Education (ISCED)[35] and was recategorized into no formal education, primary education, secondary education, higher education, and unknown.*
- *Causes of death were identified using codes from the 10th revision of the International Classification of Diseases (ICD-10). Decedents were classified according to their underlying or contributory causes of death, distinguishing those potentially amenable to palliative care from those that were not. [36] The underlying causes of death were also used to classify based on whether the death was sudden/accidental or not. Given the high prevalence of dementia and cancer among nursing home residents, we identified residents with these conditions if their cause of death included dementia or cancer (see **Supplementary file 3.1** for the algorithmic definition of these measures the data sources for each variables).*

Health care utilization in the 12 - 4 months prior to death was assessed on the basis of:

- *Hospitalizations, emergency department visits, and intensive care unit (ICU) admissions, considering residents as admitted if they were transferred from a nursing home (see **Supplementary file 3.1** for the nomenclature codes used to define these measures).*
- *The number of concurrent chronic reimbursed medications used in the same period, including both PIMs and non-PIMs. Medication use was categorized as no polypharmacy (fewer than five medications), polypharmacy (5–9 medications), and excessive polypharmacy (ten or more medications).*

2.4. Data analysis

Descriptive statistics were employed to summarize the socio-demographic and healthcare utilization variables. For the trend analysis of at least one PIM deprescribed, we used the Joinpoint Regression Program version 5.0.2.[37] Joinpoint regression involves fitting multiple linear segments to data, with each segment representing a different trend. The points where these segments meet are called "Joinpoint." This method can test the statistical significance of changes in trends, providing insights into the effectiveness of deprescribing efforts. We calculated the average quarter percent change (AQPC) and 95% CIs as a summary measure of the trend over the overall observation periods. The AQPC was calculated using the weighted average of the slope coefficients for each linear segment of the underlying joinpoint regression model and this weighted average was transformed to a quarterly percent change (QPC). [38] We conducted a sensitivity analysis, excluding sudden or accidental causes of death.

An interrupted time series analyses was performed using SAS version 9.4 software (SAS Institute, Inc.) and SAS Enterprise Guide 8.3 to assess the impact of the guidelines. An Autoregressive Integrated

Moving Average (ARIMA) model was fitted based on the Box-Jenkins method.[39] Formal augmented dicky fuller test was used to assess the stationarity. We applied differencing to induce stationarity and eliminate trends and combined it with a log transformation to stabilize variance when differencing alone was insufficient.[40, 41] Subsequently, we determined the ARIMA model orders, denoted as ARIMA (p, d, q), where 'p' represents the autoregressive order (AR), 'd' represents the differencing order (I), and 'q' represents the moving average order (MA). We plotted the autocorrelation function (ACF) and partial autocorrelation function (PACF) of the stationary data to determine the potential AR/MA orders. The most appropriate model was selected on the basis of the lowest values of AIC (Akaike Information Criterion) and SBC (Schwarz Bayesian Criterion), ensuring that non-significant autocorrelation exists in the residuals for the Ljung-Box test for white noise.[41, 42] On the basis of this approach, we selected the final ARIMA models for individual medications selected to assess the impact of guidelines. The timeline for assessing the impact of PPIs and antipsychotics was divided into three segments: the pre-intervention period (months 1–37), the period after the first intervention (months 38–51), and the period after the second intervention (months 52–72). As intervention 2 did not relate to lipid modifying agents and calcium supplements, a 2 segmented timeline was used for that analysis. Accordingly, we fitted the model for the four medications: lipid modifying agents (ARIMA (1, 1, 1)), calcium on the log transformed data (ARIMA (1, 1, 2)), antipsychotics (ARIMA (1, 1, 1)), and PPI (ARIMA (1, 1, 0)). In addition to the AR and MA terms, we included an input variable, 'months since intervention,' in the model to see the impact of the intervention over time (slope change).

3. Results

3.1. Cohort Selection and characteristics of residents

A total of 244,865 individuals who received reimbursed care in a NH during their last years of life and who died between 2014 and 2019 were included in the analysis (**Fig.2**).

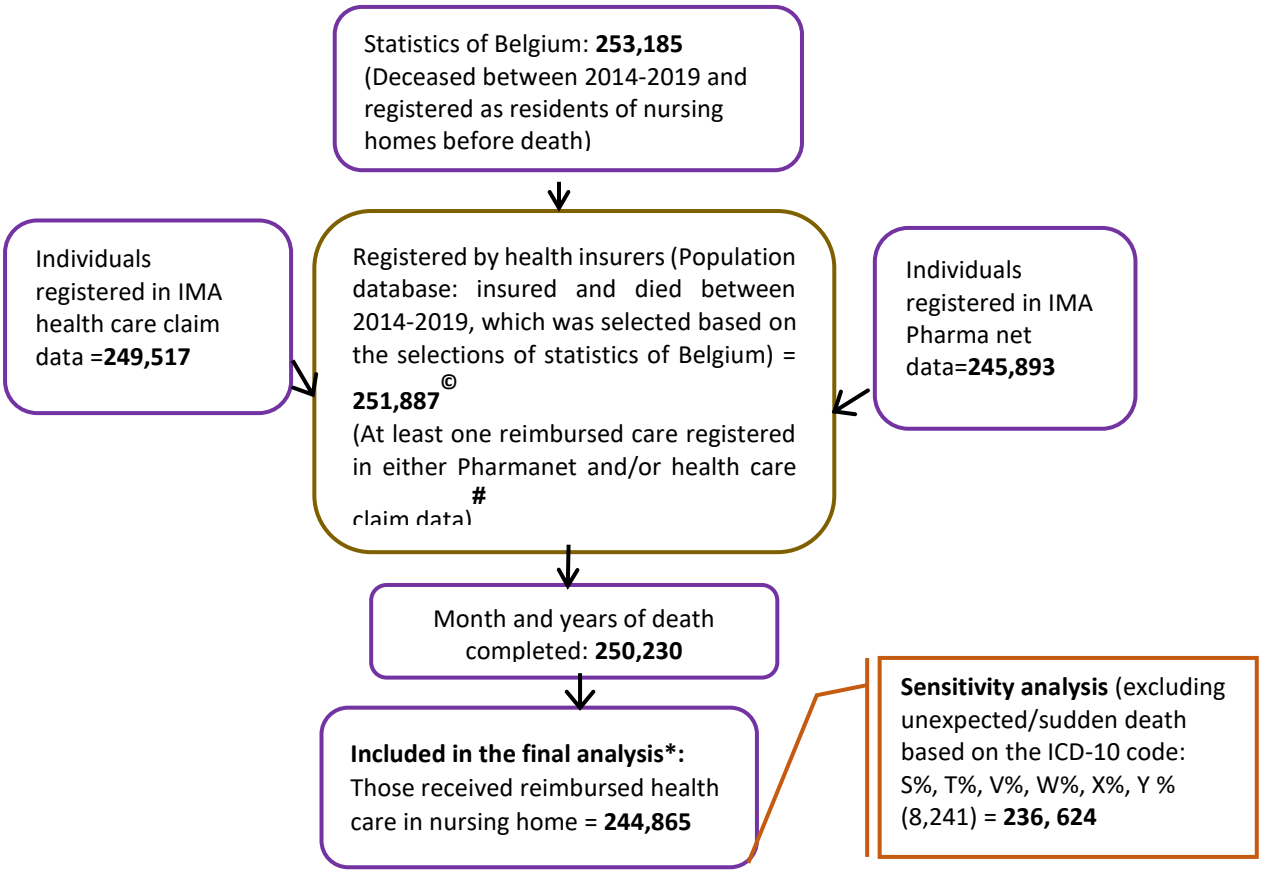


Fig.2: Cohort selection flow chart. ©StatBEL's data shows a higher number of NH residents because they include everyone, regardless of insurance status. In contrast, IMA's data is limited to insured residents actively using services, resulting in a lower count. # For individuals registered in Pharmanet community pharmacies delivered their medications. This is in case that the resident's family gets the medication themselves or the NH has an agreement with the community pharmacy to deliver all medications to the NH (245.893). For individuals registered in IMA health care claim, they receive medication from the hospital pharmacy because they 1) are admitted to hospital OR 2) are admitted to a NH that has an agreement with a hospital pharmacy to deliver the medication of all its residents. Thus, it is possible that the same resident receives medication from hospital when he/she is admitted there and medication from a community pharmacy while staying at the NH. * 5,365 the service provided at day care.

Of these, 165,798 (67.70%) were aged 85 years and above at the time of death, and 65.72% were female. Sudden/accidental causes contributed to 3.37% of deaths. During their last years of life, residents were chronically prescribed a median of 12 medications (IQR: 8–17). In the 6-12 months prior to death, 169,782 (69.30%) residents had at least 1 of the 15 PIMs prescribed. Of these, 50,487 (29.74%) residents had at least one PIM discontinued in the last 4 months. The proportion with a deprescription was higher when hospital, intensive care unit (ICU) or emergency department (ED) admission happened in the final 4 months (**Table 2**).

Table 2: Characteristics of deceased NH residents in Belgium (2014-2019, n=244,865), and the proportions receiving at least one PIM and having at least one PIM deprescribed.

Socio-demographic	Total included in the study[a]	At least one PIM prescribed 2X in the period 6-12 months prior to death[b]	At least one PIM deprescribed in the last 4 months (15 PIMs)[c]
Total	244,865 (100%)	169,782 (69.3%)	50,487 (29.7%)
Age			
65-74	15,166 (6.19 %)	11,595 (76.45 %)	3,753 (32.37 %)
75-84	63,901 (26.10 %)	47,179 (73.83 %)	15,389 (32.62 %)
85 and over	165,798 (67.71 %)	111,008 (66.95%)	31,345 (28.24%)
Sex			
Female	160,922 (65.72%)	111,837 (69.50%)	32,730 (29.27%)
Male	83,943 (34.28%)	57,945 (69.03%)	17,757 (30.64%)
Educational status			
No formal education	18,990(7.76%)	13,657(71.92%)	4,028(29.49%)
Primary education	89,598(36.59%)	63,490(70.86%)	18,555(29.23%)
Secondary education	85,721(35.01%)	58,392(68.12%)	17,707(30.32%)
Higher education	19,798(8.09%)	13,081(66.07%)	4,006(30.62%)
Unknown	30,758(12.56%)	21,162(68.80%)	6,191(29.26%)
Place of death			
Private house	7,857 (3.21%)	5,300 (67.46%)	1,881 (35.49%)
Hospital	68,209 (27.86%)	48,617 (71.28%)	14,827 (30.50%)
Institution	167,678 (68.48%)	115,120 (68.66%)	33,548 (29.14%)
Others	1,121 (0.46%)	745 (66.46%)	231 (31.01%)
Service and Clinical variables			
Sudden/accidental death			
No	236,624 (96.63%)	164,217 (69.40%)	48,950 (29.81%)
Yes	8,241 (3.37%)	5,565 (67.53%)	1,537 (27.62%)
Trajectory of illness			
Amenable to pallative care	188, 855 (77.13%)	131, 126 (69.43%)	39,662 (30.25%)
Not amenable to pallative care	56, 010 (22.87 %)	38, 656 (69.02 %)	10825 (28.00 %)
Cancer case			
No	209,542(85.57%)	145,351(69.37%)	41,533(28.57%)
Yes	35,323 (14.43%)	24,431(69.16%)	8,954(36.65%)
Dementia case			
No	198,116 (80.91%)	138,319 (69.82%)	41,887 (30.28%)
Yes	46,749 (19.09%)	31,463 (67.30%)	8,600 (27.33%)
Hospitalization (4 -12 months) prior to death.			
No	153,860 (62.83%)	101,842 (66.2%)	20,888 (20.51%)
Yes	91,005 (37.17%)	67,940 (74.65%)	29,599 (43.56%)
ICU admission (4 -12 months) prior to death.			
No	241,418 (98.59%)	167,133 (69.23%)	49,185 (29.43%)
Yes	3,447 (1.41%)	2,649 (76.85%)	1,302 (49.15%)
Emergency admission (4 -12 months) prior to death.			
No	154,987 (63.29%)	103,214 (66.6%)	22,620 (21.92%)
Yes	89,878 (36.71%)	66,568 (70.06%)	27,867 (41.86%)
Chronic medication use (4 -12 months) prior to death.			
< 5	44,565 (18.20%)	15,093 (33.87%)	3,047 (20.19%)
5-9	108,268 (44.22%)	75,016 (69.29 %)	16,964 (22.61%)
10 and above	92,032 (37.58%)	79,673 (86.57%)	30,476 (38.25%)
Number of medications in last years of life (median with IQR)	12 (8–17)	13 (9-18)	15 (11-21)

[a] Column percentage; [b] Row percentage

[c] Percentage expresses proportion of PIM users within each category for which at least one PIM was discontinued; IQR: Inter quartile range

3.2. Deprescribing trends of PIMs

Across all six observation years (2014-2019), at least 1 of the 15 PIM was discontinued for 50,487 residents (29.7%). Within the 15 PIMs, NSAIDs were most often discontinued (58.4%). PPIs were the most often prescribed PIM (37.6% of all residents) and the least often discontinued one (9.5%) **(Fig.3).**

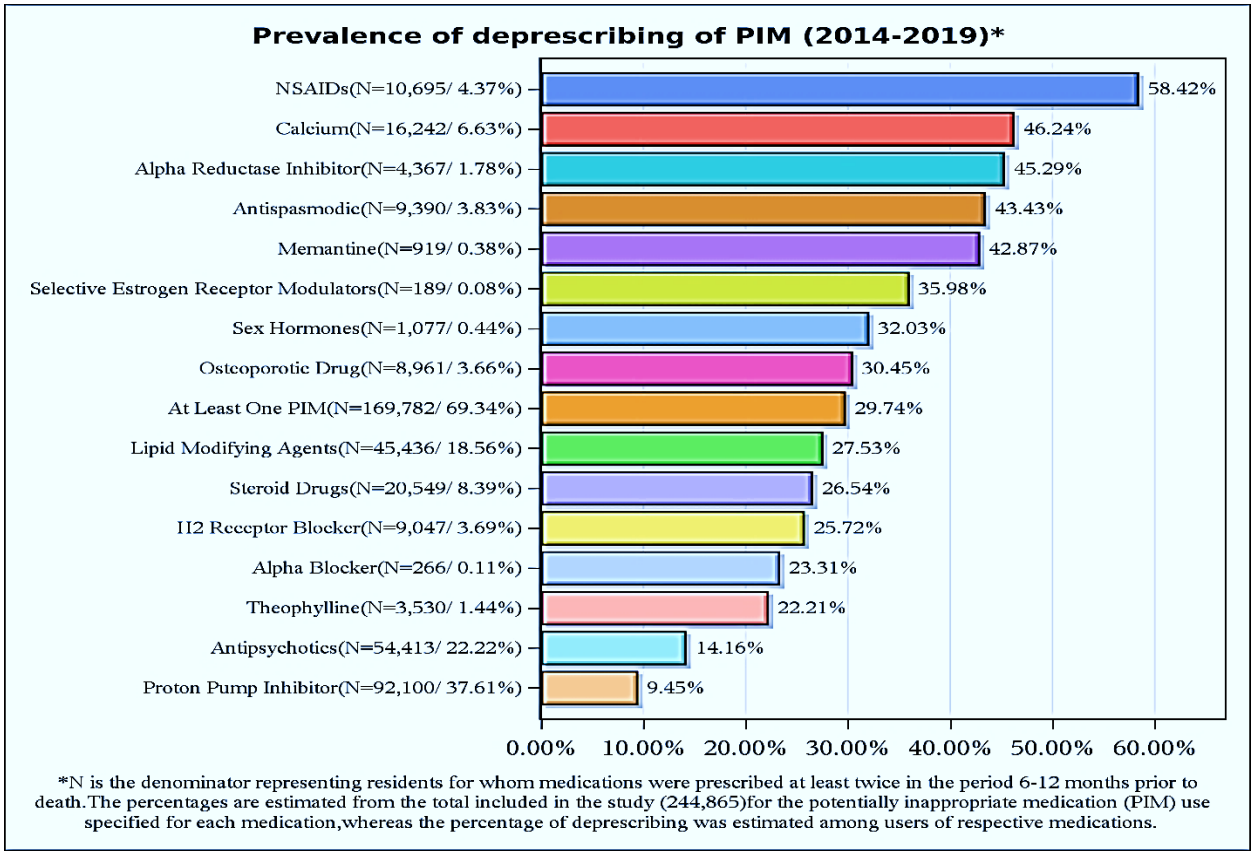
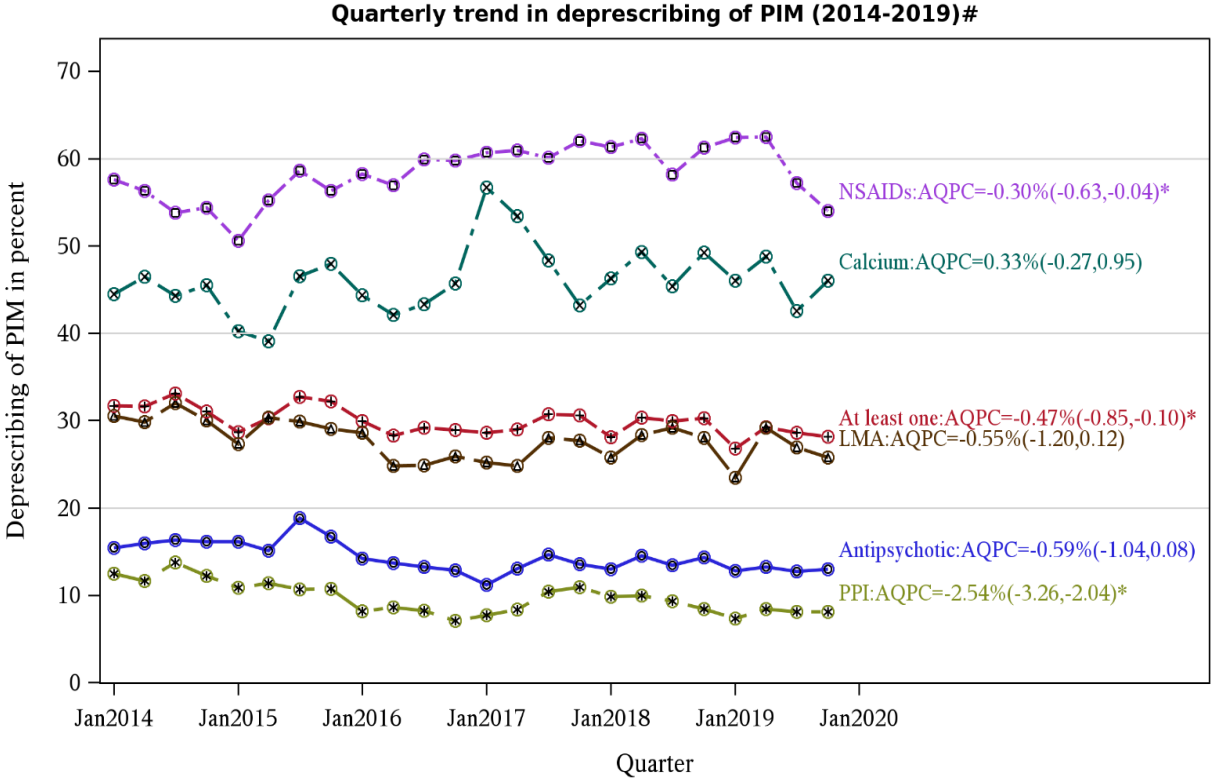


Fig.3: Prevalence of deprescribing of 15 potentially inappropriate medications over six years (2014-2019).

From the first quarter of 2014 to the fourth quarter of 2019, the prevalence of prescribing at least one PIM increased from 66.42% to 71.18%, with an AQPC of 0.31% (CI: 0.22%–0.42%), while deprescribing at least one PIM decreased from 31.7% to 27.66%, with an AQPC of -0.47% (CI: -0.85% to -0.10%). The analysis of the deprescribing trend showed no joinpoints, indicating a consistent linear trend without interruptions. At the individual PIM level, significant decreases were observed for NSAIDs (AQPC: -0.30, 95% CI: -0.63, -0.04) and PPIs (AQPC: -2.54, 95% CI: -3.26, -2.04). However, the AQPC for lipid modifying agents, calcium supplements, and antipsychotics was not significantly different from zero (**Fig.4**) (see **Supplementary file 3.2** for joinpoint analysis output). A sensitivity analysis excluding sudden or accidental deaths showed that the results were similar (**Supplementary file 3.2**).



#The percentages represent the proportion of PIM users who discontinued their respective PIMs. For 'At least one PIM deprescribed,' the percentage indicates the discontinuation among users of at least one PIM.\
*Significant decline in the trend\ NSAIDS: Non-Steroidal Anti-Inflammatory Drugs\ AQPC: average quarterly percent change\ LMA: Lipid modifying agents\ PPI: Proton pump inhibitors\

Fig.4: Quarterly deprescribing trends of at least one PIM and individual medications with corresponding average quarterly percent change based on Joinpoint regression analysis.

The trend of decreased deprescription was relatively consistent across different patient groups, although the decrease was significantly more noticeable in those residents that were 85+, had a low educational attainment and were hospitalized (**Supplementary file 3.3**).

3.3. Impact of the interventions': publication of deprescribing guidelines

The ARIMA modeling analysis found that the interventions did not significantly affect deprescribing rates for any of the medications studied (**Table 3**). After the publication of the STOPPFrail guidelines, each month calcium deprescribing rate was insignificantly increased by approximately 1 per 1,000 residents taking calcium chronically (estimated slope change of 0.99; 95% CI: -0.98 to 2.97; p = 0.6291). Similarly, for lipid-modifying agents, the estimate was insignificantly increased with a slope change of 0.24 (95% CI: -1.699 to 2.183; p = 0.8071).For PPI and antipsychotics, neither the STOPPFrail guidelines nor the drug-specific (PPI and Antipsychotics) deprescribing guidelines introduced a statistically significant change to deprescription rates. The STOPPFrail guideline estimates for PPIs and antipsychotics showed insignificant increments of the slope, 1.73 (95% CI: -2.526 to 5.976; p = 0.4263) and 1.305 (95% CI: -2.238 to 4.842; p = 0.4710) respectively. On the other hand, the drug-specific guideline estimates for PPIs and antipsychotics showed insignificant decrements of -2.52 (95% CI: -8.038 to 2.995; p = 0.3703) and -1.77 (95% CI: -6.425 to 2.881; p = 0.4555) respectively. The lack of a significant influence of the guidelines on deprescribing practices is visually evident from the similarity

between the counterfactual values (i.e., predicted values from our ARIMA model in the absence of the interventions) and the observed values (**Fig.5.**).

Table 3: Summary of ARIMA model fits and parameter estimates for deprescribing medications**.**

Medication	ARIMA model (p,d,q)[#]	Parameter included in the model*	Parameter estimate (95% CI)[@]	P-value for the estimate
Lipid modifying agents	ARIMA (1,1,1)	AR1,1	0.31 (0.001, 0.623)	0.0490
		MA1,1	0.85 (0.677, 1.029)	<.0001
		STOPPFrail	0.24 (-1.699, 2.183)	0.8071
Calcium	ARIMA (1,1,2)	AR1,1	0.39 (0.331, 0.452)	<.0001
		MA1,1	0.71 (0.530, 0.945)	0.0191
		MA1,2	1.6 (1.225, 2.079)	0.0005
		STOPPFrail	0.99 (-0.98, 2.97)	0.6291
Antipsychotics	ARIMA (0,1,1)	MA1,1	0.55 (0.347,0.749)	<.0001
		STOPPFrail	1.305 (-2.238, 4.842)	0.4710
		Antipsychotics guideline	-1.77 (-6.425, 2.881)	0.4555
Proton pump inhibitors	ARIMA (1, 1, 0)	AR1,1	-0.44 (-0.656,-0.231)	<0.0001
		STOPPFrail	1.73 (-2.526, 5.976)	0.4263
		PPI guideline	-2.52 (-8.038, 2.995)	0.3703

ARIMA: Autoregressive Integrated Moving Average, CI: confidence interval, PPI: proton pump inhibitors, STOPPFrail: Screening Tool of Older Persons Prescriptions in Frail adults with limited life expectancy

[#] Autoregressive Integrated Moving Average (ARIMA), denoted as ARIMA (p, d, q), where 'p' represents the autoregressive order (AR), indicating the number of past observations/lags included to predict the current value; 'd' represents the differencing order (I), indicating how many times the data series is differenced to achieve stationarity (i.e., to remove trends or seasonality); and 'q' represents the moving average order (MA), indicating the number of past forecast errors/lags considered to predict future values.

*The interventions involved only a slope change (i.e. months after the publication of the guidelines).

[@] The parameter estimate interpretation: although the trends did not change significantly after the publication of the guidelines, the positive estimate indicates that the number of deprescribing instances increased per month per 1,000 residents taking the medications, while the negative estimate, by contrast, indicates a decrease in deprescribing per month per 1,000 residents. For example, following the publication of the STOPPFrail guideline in February 2017, each month calcium deprescribing increased by approximately 1 per 1,000 residents among those taking calcium chronically (with an estimated slope change of 0.99 discontinuations; 95% CI -0.98 to 2.97), with a p-value of 0.6291, suggesting that the guideline did not have a statistically significant impact on calcium deprescribing, as the confidence interval includes zero and the p-value is well above the significance threshold. The ARIMA model for calcium (ARIMA (1, 1, 2)) includes p = 1 (AutoRegressive term), d = 1 (Differencing term), and q = 2 (Moving Average terms). In this model, p = 1 indicates that the current month's calcium deprescribing is influenced by the value of deprescribing in the previous month. The d = 1 suggests that the data was differenced from thier immediate prior values to make it stationary, meaning that trends or seasonality in the data were removed to allow for a more accurate model. The q = 2 indicates that the forecast errors from the two previous months are incorporated to predict the current month's deprescribing. The AR (1) term has an estimate of 0.39 (95% CI: 0.331, 0.452), with a p-value of <0.0001, indicating a significant positive relationship between calcium deprescribing in the current month and the previous month. This suggests that higher deprescribing rates in the prior month are associated with higher rates in the current month. The MA (1) term is estimated at 0.71 (95% CI: 0.530, 0.945), with a p-value of 0.0191, showing that forecast errors from the previous month have a significant positive influence on current deprescribing. Similarly, the MA (2) term has an estimate of 1.6 (95% CI: 1.225, 2.079), and a p-value of 0.0005, indicating that forecast errors from two months ago also significantly affect the current month's deprescribing, with a stronger influence.

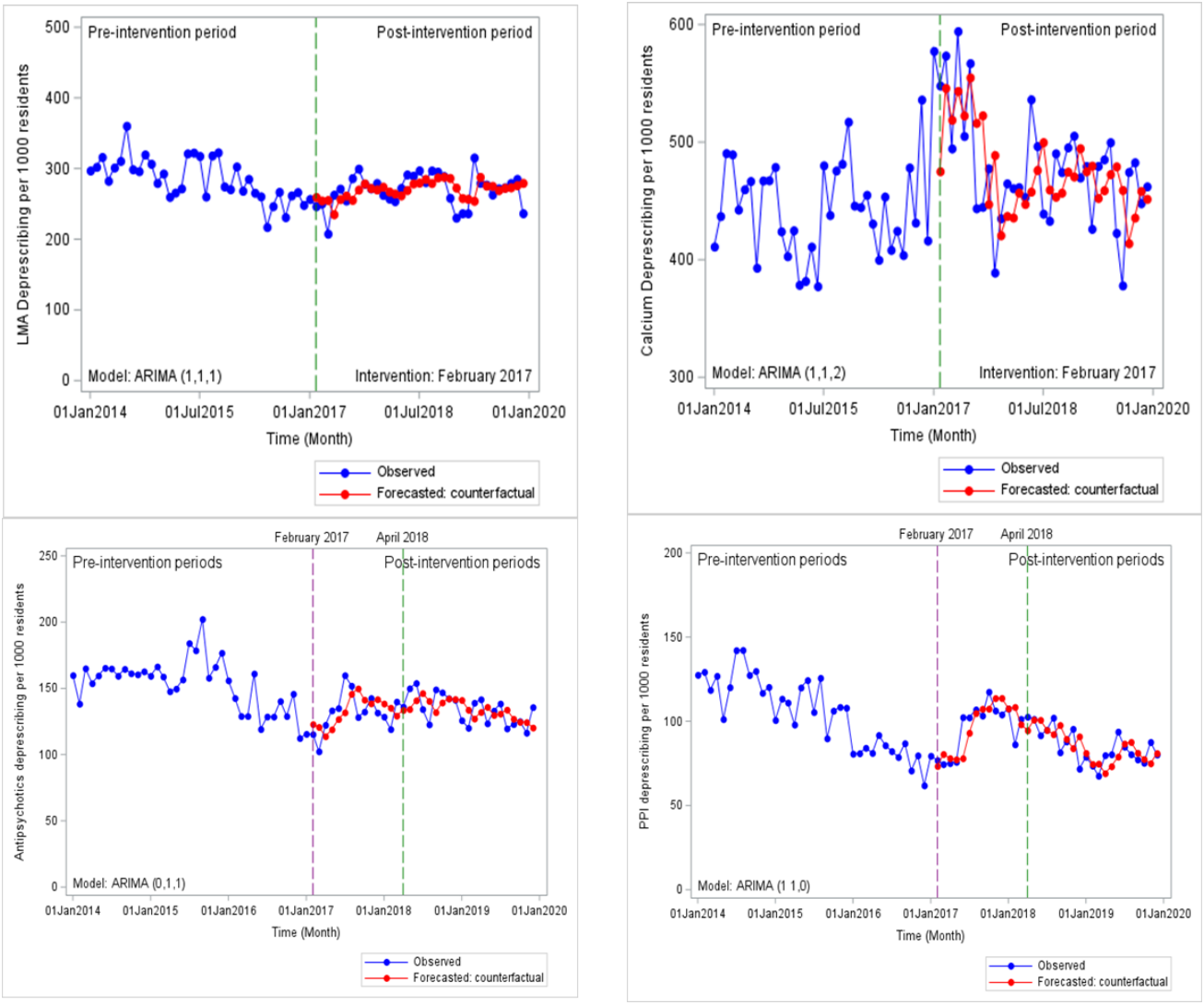


Fig.5: Monthly observed and counterfactual deprescribing rates per 1,000 residents based on the ARIMA model for four selected medications: lipid-modifying agent deprescribing (one intervention), calcium deprescribing (one intervention), antipsychotics deprescribing (two interventions), and proton pump inhibitor deprescribing (two interventions).

4. DISCUSSION

4.1. Key findings

Using nationwide linked administrative healthcare data from Belgium, our study found that the application of generic and drug-specific deprescription guidelines in our retrospective analysis showed that the publication of these guidelines did not influence the deprescription practices of PIMs in the final months of life in NH residents. Nevertheless, PIM use was shown to be frequent in the population with 69% taking at least one PIM. Across the period 2014-2019, 29.7% of deceased residents aged 65+ had at least one PIM discontinued in their final months of life. A small but statistically significant negative trend in deprescription practices was observed across this period with deprescription of at least one PIM declining from 31.7% to 27.66% (average quarter percent change of -0.47%). Joinpoint regression analysis revealed no significant joinpoints for at least one PIM, indicating no observable changes in the trend over time. Similarly, ARIMA analysis found no indications of any influence of the publication of deprescribing guidelines, including the STOPPFrail and Bruyère guidelines, on the deprescription of calcium supplements, lipid modifying agents, PPIs, or antipsychotics.

4.2. Strength and limitations

Our study used a comprehensive, population-level, linked healthcare administrative database in Belgium, with complete data coverage of reimbursed medication dispensation across hospital, NH, and home care settings. The quality, completeness and reliability of these data have been described elsewhere.[31] The data provided a unique opportunity to study real-world evidence about the impact of deprescribing guideline publications on actual practice, making this, to our knowledge, the first study to investigate this causal question. Interrupted time series designs are considered a suitable design to examine the causal influence of exposures to a full population such as nationally available guidelines or policies. Many time points (72) used in our study reduces the risk of history bias. [43] The study employs internationally recognized deprescribing tools (STOPPFrail and Bruyère guidelines), to assess the prevalence of deprescribing based on repeated measurements from 2014 to 2019. This approach enabled tracking of reimbursed medication dispensing and discontinuation up to one year prior to death, providing valuable insights into the dynamics of deprescribing over time.

Several limitations have to be acknowledged. First, the use of claims-based dispensing data provides relatively reliable information about reimbursed medications. However, some of the medications of interest, such as NSAIDs and calcium, are also available over-the-counter. This could potentially lead to a biased estimation of the prevalence of deprescribing if residents obtain these medications through prescriptions and subsequently purchase them over-the-counter. Nevertheless, since the study was conducted among institutionalized residents, it is likely that their prescriptions are filled through formal channels and that the use of over-the-counter medications is less common owing their cost. Thus, this limitation is unlikely to significantly impact the study's findings.[33]

Second, once a drug has been dispensed, there is no guarantee that it will be taken by the patient. To counterbalance this limitation, in accordance with studies on compliance using administrative databases, we defined discontinuation as occurring when a medication was dispensed at least twice within 6-12 months prior to death, with no dispensing in the last 4 months of life.[33] Measuring deprescribing solely by discontinuation could underestimate its prevalence because tapering or dose reductions are not captured. This limitation arises from the study lacking data on daily dosage and the total number of days the medication was prescribed. However, in Belgium, medications are typically valid for 3 months,[44] and by considering the number of prescriptions in the definition of discontinuation, the impact of this limitation on the study's findings was likely mitigated for most of the PIMs included in the analysis. Specifically for NSAIDs, which are considered PIMs if used long-term (>2 months),[20] chronic use in the current study was defined as two prescriptions. This approach could overestimate the prevalence of NSAID discontinuation, as NSAIDs are generally prescribed for shorter durations.

Third, owing to the retrospective nature of the study, our assessment of STOPPFrail was not fully comprehensive, as real-time clinical data were not taken into account and criteria were applied retrospectively. It could only be validly conducted for 15 of the 27 PIMs. Studies have shown that criteria not dependent on clinical information can be effectively used to identify PIMs through structured screening tools.[45] However, for the other 12 criteria, additional patient-level clinical information would have been necessary, but such information was inaccessible through our data. In addition, owing to statistical power, we were able to examine the interruption of trends for only four of the specific PIMs. However, the exploratory joinpoint analysis of individual medications revealed a

similar finding: the average quarterly percent change in deprescribing either decreased or remained unchanged, indicating no observable increasing trend over time. This provides overall insight into the impact of guidelines on the trends of all PIMs. The finding further raises questions about the quality of prescribing at nursing home levels, taking deprescribing as an indicator to monitor the quality of prescribing. Fourth, our study assumes eligibility for STOPPFrail criteria based on the deaths of the observed residents. While the disadvantages of assuming limiting life expectancy by looking back from actual death in decedent cohort studies have been discussed,[46] they are likely less a threat to the validity in a population of older NH residents in Belgium where older persons are typically admitted when staying at home is no longer feasible.[47] Moreover, our sensitivity analysis removing sudden and acute deaths indicated reliability of the findings.

Fifth, our analysis of trends was limited to data up until 2019. Hence, possible more recent trends in deprescribing and delayed impact of the guidelines (e.g. owing to increased familiarity with the guidelines) may have been missed. Nevertheless, up until 35 months after the publication of the guidelines no influence could be observed.

4.3. Interpretation of the findings

Deprescribing of PIMs has received increasing attention in the field of geriatrics and pharmacology.[48] This is particularly also the case in older adults with limited life expectancy where drug use is high, often involving adverse side-effects and incurring avoidable health care resources. The increased attention to identifying PIMs and deprescribing has resulted in several expert-validated lists. The question of whether the publication and spread of the guidelines have actually impacted deprescribing practices in the real world had remained unanswered before our study. Our study is the first to provide evidence that, on a population level, the publication of international deprescribing guideline in a real-world setting outside of clinical trials or pilot programs had no noticeable effects on practices up until 35 months after their publication. The publication of STOPPFrail and specific PIM deprescribing guidelines for PPI and antipsychotic deprescribing did not significantly impact deprescribing trends. This finding corroborates a Canadian study in long-term care homes that also observed no sustained reduction in PPI use 12 months after implementing a deprescribing guideline.[49] PPI use initially decreased but returned to baseline levels within six months, suggesting that sustaining deprescribing efforts is challenging. [49] Several factors may explain this limited impact in the real world. First, guidelines requiring medication reviews are often seen as complex and difficult to implement owing to a lack of time for proper review. Many healthcare professionals struggle to apply them effectively. [50] Second, while the guidelines were published and made available they have largely remained standalone guidelines without adequate implementation strategies, including their integration into broader clinical practice guidelines. [28] Third, the lack of effect of the guidelines is not a surprise from an implementation science perspective. It is clear that much more implementation strategy and effort, including whole-systems implementation approaches, are needed that go well beyond the mere publication and distribution of the guidelines in order to influence a new clinical practice and normalize these new behaviors [51, 52] to implementation frameworks or theories like Normalization Process Theory (NPT) [53] and Behavioral Change Techniques (BCTs).[54] Our finding that guideline publication has had no impact on deprescribing practices in NHs suggests that specific implementation efforts and strategies will be needed to change practices in complex care environments like nursing homes. These could include structured multidisciplinary approaches. Although the STOPPFrail guideline has not been translated or fully adapted to the Belgian context, a previous qualitative study

in Belgium suggested that prescribers (family physicians) had reported awareness of the guidelines.[55] The Belgian Centre for Pharmacotherapeutic Information (BCFI), with members of different universities, scientific organisations for physicians and pharmacists, and the Federal Agency for Medicines and Health Products (FAMHP), provides crucial information about medications for healthcare professionals, particularly regarding the use and deprescribing options of medications like PPIs. [56] Also, Bruyère's PPI guidelines are disseminated via their website. Additionally, an algorithm for antipsychotic prescribing and discontinuation, designed to reduce falls in older adults, was developed as an educational tool. [57] However, no national information or education campaign or translation into practice guideline was made.

5. CONCLUSION

Our study found no visible influence of the publication of deprescribing guidelines, including STOPPFrail, PPI, and antipsychotics guidelines, on deprescribing trends for key medication classes such as PPIs, antipsychotics, calcium, and lipid modifying agents. Even acknowledging some of the methodological limitations related to measurement of PIMs, the lack of an interruption in the time series after the publication of the deprescribing guidelines, zero joint points in the deprescribing trend over a six-year observation period, and even a consistent trend of decreased deprescription lend strong support to the hypothesis that the mere publications of deprescribing guidelines do not change deprescribing practices. This shows probably there are barriers to the wide implementation and reach of deprescribing guidelines which may be limiting the implementation of deprescribing into practice. If health care systems are truly concerned about the consequences of high use of PIMs and would like to see more appropriate timely deprescription of these medications, particularly in older people with limited life expectancy, more comprehensive implementation efforts and strategies are required that go well beyond guideline publication and spread.

References

1. Veehof L, Stewart R, Haaijer-Ruskamp F*, et al.* The development of polypharmacy. A longitudinal study. Fam Pract. 2000;17(3):261-7.
2. Morin L, Laroche ML, Texier G*, et al.* Prevalence of Potentially Inappropriate Medication Use in Older Adults Living in Nursing Homes: A Systematic Review. J Am Med Dir Assoc. 2016;17(9):862.e1-9.
3. Tamura BK, Bell CL, Inaba M*, et al.* Outcomes of Polypharmacy in Nursing Home Residents. Clin Geriatr Med. 2012;28(2):217-36.
4. Lion S, Evrard P, Foulon V*, et al.* Drug-drug interactions in nursing home residents: analysis from the COME-ON trial. Age Ageing. 2023;52(1).
5. Storms H, Marquet K, Aertgeerts B*, et al.* Prevalence of inappropriate medication use in residential long-term care facilities for the elderly: A systematic review. Eur J Gen Pract. 2017;23(1):69-77.
6. Anrys PMS, Strauven GC, Foulon V*, et al.* Potentially Inappropriate Prescribing in Belgian Nursing Homes: Prevalence and Associated Factors. J Am Med Dir Assoc. 2018;19(10):884-90.
7. Wallace E, McDowell R, Bennett K*, et al.* Impact of Potentially Inappropriate Prescribing on Adverse Drug Events, Health Related Quality of Life and Emergency Hospital Attendance in Older People Attending General Practice: A Prospective Cohort Study. The Journals of Gerontology: Series A. 2016;72(2):271-7.
8. Ruggiero C, Dell'Aquila G, Gasperini B*, et al.* Potentially inappropriate drug prescriptions and risk of hospitalization among older, Italian, nursing home residents: the ULISSE project. Drugs Aging. 2010;27(9):747-58.
9. Dalleur O, Spinewine A, Henrard S*, et al.* Inappropriate prescribing and related hospital admissions in frail older persons according to the STOPP and START criteria. Drugs Aging. 2012;29(10):829-37.
10. Guillot J, Justice AC, Gordon KS*, et al.* Contribution of Potentially Inappropriate Medications to Polypharmacy-Associated Risk of Mortality in Middle-Aged Patients: A National Cohort Study. J Gen Intern Med. 2024.
11. Alshammari H, Al-Saeed E, Ahmed Z*, et al.* Reviewing Potentially Inappropriate Medication in Hospitalized Patients Over 65 Using Explicit Criteria: A Systematic Literature Review. Drug, Healthcare and Patient Safety. 2021;13(null):183-210.
12. Hurley E, Dalton K, Byrne S*, et al.* Pharmacist-Led Deprescribing Using STOPPFrail for Frail Older Adults in Nursing Homes. J Am Med Dir Assoc. 2024;25(9):105122.
13. Roh E, Cota E, Lee JP*, et al.* Polypharmacy in Nursing Homes. Clin Geriatr Med. 2022;38(4):653-66.
14. Statbel en het Federaal Planbureau. Bevolkingsvooruitzichten 2023-2070 [updated February 13, 2024; cited 2024 April 08]. Available from: https://www.plan.be/databases/data-35-nl-bevolkingsvooruitzichten_2022_2070.
15. KCE Report 376: Performance of the Belgian health system – report 2024.
16. Anlay DZ, Paque K, Van Leeuwen E*, et al.* Tools and guidelines to assess the appropriateness of medication and aid deprescribing: An umbrella review. Br J Clin Pharmacol. 2024;90(1):12-106.
17. Nyborg G, Straand J, Klovning A*, et al.* The Norwegian general practice–nursing home criteria (NORGEP-NH) for potentially inappropriate medication use: a web-based Delphi study. Scand J Prim Health Care. 2015;33(2):134-41.
18. Khodyakov D, Ochoa A, Olivieri-Mui BL*, et al.* Screening tool of older person's prescriptions/screening tools to alert doctors to right treatment medication criteria modified for US nursing home setting. J Am Geriatr Soc. 2017;65(3):586-91.
19. Dijk MMT, A.M. Pouw CK, Hertogh CMPM*, et al.* Medication Appropriateness for Older Nursing Home Patients With a Limited Life Expectancy: From STOPP/START Version 2 to the ReNeWAL Criteria. J Am Med Dir Assoc. 2024:105143.
20. Lavan AH, Gallagher P, Parsons C*, et al.* STOPPFrail (Screening Tool of Older Persons Prescriptions in Frail adults with limited life expectancy): consensus validation. Age Ageing. 2017;46(4):600-7.
21. Morin L, Laroche ML, Vetrano DL*, et al.* Adequate, questionable, and inadequate drug prescribing for older adults at the end of life: a European expert consensus. Eur J Clin Pharmacol. 2018;74(10):1333-42.
22. Curtin D, Gallagher P, O'Mahony D. Deprescribing in older people approaching end-of-life: development and validation of STOPPFrail version 2. Age Ageing. 2021;50(2):465-71.
23. Bjerre LM, Farrell B, Hogel M*, et al.* Deprescribing antipsychotics for behavioural and psychological symptoms of dementia and insomnia: Evidence-based clinical practice guideline. Canadian family physician Medecin de famille canadien. 2018;64(1):17-27.
24. Tordoff JM, Ailabouni NJ, Browne DP*, et al.* Improvements in the prescribing of antipsychotics in dementia and psychogeriatric units in New Zealand. Int J Clin Pharm. 2016;38(4):941-9.
25. Farrell B, Pottie K, Thompson W*, et al.* Deprescribing proton pump inhibitors: evidence-based clinical practice guideline. Can Fam Physician. 2017;63(5):354-64.
26. Curtin D, Jennings E, Daunt R*, et al.* Deprescribing in older people approaching end of life: a randomized controlled trial using STOPPFrail criteria. J Am Geriatr Soc. 2020;68(4):762-9.
27. Farrell B, Conklin J, Dolovich L*, et al.* Deprescribing guidelines: An international symposium on development, implementation, research and health professional education. Research in Social and Administrative Pharmacy. 2019;15(6):780-9.
28. Langford AV, Warriach I, McEvoy AM*, et al.* What do clinical practice guidelines say about deprescribing? A scoping review. BMJ Qual Saf. 2024.
29. Evrard P, Damiaens A, Patey AM*, et al.* Barriers and enablers towards benzodiazepine-receptor agonists deprescribing in nursing homes: A qualitative study of stakeholder groups. Exploratory Research in Clinical and Social Pharmacy. 2023;9:100258.

30. Benchimol EI, Smeeth L, Guttmann A*, et al.* The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement. PLoS Med. 2015;12(10):e1001885.
31. Maetens A, De Schreye R, Faes K*, et al.* Using linked administrative and disease-specific databases to study end-of-life care on a population level. BMC Palliat Care. 2016;15:1-10.
32. Norwegian Institute of Public Health. ATC/DDD Index. Available from: https://atcddd.fhi.no/atc_ddd_index/. Accessed August 6, 2024. [
33. Paque K, De Schreye R, Elseviers M*, et al.* Discontinuation of medications at the end of life: A population study in Belgium, based on linked administrative databases. Br J Clin Pharmacol. 2019;85(4):827-37.
34. Deprescribing Guidelines and Algorithms. https://deprescribing.org/resources/deprescribing-guidelines-algorithms/ [cited 2022 /06/12].
35. UNESCO Institute for Statistics. International Standard Classification of Education: ISCED 2011 [Internet]. Montreal: UNESCO Institute for Statistics; 2012 [cited 2025 Feb 4]. Available from: http://uis.unesco.org/sites/default/files/documents/international-standard-classification-of-education-isced-2011-en.pdf.
36. Morin L, Aubry R, Frova L*, et al.* Estimating the need for palliative care at the population level: a cross-national study in 12 countries. Palliat Med. 2017;31(6):526-36.
37. Joinpoint Regression Program, Version 5.2.0.0. April, 2024; Statistical Research and Applications Branch, National Cancer Institute. https://surveillance.cancer.gov/joinpoint/ [
38. Clegg LX, Hankey BF, Tiwari R*, et al.* Estimating average annual per cent change in trend analysis. Stat Med. 2009;28(29):3670-82.
39. Box GEP, Jenkins GM, Reinsel GC. Time series analysis: forecasting and control. Hoboken, NJ: John Wiley & Sons, Inc.; 2008. https://doi.org/10.1002/9781118619193.
40. Liu T, Liu S, Shi L. ARIMA Modelling and Forecasting. In: Liu T, Liu S, Shi L, editors. Time Series Analysis Using SAS Enterprise Guide. Singapore: Springer Singapore; 2020. p. 61-85.
41. Schaffer AL, Dobbins TA, Pearson SA. Interrupted time series analysis using autoregressive integrated moving average (ARIMA) models: a guide for evaluating large-scale health interventions. BMC Med Res Methodol. 2021;21(1):58.
42. LJUNG GM, BOX GEP. On a measure of lack of fit in time series models. Biometrika. 1978;65(2):297-303.
43. Bernal JL, Cummins S, Gasparrini A. Interrupted time series regression for the evaluation of public health interventions: a tutorial. Int J Epidemiol. 2017;46(1):348-55.
44. Rijksinstituut voor ziekte- en invaliditeitsverzekering. Hoe lang kan u uw geneesmiddelen afhalen en vergoed krijgen? [cited 2024 27/10/]. Available from: https://www.riziv.fgov.be/nl/thema-s/verzorging-kosten-en-terugbetaling/wat-het-ziekenfonds-terugbetaalt/geneesmiddelen/geneesmiddel-voorschrijven/hoe-lang-kan-u-uw-geneesmiddelen-afhalen-en-vergoed-krijgen-.
45. Ryan C, O'Mahony D, O'Donovan DÓ*, et al.* A comparison of the application of STOPP/START to patients' drug lists with and without clinical information. Int J Clin Pharm. 2013;35(2):230-5.
46. Einav L, Finkelstein A, Mullainathan S*, et al.* Predictive modeling of U.S. health care spending in late life. Science. 2018;360(6396):1462-5.
47. Sciensano. Life Expectancy and Quality of Life: Life Expectancy, Health Status Report, 15 Jul 2024, Brussels, Belgium, https://www.healthybelgium.be/en/health-status/life-expectancy-and-quality-of-life/life-expectancy [
48. van Poelgeest E, Seppala L, Bahat G*, et al.* Optimizing pharmacotherapy and deprescribing strategies in older adults living with multimorbidity and polypharmacy: EuGMS SIG on pharmacology position paper. Eur Geriatr Med. 2023;14(6):1195-209.
49. Thompson W, Hogel M, Li Y*, et al.* Effect of a Proton Pump Inhibitor Deprescribing Guideline on Drug Usage and Costs in Long-Term Care. J Am Med Dir Assoc. 2016;17(7):673.e1-4.
50. Visser AGR, de-Bruijn JBGP, Spaetgens B*, et al.* Unlocking Deprescribing Potential in Nursing Homes: Insights from a Focus Group Study with Healthcare Professionals. Drugs Aging. 2024;41(3):261-70.
51. Thompson W, Reeve E. Deprescribing: Moving beyond barriers and facilitators. Research in Social and Administrative Pharmacy. 2022;18(3):2547-9.
52. Sawan M, Reeve E, Turner J*, et al.* A systems approach to identifying the challenges of implementing deprescribing in older adults across different health-care settings and countries: a narrative review. Expert Rev Clin Pharmacol. 2020;13(3):233-45.
53. Murray E, Treweek S, Pope C*, et al.* Normalisation process theory: a framework for developing, evaluating and implementing complex interventions. BMC Med. 2010;8(1):63.
54. Hansen CR, O'Mahony D, Kearney PM*, et al.* Identification of behaviour change techniques in deprescribing interventions: a systematic review and meta-analysis. Br J Clin Pharmacol. 2018;84(12):2716-28.
55. Anlay DZ, Peremans L, Cohen J*, et al.* Deprescribing for nursing home residents with limited life expectancy: A qualitative study to identify barriers and enablers for healthcare professionals. Geriatr Nurs. 2025;62(Pt B):1-11.
56. Belgian Centre for Pharmacotherapeutic Information (BCFI asbl). Deprescribing: Deel 2 Feburary 2015 [cited 2024/ 07/10]. Available from: https://farmaka.bcfi.be/frontend/files/publications/files/deprescribing-deel-2.pdf.
57. Expertisecentrum Val- en fractuurpreventie Vlaanderen (EVV), Departement Maatschappelijke Gezondheidszorg en Eerstelijnszorg, Academisch Centrum voor Verpleeg- en Vroedkunde (accentVV). Algoritme oordeelkundig gebruik antipsychotica i.k.v. valrisico bij ouderen Feburary 2017 [cited 2024/ 07/10]. Available from: https://www.preventiemethodieken.be/algoritme-oordeelkundig-gebruik-antipsychotica-ikv-valrisico-bij-ouderen.

Chapter 4

Deprescribing for nursing home residents with limited life expectancy: a qualitative study to identify barriers and enablers for healthcare professionals

Published:
Anlay DZ, Peremans L, Cohen J, Dilles T, Paque K. Deprescribing for nursing home residents with limited life expectancy: a qualitative study to identify barriers and enablers for healthcare professionals.
Geriatric Nursing 62 (2025)1-11. DOI: https://doi.org/10.1016/j.gerinurse.2025.01.049

Abstract

Nursing home residents with limited life expectancy often take many medications eligible to deprescribing. Deprescribing is crucial but not yet routinely implemented. Therefore, the aim of this study was to explore healthcare professionals (HCPs) barriers to and enablers for deprescribing and to identify theoretical domains for behavior change to be included into future interventions. A qualitative descriptive study using semi-structured interviews was conducted among 28 HCPs working in Belgian nursing homes. The data were analysed inductively using thematic analysis followed by mapping barriers and enablers to theoretical domain framework (TDF), and linking the domains to behavioral change techniques (BCTs). We identified multifaceted barriers and enablers across six themes: healthcare system and policy factors, resource- and organization-level factors, professional role and competency factors, interprofessional collaboration and communication factors, attitudes and perceptions towards deprescribing, and triadic dynamics in deprescribing. These barriers and enablers were mapped to 13 of the 14 TDF domains.

Keywords: Behavioral Change Technique (BCT); Deprescription; Healthcare Professional; Qualitative; Nursing Home; Theoretical Domains Framework (TDF)

Abbreviations

BCT: Behavioral Change Techniques, **HCP**: Healthcare Professional, **LLE**: Limited Life Expectancy, **NH**: Nursing Homes, **PIM**: Potentially Inappropriate Medication; **TDF**: Theoretical Domain Framework

Introduction

Polypharmacy, the concurrent use of five or more chronic medications with systemic effects,[1] is prevalent among nursing home (NH) residents. In recent years, due to policy and financial issues, NH primarily provide care for older persons with multimorbidity and serious functional disabilities, including difficulties in activities of daily living and cognitive impairment. The increasing care needs of these older individuals can no longer be met at home. Therefore, those admitted to NHs often suffer from frailty and deteriorated health, and they have limited life expectancy (LLE).[2, 3] Additional medications for symptom management are prescribed, contributing to a high prevalence of polypharmacy in NH residents with LLE (25% - 88%).[4-7] These populations are at higher risk of potentially inappropriate medication (PIM) use associated with adverse health outcomes such as hospitalization, falls, mortality, and reduced quality of life. [8, 9] PIMs are potential candidates for deprescribing,[10] which is defined as *"the systematic process of identifying and discontinuing drugs in instances in which existing or potential harms outweigh existing or potential benefits within the context of an individual patient's care goals, current level of functioning, life expectancy, values, and preferences".*[11]

Previous studies have demonstrated that deprescribing of PIM is safe, feasible, and likely beneficial for the patients, as it can reduce mortality, hospitalization, and fall in different settings including in NHs.[12-14] Tools, guidelines, and criteria exist to help clinicians deprescribe PIM in older persons with LLE (e.g., STOPPFrail).[15, 16] However, deprescribing is not yet a routine practice and the rates remain low. [17, 18] An expert review highlighted the need to improve deprescribing implementation and translation in clinical practice across healthcare systems. [19] One suggested strategies is to identify context-specific barriers and enablers across countries and settings. Healthcare professionals (HCPs) are key players in deprescribing.

In Belgian NHs, a mix of permanent and temporary staff manages resident care, with both types of nursing staff handling residents' daily health and personal care needs. Family physicians (FPs) are not stationed on-site full-time; instead, each resident can freely choose their own FP. Most residents continue to be treated by their personal FP, allowing a diverse group of FPs to visit each NH without restrictions on the number providing care. Each FP independently manages the diagnosis and treatment of their respective patients, including prescribing medications, with visits based on each resident's health requirements and preferences and coordinated through communication with the resident, family and NH staff. Additionally, every NH in Belgium is required to appoint a Coordinating and Consulting Physician (CCP), who oversees the NHs medical policy, supports clinical care, and who is allowed to provide general recommendations regarding treatment to the visiting FPs. However, following the CCP's recommendations is not mandatory for these FPs. The CCP also acts as the main contact for NH staff and may step in as a resident's primary physician if their usual FP becomes unavailable. Medications for all residents are supplied by a designated pharmacy, either community- or hospital-based, but because medication review activities are generally unfunded, the pharmacist's role is primarily limited to medication delivery rather than comprehensive review. This complex organization of care in Belgian NHs likely contributes to deprescribing challenges, underscoring the need for context-based research to identify potential barriers and enablers for healthcare providers in deprescribing medications.[20-22]

Studies have explored HCPs perspectives on deprescribing barriers and enablers; however, these studies mainly focus on primary care settings, which may not fully transferable to NH contexts or on

long-term care facilities that lack an end-of-life care focus. [23-26] Evidence is particularly limited for NH residents with LLE or end-of-life needs. [27, 28] Similarly, in Belgium, research on deprescribing barriers and enablers in NHs has focused on specific drug classes, such as benzodiazepine-receptor agonists, [22] with no studies specifically addressing barriers and enablers related to end-of-life care in NH settings.

To effectively implement evidence-informed practice, it is essential to begin by comprehensively understanding the problems.[29] Behavioral and implementation science can help translate this knowledge into sustainable interventions in practice.[19] The Theoretical Domains Framework (TDF) explores the factors influencing HCPs behavior in implementing evidence-based recommendations.[30, 31] It can provide a perspective on the affective, cognitive, social, and environmental determinants of behavior. [32] Using TDF allows for theory-based intervention development, where domains are linked to behavior change techniques (BCTs) that form the intervention components and support the transition from exploring deprescribing barriers and enablers to intervention.[32] Therefore the aim of this study was to explore HCPs barriers to and enablers for deprescribing medications for NH residents with LLE, and using TDF identify theoretical domains and map these domains to BCTs (intervention components), which could be utilized in the future deprescribing interventions to target behaviour change.

Methods

Study design

A qualitative descriptive study was conducted using semi- structured interviews. This study was reported in accordance with the Consolidated criteria for Reporting Qualitative research (COREQ).[33]

Study setting and sampling

We interviewed a purposive sample of HCPs deemed to be involved in deprescribing decisions in NHs in Flanders, Belgium. We sent an invitation letter with a Qualtrics survey link to various care organizations, networks, and professional associations by email. The directors or senior managers forwarded the invitation to their employees and/or members. We identified eligible HCPs who were interested based on their registration responses (**Supplementary file 4.1**).

The eligibility criteria were:

- Physicians who treated NH residents as family physician, geriatrician, or coordinating and consulting physicians
- Nurses who worked in a NH
- Pharmacists who delivered medication to a NH
- Physicians and nurses who had at least one year of experience

To get a broader insight into the barriers and enablers of deprescribing, we selected a heterogeneous group of HCPs for interviews based on years of experience in their current working profession (<10 or >10 years), palliative care training (received or not received), and for physicians (family physician versus geriatrician versus coordinating and consulting physician). Using these criteria, we invited participants in the order in which they filled out the survey, emailing each with an informed consent form, an information sheet, and a scheduled interview time, along with the Zoom link. Selected participants had no prior contact or collaboration with researchers and/or interviewer.

Data collection

A semi-structured interview guide was developed based on a literature review of barriers and enablers to deprescribing medications. The guide included general questions and TDF-guided prompts to elicit HCPs experiences, views, and perspectives on deprescribing (**Supplementary file 4.2**).[34] Before and after the pilot interview, conducted by two interviewers—CP, a nurse, and GV, a psychologist—the research team discussed the guide and confirmed its clarity without requiring any modifications. All interviews took place online via Zoom Video Meeting, with audio recordings and field notes being taken. We conducted interviews from January 2021 to May 2022 until data saturation was reached. [35]

Data analyses

Interviews were transcribed verbatim and analysed with NVivo 1.6.1. The analysis was concurrent with data collection to explore new themes in subsequent interviews.[35] The analysis involved the following stages:

Thematic analysis

In the first stage, using Braun and Clarke's thematic analysis,[36] we identified themes by generating initial codes from transcripts, identifying deprescribing barriers and enablers. A code tree was developed based on these codes. Additional codes from other interviews were added to the code tree, leading to theme identification. The codes were merged into themes. Initially, the coding was done separately for physicians, nurses and pharmacists, and then the codes from each group of HCPs were combined within the themes. The first two interviews of every group of HCPs were independently coded by two researchers (DZA and KP or CP and KP). For the subsequent interviews, either DZA or CP performed the analysis, while KP checked and provided input. To enhance reflexivity and to resolve disagreements in the analysis process, codes were regularly reviewed and discussed with the research team. The personal and professional views and expertise of the research team were diverse, as it consisted of three nurses (DA, TD, KP), a family physician (LP) and a sociologist (JC) with in-depth knowledge and expertise in clinical pharmacology (DA, TD, KP, LP), palliative and end-of-life care (DA, KP, LP, JC) and qualitative research (KP, JC, LP). We regularly reflected on our findings and interpretation of these findings in the research team, and we used a reflexive journal. Thus, researchers' characteristics and reflections have potentially affected our study results, without jeopardising rigour. Additionally, the link between these codes and the assigned themes was discussed, and appropriate names and descriptions for themes were provided. Finally, we employed an approach where we identified that these themes occur at three levels: Macro-level factors (legal, regulatory, policy, economic barriers, and enablers at the national/international level), Meso-level factors (local institutional factors defining service delivery within NHs), and Micro-level factors (day-to-day practices and attributes of HCPs within the HCP-resident interface).[37]

Linking barriers and enablers of deprescribing to theoretical domain framework

In a second, deductive, stage the determinants (barriers and enablers) of deprescribing within each of the inductive themes were mapped to the TDF domains based on the definition provided by Cane *et al.* [31] We used the second version of TDF which included 14 domains and each domain involved a varying number of constructs.[32]

Mapping TDF domains to behavioral change techniques

In the third stage, the TDF domains linked to the determinants of deprescribing in stage 2 were mapped to BCTs, using previous studies as guidance.[34, 38, 39] Multiple BCTs were suggested for each targeted domain in these literatures. We mapped and presented the selected BCTs to these domains,

considering local contexts and the level of influence on the target behaviour, with the aim of integrating deprescribing into routine practice. All members of the research team independently mapped the barriers and enablers to the TDF, and then mapped the TDF to the intervention components (BCTs). The most frequently selected BCTs for each domain were reported in this study as prioritized interventions. Any discrepancies in selections and mappings were discussed and resolved during research team meetings.

Results

Selection and characterstics of participants

A total of 63 HCPs (27 physicians, 25 nurses, and 11 pharmacists) were screened for eligibility through a qualtrics survey. Among them, 27 physicians, 17 nurses, and 6 pharmacists met the eligibility criteria. In total, we interviewed 28 HCPs **(Table 1)**. The interviews had a median duration of 54 minutes, ranging from 40 to 120 minutes.

Table 1: Characteristics of study participants (n=28)

Characteristics	Number of participants
Age in years (median with interquartile range)	44 (33-69)
Sex	
Male	10
Female	18
Professional role	
physicians (total):	18
Family physicians	6
physician with coordinating and consulting role in nursing homes	7
Geriatrician	5
Pharmacist	6
Nurse	4
Years of professional experience	
≤ 5	4
6-10	7
>10	17
Primary work setting	
General practice	11
Palliative setting	3
Geriatric setting/ward	4
Community pharmacy	6
Nursing home	4
Experience with deprescribing at the end of life	
Yes	22
No	6
Work with the Global Medical Record(GMR)/ Global Pharmaceutical Record (GPR)[a]	
Yes	9
No	13
Training related to palliative care	
Yes	17
No	11
LEIF doctor/nurse[b]	
Yes	18
No	6

[a]GMD is a comprehensive electronic summary of current health status, created by the family physicians. A Global Pharmaceutical Record (GPD) is an electronic summary of all the medications the patient has been prescribed in Belgium. It contains information about the medication name, dosage, duration of treatment, and prescribing physician (n=22)
[b]**L**evens**E**inde **I**nformation**F**orum (LEIF) doctor/nurse (n=24)

- An open initiative of people and associations that strive for a dignified end of life for everyone, with respect for the patient's will as a top priority. They provide information and support to both patients and healthcare providers on end-of-life care and advance care planning
- Undergoing training on the problems of euthanasia, end-of-life decisions and who know the possibilities of palliative care.

Barriers and enablers of deprescribing

Six interlinked themes related to deprescribing barriers and enablers were identified at macro, meso, and micro levels (**Fig.1)**. Within these six themes, we identified 33 barriers and 13 enablers to deprescribing.

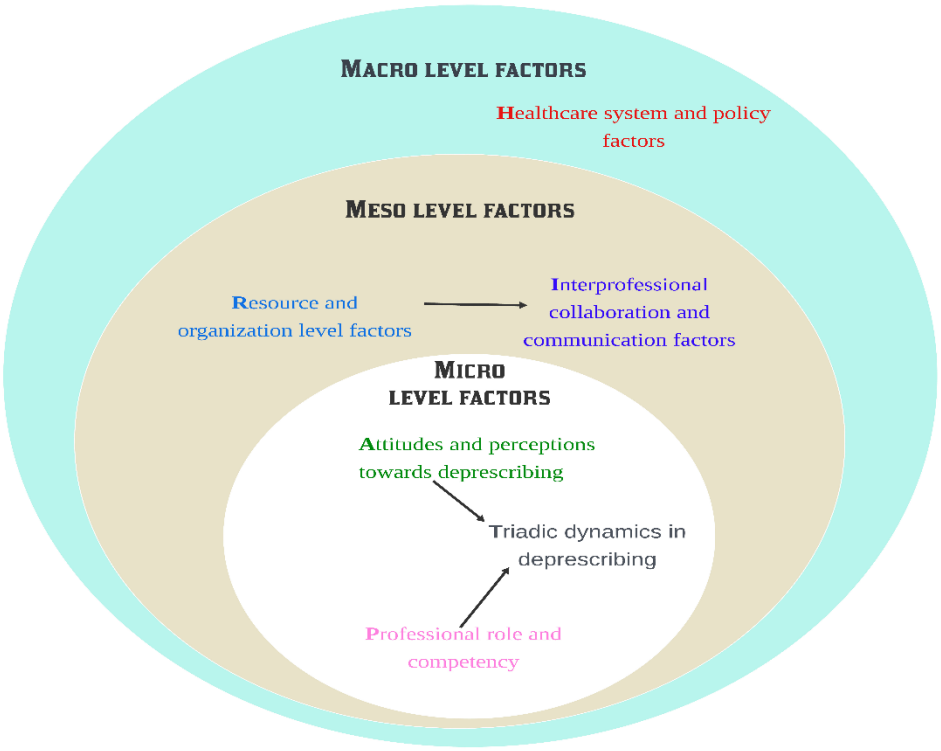


Fig.1: Relationship between the six themes identified at the macro, meso, and micro-levels. The macro level influences meso and micro-level factors, and the meso level impacts micro-level factors. Arrows within the circles of the meso and micro levels indicate the influence of themes on each other

Theme 1: Healthcare system and policy factors

In NHs, participants described the absence of a clear and organized approach to review medications, as well as the lack of specific deprescribing guidelines tailored to the Flemish context as a barrier to deprescribing medications. They highlighted that existing tools in the literature, such as STOPPFrail or Beers criteria, are unclear and complex. Using these tools is time-consuming, and their implementation in routine practice is limited. Therefore, physicians seldom use them based on their own initiatives.

"It's not that easy you know, towards stopping specifically, it is searching yourself for a good guideline. I do have a programme that shows the interactions but those things I don't think are so handy yet at the moment." (Family physician 3)

They also described that there is unclear guidance on pharmacy engagement in medication reviews and a lack of incentives for pharmacists to undertake reviews. In recent years, more time and resources have been dedicated to developing policies for COVID-19, with less emphasis on addressing inappropriate polypharmacy. Despite these barriers, participants noted that the mandatory requirement for NHs to appoint coordinating and consulting physicians can potentially facilitate the deprescription of medications by alerting treating family physicians to the residents inappropriate polypharmacy.

"And a coordinating and consulting physician too, they do a lot as well… They… write in every file that family physician needs to motivate [his decision] if he prescribes more than 5 drugs, and they also offer courses to nurses about polypharmacy… That's a doctor, they go all the way and spur the nurses on [to do the same]." (Nurse 2)

Theme 2: Resource and organization level factors

At the NH level, HCPs described resource constraints, such as limited staff, that lead to increased workload and insufficient time for medication review and deprescribing as barriers. Moreover, they expressed that a systematic approach to medication review and deprescribing is often not a priority in NHs.

"Yeah, this (medication review) is something you cannot do in two minutes. You have to check the whole medication list and apply those criteria (STOPPFrail or Beers) to the list. That takes at least 15 minutes to half an hour … It's difficult to find the time to apply these criteria to the (patient's) medication list…" (Family physician 5)

Deprescribing is a complex and individualized process that participants perceive hospitalization and NH admission as ideal for. However, they report poor documentation systems in the NH that limit medication information sharing among HCPs. For example, pharmacists cannot access the residents' medical file and base their deprescribing suggestions only on the medication chart.

"Pharmacists don't have access to the medical file of the residents, so if they suggest something [they do so] without knowing the medical file and then some suggestions simply don't make sense." (Coordinating and consulting physician 2)

Theme 3: Professional role and competency factors

Participants expressed that family physicians, who were considered to be primarily responsible for deprescribing medications, lacked the knowledge and expertise to initiate deprescribing. This limits their confidence to engage practically in deprescribing in NHs. Similarly, nurses, who act as advocates for their residents, faced a knowledge gap in pharmacology. They were also constrained by legal boundaries that do not allow them to (de)prescribe, leading them to perceive deprescribing as not within their role. According to coordinating and consulting physicians, and pharmacists' views, if nurses possess the necessary knowledge about medications and their residents' conditions, they can play an important role in deprescribing.

Pharmacists' training and expertise in pharmacology were perceived as crucial for deprescribing. Despite their valuable knowledge of pharmacokinetics and pharmacodynamics, barriers such as

unclear involvement and limited presence in NHs hindered their ability to contribute to informed deprescribing decisions within multidisciplinary teams.

> *"I have worked with clinical pharmacists myself in the ward and the vision of a pharmacist is the one of the pharmacy so a little less with the medical background that we work with. They do have a good vision on interactions and indications." (Geriatrician 1)*

The coordinating and consulting physician described their role as primarily limited to coordinating and providing advice regarding patients' medications, including discontinuation. However, they do not have the authority to make decisions on behalf of the family physician. Consequently, the impact of their role depends on the prescribing behavior of the family physician.

> *"I am a coordinating and consulting physician so I'm definitely very much dependent on the prescription behaviour of my colleagues. And maybe, to me, that's a hindrance." (Coordinating and consulting physician 1)*

Theme 4: Interprofessional collaboration and communication factors

Participants recognized the importance of interdisciplinary collaboration and communication in the deprescribing process, despite expressing doubts about the knowledge and skills of other professions in this area. They acknowledged that each HCPs could bring a distinct contribution to the deprescribing process. Family physicians were seen as primarily responsible for making deprescribing decisions, gathering input from other HCPs. Geriatricians could provide support and advice to family physicians, particularly in more complex cases. Nurses played a proactive role by providing critical observations and questioning the continued use of potentially non-beneficial medications. Coordinating and consulting physicians, who closely review medication charts, can play an important role in deprescribing by sharing expertise and giving advice to treating family physicians through alerts about inappropriate polypharmacy. Pharmacists contributed by conducting detailed medication reviews and offering suggestions for deprescribing using their pharmacokinetics and pharmacodynamics knowledge.

> *"I think it would be useful that there is a systematic screening of medication-related problems by the nurses and that could be a kind of cascade system where that indeed the pharmacist is contacted. The pharmacist checks the medication regimen, and then that can be discussed with the doctor. Either the nurse alone with the doctor, or a multidisciplinary consultation. And I am still in favour of a multidisciplinary consultation." (Pharmacist 5)*

> *"I know that my colleagues in hospital organize separate consultations for medication review to support the family physician in that (deprescribing)." (Geriatrician 3)*

HCPs also described barriers to interprofessional collaboration. For example, the limited time family physicians allocate during resident visits hampers knowledge exchange and interdisciplinary communication. Additionally, there is a lack of trust and recognition of nurses, particularly by family physicians. The protective attitude of physicians towards involving nurses in prescribing and deprescribing, along with a hierarchical relationship where more senior physicians are not questioned, further accentuates the challenges in nurse involvement in deprescribing.

Nurses themselves indicated that interdisciplinary collaboration could run more smoothly if they were involved in the NH medication policy and if their recommendations for deprescribing are accepted. However, nurses sometimes feel powerless in dealing with medication policies. They emphasize the

importance of open communication with family physicians, where they would be respected for their critical attitude. However, often, their knowledge and expertise are not fully recognized.

> *"I find that residents are taking a lot of medication and that they (FPs) don't always critically examine whether it's all still necessary. And you can make a suggestion once, depending on the FP, to maybe change or stop, but usually the initiative comes from the FP" (Nurse 3)*

> *"There is still a generation of physicians in an ivory tower and they have difficulties when nurses give their opinion on it." (Nurse 1)*

HCPs reported a gap in the relationship and communication between settings, where the treating physician has less contact with NH residents, creating uncertainty about who is responsible for deprescribing. Family physicians hesitate to deprescribe medications prescribed by others, as they do not want to question their colleagues' expertise. Another reason described for this reluctance was a lack of knowledge about the indications due to poor communication.

> *"Sometimes we do get a little despondent, of course. If, indeed, a physician doesn't even visit his residents, how can you discuss medication policy? … There are a lot of frustrations though in that department. And the most frustrating thing is your own inability of course." (Nurse 4)*

Theme 5: Triadic dynamics in deprescribing

Participants expressed that the interplay between residents, families, and HCPs is crucial for deprescribing decisions. They emphasized that aligning decisions with residents' and families' treatment goals is paramount and that involving them facilitates deprescribing. Early discussions with residents and their families, by easing conversations, help to build trust and facilitate deprescribing medications. However, cognitive impairment often hinders shared decision-making with NH residents, and HCPs advocate the integration of deprescribing into advance care planning.

> *"I think that (NH residents) are not always capable to take a patient-centred deprescribing decision. You do try to involve them, but if they are left out a little cognitively, you can't always mention that to the patient." (Family physician 3)*

Participants highlighted that deprescribing is influenced by patient-family attitudes. Residents fear and resist deprescribing certain medications, such as benzodiazepines, psychotropic medications, and pain medications, due to concerns about consequences. They also expressed that family members frequently oppose deprescribing, interpreting it as an indication that the physician has given up on their loved ones. This perception, equating deprescribing with a withdrawal of care, impacts HCPs' engagement in the deprescribing process.

> *"The family thinks that if we stop medication, we are going to immediately, in fact, see their mom or dad deteriorate, and that is often not the case. Those people already have dementia; they are not going to get better, and we see that very often too." (Pharmacist 2)*

Theme 6: Attitudes and perceptions towards deprescribing

HCPs perceived that deprescribing makes care more complex and emotionally challenging. Fear of negative outcomes from deprescribing was a common barrier for them. Participants also faced dilemmas with residents or families who had different views on deprescribing. HCPs shared similar beliefs and attitudes towards medication use at the end of life. They viewed deprescribing as having the potential to enhance the quality of life for residents, and noted that this aligned with the goals of NH residents at the end of life. This positive view made them open to non-pharmacological

alternatives that could allow for a reduction in the number of medications, suggesting the incorporation of deprescribing into a palliative care model.

> *"They are after all two programs/courses that are based on geriatrics, on end-of-life, palliative care so I do absolutely have. I think in that way I'm also more open to euthanasia, palliative sedation, indeed stopping medication, starting pain medication, comfort that really comes in first at the end of life. A holistic approach as well, I think that has helped me a lot." (Coordinating and consulting physician 3)*

Nurses value the quality of life of residents at the end of life and generally hold a positive view of deprescribing, which contributes to facilitating the deprescribing process. However, when non-pharmacological interventions are perceived to increase nurses' workload due to residents' behavior, especially in cases of behavioral and psychological symptoms of dementia, they often request physicians to (re) initiate medications such as antipsychotics.

> *"… I also want to work around non-pharmaceutical treatments in the context of aggression, restlessness. And then we also see things again that family physician has less information on. It's quickly like that one is restless, so we're starting medication. But sometimes, it does ask a little more time of us as caretakers and I will say that [we] don't always have that…" (Nurse 3)*

Mapping barriers and enablers to the relevant TDF domains

The identified determinants of deprescribing (33 barriers and 13 enablers) were mapped into 13 of the 14 TDF domains. Most barriers and enablers were mapped to "environmental context and resources", "belief about capability", "social/professional role and identity", "memory, attention and decision processes", and "knowledge" domains. **Table 2** shows barriers and enablers to deprescribing per theme, mapped to the TDF domains framework.

Mapping the TDF domain to behavioral change techniques

Corresponding to frequently mapped TDF domains, "restructuring the physical environment", "social processes of encouragement, pressure, support", "action planning (including implementation intentions)", and "providing information about the health consequences of performing and not performing deprescribing" were identified as BCTs **(Table 2)**.

Table 2: Barriers to and enablers of deprescribing in nursing home residents with limited life expectancy, organized within themes and mapped to theoretical domain framework, and behavioral change techniques

Theme	Determinant: barrier (B) and enabler (E)	TDF domain	Behavioral change techniques' [a]
Healthcare system and policy factors	Lack of deprescribing guidelines tailored to the Flemish context (B)	Environmental context and resources	Restructuring the physical environment [1]
	Existing guidelines and criteria in the literature are unclear, complex and very time-consuming (B)	Environmental context and resources	Restructuring the physical environment [1]
	Lack of clear guidelines on the involvement of pharmacies with medication reviews (B)	Environmental context and resources	Restructuring the physical environment [1]
	Lack of incentives for pharmacists in conducting medication reviews (B)	Reinforcement	Anticipation of future rewards [2]
	lack of a clear structural approach to medication review (B)	Environmental context and resources	Restructuring the physical environment [1]
	Mandatory appointment of coordinating and consulting physician by nursing homes (E)	Environmental context and resources	Restructuring the physical environment[1]
Resource and organization level factors	Constraints in resources: limited time, budget, staff (B)	Environmental context and resources	Restructuring the physical environment [1]
	Poor documentation (B)	Behavioral regulation	Self-monitoring of behaviour[2]
	Increased workload (B)	Beliefs about Consequences	Restructuring the physical environment [1]
	Lack of access to residents' medical files for pharmacists (B)	Environmental context and resources	Restructuring the physical environment [1]
	Strong vision to deprescribing is not a priority (B)	Goals	Action planning (including implementation intentions Goal Setting (behavior) [1]
	A perception that hospitalization is a preferred venue for deprescribing Practices (B)	Social/professional Role and Identity	Social processes of encouragement, pressure, support [3]
	Nursing home admission is an opportunity for deprescribing (E)	Environmental context and resources	Restructuring the physical environment [1]
Interprofessional collaboration and communication factors	Shorter time allocated by FP during resident visits limit knowledge exchange and interdisciplinary communication (B)	Environmental context and resources	Restructuring the social environment [1]
	Lack of recognition of nurses' knowledge by FP (B)	Social/professional role and identity	Social processes of encouragement, pressure, support [3]
	Hierarchical relationship between physicians and nurses (B)	Social/professional role and identity	Social processes of encouragement, pressure, support [3]
	Lack of confidence of FP towards pharmacist reviews of medications and deprescribing recommendations(B)	Beliefs about capabilities	Self-monitoring Social processes of encouragement, pressure, support [3]
	Reluctance of FP to deprescribe medications ordered by their colleagues (B)	Social influence	Restructuring the social environment Social support/emotional Social support/practical [1]
	Insufficient information access regarding indications of medications ordered outside of nursing home settings (B)	Environmental context and resources	Restructuring the physical environment [1]
	Discontinuity in the relationship and communication between different physicians or between the FP and the resident (B)	Environmental context and resources	Restructuring the physical environment [1]
	Fragmented care between health care setting (B)	Environmental context and resources	Restructuring the physical environment [1]

	Poor communication and collaboration with medical specialists (B)	Environmental context and resources	Restructuring the social environment [1]
	Report linkage between nurses and FP (B)	Environmental context and resources	Restructuring the physical environment [1]
	Sharing expertise and advice by the coordinating and consulting physician to deprescribe medications (E)	Environmental context and resources	Discriminative (learned) Cue [1]
	Good communication of nurse with pharmacist, and coordinating and consulting physician (E)	Skill	Habit Formation Modelling/demonstration of behavior by others [2]
	Geriatricians have confidence in deprescribing and are equipped to offer support and advice regarding the discontinuation of medications (E)	Beliefs about capabilities	Self-monitoring Social processes of encouragement, pressure, support [3]
Professional role and competency	Limited role of coordinating and consulting physician to coordinate and give advice in patients' medication not to actually decide in the part of FP (B)	Social/professional role and identity	Social processes of encouragement, pressure, support [3]
	Nurses' medication knowledge gap (B)	Knowledge	Health consequences [2]
	Lack of confidence of FP to initiate deprescribing (B)	Beliefs about capabilities	Self-monitoring Social processes of encouragement, pressure, support [3]
	Nurses perceived deprescribing is not their role (B)	Social/professional role and identity	Social processes of encouragement, pressure, support [3]
	Lack of knowledge and expertise of the FP to initiate deprescribing (B)	Knowledge Skill	Health consequences Habit Reversal Habit Formation Modelling/demonstration of behavior by others [2]
	Pharmacists' knowledge in pharmacokinetics and pharmacodynamics (E)	Knowledge	Health consequences [2]
Triadic dynamics in deprescribing	Residents' fear and resistance to deprescribe specific medications (B)	Beliefs about Consequences Emotion	Information about emotional consequences Information about social and environmental consequences [1] Stress management [3]
	Family resistance to deprescribing due to the perception that the FP has given up on their loved ones and equate to withdrawal of care (B)	Social influence Emotion	Modeling or demonstrating the behaviour[1] Stress management [3]
	Cognitive impairment in residents limits shared decision-making (B)	Memory, attention and decision processes	Action planning [2]
	Resident and family trust in HCPs (E)	Beliefs about capabilities	Social processes of encouragement, pressure, support[3]
	Involving resident and family in decision making (E)	Memory, attention and decision processes	Action Planning (including implementation intentions)[1]
	Advance care planning : talking about deprescribing beforehand (E)	Goals	Action Planning (including implementation intentions)[1]
Attitudes and perceptions	Physician seen deprescribing at the end of life as sign of giving up on their patients (B)	Optimism Emotion	Information about past success[2]

towards deprescribing	Deprescribing increases complexity of care (B)	Environmental context and resources	Restructuring the physical environment[1]
	Fear of negative patient outcomes due to deprescribing (B)	Beliefs about Consequences Emotion	salience of consequence[1]
	Emotional charge of deprescribing /impact or intensity associated with the process of deprescribing medications (B)	Memory, attention and decision processes	Action Planning (including implementation intentions)[1]
	Nurses, with intimate resident contact, positively comprehend and support the medication burden, fostering a constructive stance towards deprescribing (E)	Social/professional role and identity	Social processes of encouragement, pressure, support[3]
	Open to non-pharmacological options (E)	Reinforcement	Shaping[2]
	Sharing similar beliefs and attitudes towards medications at the end of life (E)	Social Influence	Modeling or demonstrating the behaviour[1]
	Positive perceptions towards deprescribing of medications (E)	Memory, attention and decision processes	Action planning (including implementation intentions)[1]

B, barrier ; E, enabler; FP, family physician, HCPs; healthcare professionals; TDF, theoretical domain framework; [a] the behavioral change techniques obtained from three references 1: Scott S et al. (2020) [34], 2: Cane et al. (2015) [38], 3: Michie S et al. (2008) [39]

Discussion

This qualitative descriptive study explored the barriers and enablers for HCPs to deprescribing medications for NH residents with LLE. The main barriers to deprescribing include the emotional charge of deprescribing, informal caregivers equating deprescribing with withdrawals of care, insufficient resources, poor communication and coordination between settings, residents' cognitive impairments, poor documentation, lack of expertise of HCPs in deprescribing, and deprescribing not being a priority in NHs. The main enablers were resident and informal caregiver involvement in deprescribing decision-making, as well as the sharing of similar beliefs and attitudes by HCPs towards medication use at the end of life, fostering a collectively positive perception of deprescribing. Other potential facilitators of deprescribing suggested by HCPs included the role expansion of nurses, increased involvement of pharmacists in medication reviews, allowing access to residents' medical files for pharmacists, providing incentives for medication reviews, incorporating deprescribing education, and developing clear guidelines tailored to support deprescribing in the NH context. These findings are important as they identify potential targets and challenges to consider when designing a deprescribing intervention in NHs.

Utilizing the TDF, we identified several barriers and enablers that map to TDF domains. Among the 13 TDF domains identified in our study, the most frequently mapped domains closely align with those prioritized in previous research. For instance, a systematic review of barriers and enablers to deprescribing in long-term care facilities developed a best-fit model that prioritizes 11 key domains. [26] Similarly, a qualitative study on benzodiazepine-receptor agonist deprescribing in Belgian NHs identified 9 priority domains, [22] both included *"environmental context and resources," "social/professional role and identity," "beliefs about capability," "belief about consequence," "social influence,"* and *"goals."* This alignment suggests that similar barriers and enablers to deprescribing exist across different countries in long-term care settings. However, we also frequently mapped the TDF domains of *"emotion"* and *"memory, attention, and decision processes."* These domains were reflected in barriers such as worries about the negative consequences of deprescribing on the resident relationship (e.g., concerns about death), as well as the emotional burden and intensity associated with deprescribing medications for residents with complex cases. This may be attributable to our study's focus on end-of-life care, which emphasizes the unique challenges and considerations involved in deprescribing for residents with complex healthcare needs. Supporting this, a hospice-based study in Ireland on HCPs perspectives of deprescribing in older patients at the end of life also frequently mapped these domains. [40]

Barriers to deprescribing span multiple levels and are often intertwined, necessitating complex, multi-faceted interventions.[19] Similarly, this study identified barriers at the micro, meso, and macro levels. The mapping of behavioral domains into actionable BCTs holds the promise of serving as active deprescribing interventions to integrate deprescribing as a routine practice in NHs. [32] For example, aligning with the *"environmental context and resources"* domain, operationalizing *"restructuring the physical environment"* as a BCT may serve as an integral component of deprescribing interventions, addressing determinants at macro, meso, and micro levels. Pharmacists could visit NHs to provide targeted support for medication reviews and deprescribing. They could attend a day of medication reviews within NHs, propose deprescribing opportunities to FPs, and offer incentives for their involvement. Structuring this arrangement would require personal coordination, organizing medication reviews in NHs, and formulating policies to incentivize such reviews. [41] Similarly, *"action planning"*, particularly through the use of implementation intentions, may play a crucial role in

addressing the competing *"goals"* surrounding the deprescribing of medications in NHs. This perspective is supported by findings from *Evrard et al*., which indicate that NHs often prioritize treating acute conditions and maintaining a smooth environment, resulting in a lack of emphasis on deprescribing as a key component of care goals. [22] Engaging multiple stakeholders in the action planning process could help normalize deprescribing as a routine practice and enhance HCPs sense of responsibility.

Although this study is among the first few designed to explore deprescribing barriers and enablers for HCPs focusing on NH residents with LLE or at the end of life, its results are largely similar to NH-based studies that do not specifically focus on residents with LLE or those at the end of life.[26, 42] However, there are notable differences in certain aspects, such as the impact of cognitive impairment on shared decision-making and the complexity of medical conditions approaching to end of life to deprescribing decisions. This could be attributed to the fact that deprescribing is not yet implemented as a routine practice, resulting in similar barriers and enablers across different studies. Common barriers, such as resource limitations (time, staff, tailored guidelines, finances), and issues like poor documentation and lack of communication leading to discontinuity of care, [42] underscore the need to restructure the environment for the seamless integration of deprescribing into routine practice in NHs.

HCPs suggest expanding nurses and pharmacists' roles to facilitate deprescribing, consistent with an Irish hospital study.[43] Without nurses' observations, HCPs who are not NH-based lack information to support deprescribing.[41] In the current research area (Belgium, but with likely theoretical generalizability to several other countries), where nurses are not allowed to (de)prescribe medications, there was a lack of interest from them in participating in our study. This lack of interest is potentially linked to feelings of reduced involvement and responsibility in deprescribing, compounded by the increased demand on nurses during the COVID-19 period. While nurses are integral to palliative care in NHs, their lack of involvement in (de)prescribing poses a discrepancy. Addressing the discrepancy and clarifying roles, especially incorporating (de)prescribing-related responsibilities, has the potential to make nursing roles more attractive. This, in turn, could foster personal growth and enhance the quality of resident care, ultimately improving the satisfaction of nurses in NHs. This is crucial, given widespread issues of role ambiguity and job dissatisfaction among nurses in long-term care. [44] The role of pharmacists is also crucial,[40] and the European Geriatric Medicine Society advises involving them in medication reviews and deprescribing.[41] However, inadequate documentation, limited pharmacists in NHs, and no incentives for medication reviews hinder their involvement. This implies restructuring the NH environment to enable effective interdisciplinary collaboration and leverage pharmacists' specialized training by expanding their roles. Another study in long-term care also supports the role expansion.[42, 45]

HCPs have a perceived knowledge and skill gap in deprescribing for residents with LLE in NHs, particularly for those dealing with multimorbidity. The decision-making process regarding deprescribing is emotionally burdensome for them, compounded by fear of consequences. Despite their awareness of general deprescribing guidelines, the absence of specific, tailored guidelines for NH residents with LLE impedes their application. Furthermore, a prior large-scale cross-sectional study involving 54 NHs in Belgium revealed a high prevalence of PIM use among residents, with 88.3% having at least one PIM. [7] This may impact residents' quality of life, while the treatment target for most NH residents is to enhance their quality of life. This underscores the importance of integrating

deprescribing into the palliative care model, emphasizing the need for policy integration and educational initiatives or training for HCPs, reflecting the findings of other studies. [23, 26, 42, 46]

HCPs described that an interplay between patients, their families, and HCPs in shared decision-making is crucial to facilitating deprescribing. Similarly, a previous systematic review exploring the attitudes of HCPs towards deprescribing in people with LLE and a qualitative study assessing barriers and enablers in hospice care reported that shared decision-making among HCPs, patients, and families enables deprescribing. [28, 40] In the context of NHs, and residents with LLE, where cognitive impairment related to dementia is prevalent,[47] HCPs view this cognitive impairment as a barrier to deprescribing. This challenge arises from the complexities of engaging these residents in decision-making due to their cognitive limitations. The cognitive impairment that many of these residents experience can create difficulties in comprehending and actively participating in discussions about medication adjustments. Moreover, some residents exhibit resistance to deprescribing due to factors like fear of change, concerns about symptom relapse, or a lack of understanding regarding the potential benefits, which aligns with previous findings. [40, 48] These barriers underscore the need for tailored communication and decision-making strategies that accommodate cognitive limitations, while also addressing patient concerns and involve family members. Integrating deprescribing, for example, into advance care planning and initiating it early could serve as a crucial strategy to support and enhance residents' end-of-life deprescribing decisions.

Strengths and limitations

Mapping deprescribing barriers and enablers to TDF and BCTs allows for the identification of target behaviors for change and guide to develop the future deprescribing interventions. The use of researcher triangulation throughout the study bolsters internal validity.[49] Limitations included the selection of BCTs were based solely on the research team's perspective, without the involvement of various stakeholders (patients, caregivers, policymakers, representatives from NHs, and HCPs from different professions). Including these stakeholders could benefit the context based development of interventions. Additionally, Zoom interviews necessitated by COVID-19 restrictions offered less interaction and impacted data richness. The use of a nurse interviewer may introduce bias towards nurse perspectives on deprescribing practices, potentially influencing the data collected. Additionally, the indirect recruitment of study participants through care organizations and associations may have led to selection bias. To enhance reflexivity and minimize these biases, we thoroughly discussed the findings with the entire team at each stage of the study.

Conclusions

This study identified various barriers and enablers that influence HCPs' deprescribing of medications for NH residents with LLE. These factors range from individual to policy levels. To advance evidence-informed practice in deprescribing for NH residents with LLE, future changes should address healthcare providers' competency gaps through tailored education and training, utilize effective communication strategies considering the reality of cognitive impairments, and integrate deprescribing into advance care planning. Policy integration, including the adoption of guidelines and incentives for medication reviews, as well as expanding the roles of nurses and pharmacists in medication reviews and deprescribing, could enhance deprescribing efforts. These findings emphasize the need for improved documentation practices in NHs to facilitate collaboration between different settings and ensure continuity of care for deprescribing.

References

1. Veehof L, Stewart R, Haaijer-Ruskamp F*, et al.* The development of polypharmacy. A longitudinal study. Fam Pract. 2000;17(3):261-7.
2. Roh E, Cota E, Lee JP*, et al.* Polypharmacy in Nursing Homes. Clin Geriatr Med. 2022;38(4):653-66.
3. Brent RJ. Life expectancy in nursing homes. Applied Economics. 2022;54(16):1877-88.
4. McNeil MJ, Kamal AH, Kutner JS*, et al.* The Burden of Polypharmacy in Patients Near the End of Life. J Pain Symptom Manage. 2016;51(2):178-83.e2.
5. Kotlinska-Lemieszek A, Paulsen O, Kaasa S*, et al.* Polypharmacy in patients with advanced cancer and pain: a European cross-sectional study of 2282 patients. J Pain Symptom Manage. 2014;48(6):1145-59.
6. Heppenstall CP, Broad JB, Boyd M*, et al.* Medication use and potentially inappropriate medications in those with limited prognosis living in residential aged care. Australas J Ageing. 2016;35(2):E18-24.
7. Anrys PMS, Strauven GC, Foulon V*, et al.* Potentially Inappropriate Prescribing in Belgian Nursing Homes: Prevalence and Associated Factors. J Am Med Dir Assoc. 2018;19(10):884-90.
8. Mangin D, Bahat G, Golomb BA*, et al.* International Group for Reducing Inappropriate Medication Use & Polypharmacy (IGRIMUP): Position Statement and 10 Recommendations for Action. Drugs Aging. 2018;35(7):575-87.
9. Alves-Conceição V, Rocha KSS, Silva FVN*, et al.* Medication Regimen Complexity Measured by MRCI: A Systematic Review to Identify Health Outcomes. Ann Pharmacother. 2018;52(11):1117-34.
10. Simonson W. Polypharmacy, MRPs, PIMs and deprescribing. Geriatric Nursing. 2015;36(6):467-8.
11. Scott IA, Hilmer SN, Reeve E*, et al.* Reducing inappropriate polypharmacy: the process of deprescribing. JAMA Intern Med. 2015;175(5):827-34.
12. Gnjidic D, Reeve E. Deprescribing: What do we know, and where to next? Br J Clin Pharmacol. 2021;87(3):722-4.
13. Liacos M, Page AT, Etherton-Beer C. Deprescribing in older people. Aust Prescr. 2020;43(4):114-20.
14. Roux B, Rakheja B, Sirois C*, et al.* Attitudes and beliefs of older adults and caregivers towards deprescribing in French-speaking countries: a multicenter cross-sectional study. Eur J Clin Pharmacol. 2022;78(10):1633-46.
15. Lavan AH, Gallagher P, Parsons C*, et al.* STOPPFrail (Screening Tool of Older Persons Prescriptions in Frail adults with limited life expectancy): consensus validation. Age Ageing. 2017;46(4):600-7.
16. Curtin D, Dukelow T, James K*, et al.* Deprescribing in multi-morbid older people with polypharmacy: agreement between STOPPFrail explicit criteria and gold standard deprescribing using 100 standardized clinical cases. Eur J Clin Pharmacol. 2019;75(3):427-32.
17. Paque K, De Schreye R, Elseviers M*, et al.* Discontinuation of medications at the end of life: A population study in Belgium, based on linked administrative databases. Br J Clin Pharmacol. 2019;85(4):827-37.
18. Onder G, Vetrano DL, Villani ER*, et al.* Deprescribing in Nursing Home Residents on Polypharmacy: Incidence and Associated Factors. J Am Med Dir Assoc. 2019;20(9):1116-20.
19. Sawan M, Reeve E, Turner J*, et al.* A systems approach to identifying the challenges of implementing deprescribing in older adults across different health-care settings and countries: a narrative review. Expert Rev Clin Pharmacol. 2020;13(3):233-45.
20. Kool E, Cordemans K, Lepeleire JD. De Coördinerende en Raadgevende Arts in Woonzorgcentra – naar een nieuwe functieomschrijving binnen sterk interprofessioneel teamwerk. Crataegus v, Medica D, Leuven K, editors2021. 1-51 p.
21. De Vlaamse r. Besluit van de Vlaamse Regering tot wijziging van verschillende besluiten, wat betreft de invoering van infrastructuursubsidies voor woonzorgcentra en centra voor kortverblijf. 2017.
22. Evrard P, Damiaens A, Patey AM*, et al.* Barriers and enablers towards benzodiazepine-receptor agonists deprescribing in nursing homes: A qualitative study of stakeholder groups. Exploratory Research in Clinical and Social Pharmacy. 2023;9:100258.
23. Okeowo DA, Zaidi STR, Fylan B*, et al.* Barriers and facilitators of implementing proactive deprescribing within primary care: a systematic review. Int J Pharm Pract. 2023;31(2):126-52.
24. Doherty AJ, Boland P, Reed J*, et al.* Barriers and facilitators to deprescribing in primary care: a systematic review. BJGP Open. 2020;4(3).
25. Brunner L, Rodondi N, Aubert CE. Barriers and facilitators to deprescribing of cardiovascular medications: a systematic review. BMJ Open. 2022;12(12):e061686.
26. Heinrich CH, Hurley E, McCarthy S*, et al.* Barriers and enablers to deprescribing in long-term care facilities: a 'best-fit' framework synthesis of the qualitative evidence. Age Ageing. 2022;51(1).
27. Paque K, Vander Stichele R, Elseviers M*, et al.* Barriers and enablers to deprescribing in people with a life-limiting disease: a systematic review. Palliat Med. 2019;33(1):37-48.
28. Lundby C, Graabaek T, Ryg J*, et al.* Health care professionals' attitudes towards deprescribing in older patients with limited life expectancy: A systematic review. Br J Clin Pharmacol. 2019;85(5):868-92.
29. Michie S, Atkins L, West R. The behaviour change wheel. A guide to designing interventions 1st ed Great Britain: Silverback Publishing. 2014;1003:1010.
30. Michie S, Johnston M, Abraham C*, et al.* Making psychological theory useful for implementing evidence based practice: a consensus approach. Qual Saf Health Care. 2005;14(1):26-33.
31. Cane J, O'Connor D, Michie S. Validation of the theoretical domains framework for use in behaviour change and implementation research. Implement Sci. 2012;7:37.

32. Atkins L, Francis J, Islam R*, et al.* A guide to using the Theoretical Domains Framework of behaviour change to investigate implementation problems. Implement Sci. 2017;12(1):77.
33. Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. Int J Qual Health Care. 2007;19(6):349-57.
34. Scott S, Twigg MJ, Clark A*, et al.* Development of a hospital deprescribing implementation framework: A focus group study with geriatricians and pharmacists. Age Ageing. 2019;49(1):102-10.
35. Francis JJ, Johnston M, Robertson C*, et al.* What is an adequate sample size? Operationalising data saturation for theory-based interview studies. Psychol Health. 2010;25(10):1229-45.
36. Braun V, Clarke V. Using thematic analysis in psychology. Qualitative Research in Psychology. 2006;3(2):77-101.
37. Smith T, McNeil K, Mitchell R*, et al.* A study of macro-, meso- and micro-barriers and enablers affecting extended scopes of practice: the case of rural nurse practitioners in Australia. BMC Nurs. 2019;18(1):14.
38. Cane J, Richardson M, Johnston M*, et al.* From lists of behaviour change techniques (BCTs) to structured hierarchies: comparison of two methods of developing a hierarchy of BCTs. Br J Health Psychol. 2015;20(1):130-50.
39. Michie S, Johnston M, Francis J*, et al.* From theory to intervention: Mapping theoretically derived behavioural determinants to behaviour change techniques. Applied Psychology: An International Review. 2008;57(4):660-80.
40. Alwidyan T, McCorry NK, Parsons C. Healthcare professionals' perspectives of deprescribing in older patients at the end of life in hospice care: a qualitative study using the Theoretical Domains Framework. Int J Pharm Pract. 2023;31(3):305-13.
41. van Poelgeest E, Seppala L, Bahat G*, et al.* Optimizing pharmacotherapy and deprescribing strategies in older adults living with multimorbidity and polypharmacy: EuGMS SIG on pharmacology position paper. Eur Geriatr Med. 2023.
42. Heinrich CH, McHugh S, McCarthy S*, et al.* Barriers and enablers to deprescribing in long-term care: A qualitative investigation into the opinions of healthcare professionals in Ireland. PLoS One. 2022;17(12):e0274552.
43. Kalim RA, Cunningham CJ, Ryder SA*, et al.* Deprescribing Medications that Increase the Risk of Falls in Older People: Exploring Doctors' Perspectives Using the Theoretical Domains Framework (TDF). Drugs Aging. 2022;39(12):935-47.
44. Stewart C, Berta WB, Laporte A*, et al.* Nurses' work, work psychology, and the evolution & devolution of care provision in nursing homes: A scoping review. International Journal of Nursing Studies Advances. 2023;5:100133.
45. Rowe S, Pittman N, Balsom C*, et al.* Beliefs and attitudes of residents, family members and healthcare professionals regarding deprescribing in long-term care: a qualitative study. Int J Clin Pharm. 2022;44(6):1370-9.
46. van Poelgeest EP, Seppala LJ, Lee JM*, et al.* Deprescribing practices, habits and attitudes of geriatricians and geriatricians-in-training across Europe: a large web-based survey. Eur Geriatr Med. 2022;13(6):1455-66.
47. Miranda R, Smets T, Van Den Noortgate N*, et al.* Higher Prevalence of Dementia but No Change in Total Comfort While Dying among Nursing Home Residents with Dementia between 2010 and 2015: Results from Two Retrospective Epidemiological Studies. Int J Environ Res Public Health. 2021;18(4).
48. Robinson M, Mokrzecki S, Mallett AJ. Attitudes and barriers towards deprescribing in older patients experiencing polypharmacy: a narrative review. npj Aging. 2024;10(1):6.
49. Byrne M. Increasing the impact of behavior change intervention research: Is there a role for stakeholder engagement? Health Psychol. 2019;38(4):290-6.

Chapter 5

Balancing Palliative Care Needs and Medication Appropriateness: Initiation and Reinitiation of Medications at the End of Life

Published:
Anlay DZ, Paque K, Brys ADH, Cohen J, Dilles T. Balancing Palliative Care Needs and Medication Appropriateness: Initiation and Reinitiation of Medications at the End of Life.
Archives of Gerontology and Geriatrics 42, 485–499 (2025). DOI:
https://doi.org/10.1016/j.archger.2025.105994

Abstract

Background

Medications deemed inappropriate and discontinued in the earlier stages of life-limiting disease may become relevant in palliative care context at the end of life. This study aims to determine the incidence of and factors associated with initiation and reinitiation of medications deemed inappropriate according to the STOPPFrail guideline.

Methods

A retrospective cohort study using linked healthcare reimbursement data. We included nursing home residents aged ≥65 who died with a condition potentially amenable to palliative care between 2015 and 2019 in Belgium. Outcomes were (1) reinitiation of previously discontinued STOPPFrail-listed medications and (2) initiation of these medications, regardless of prior use, in the last three months. Log-binomial regression was used to estimate relative risks (RR) with 95% confidence intervals (CI).

Results

Among 158,689 decedents, 29.7% had at least one medication initiated, and 16.96% reinitiated among those with at least one medication discontinued (n=13,724). By medication type, initiation and reinitiation were significantly higher for symptomatic medications than preventive ones (initiation: 25.5% symptomatic vs. 6.7% preventive; reinitiation: 20.3% symptomatic vs. 11% preventive). The risk was higher among residents with cancer, who were hospitalized, or taking ≥10 chronic medications.

Conclusions

A significant proportion of residents undergo initiation or reinitiation of medications deemed inappropriate at the end of life per existing guidelines. Many were likely prescribed for palliative purposes. Thus, guidelines on medication appropriateness may need to more explicitly address palliative care contexts. A notable number also received preventive medications, suggesting inappropriate prescribing at the end of life that has received little attention.

Key words: Drug Utilization; Palliative Care; Nursing Homes; cohort study; end of life; Potentially Inappropriate Medication List

1. Introduction

As individuals approach the end of life, it becomes increasingly important to weigh the potential benefits and risks of medications while also considering life expectancy. With a shorter life expectancy, the focus of care often shifts from reducing mortality and morbidity to prioritizing symptom management [1]. This is particularly relevant for nursing home residents, who represent some of the most vulnerable and frail older adults [2]. Nursing home residents often present with significant medical complexity, frequently requiring numerous medications to manage their conditions. This complex medical profile, combined with age-related changes in pharmacokinetics and pharmacodynamics, places them at an increased risk of experiencing adverse medication outcomes [3]. These risks necessitate a careful and individualized approach to prescribing, emphasizing the balance between therapeutic benefits and potential harms.

The Palliative Care for Older People in Care and Nursing Homes in Europe (PACE) study estimated the median length of stay in nursing homes across six European countries, including Belgium, at 73.4 weeks, with 42% of residents dying within one year of admission [4]. The short life expectancy of residents after being admitted to nursing homes makes nursing homes one of the institutions with the highest prevalence of palliative care needs [5]. Palliative care often lasts far less than the assumed 3–4 months needed to realize its full benefits, with a systematic review across 23 countries showing a median duration of just 18.9 days prior to death [6]. In the context of palliative care the focus of care shifts from life extension and prevention to symptom management and comfort [7], which requires balancing medication use [8]. Balancing medication use at the end of life involves thoroughly evaluating the benefit-risk ratio of each newly prescribed medication, as well as re-assessing the necessity and impact of medications previously prescribed in the trajectory of a life-limiting disease [8, 9].

Treatment for life-limiting diseases is often supplemented with medications for symptom relief, management of co-morbidities, and long-term prevention [10]. As death approaches, the use of symptom-relief medications typically increases [11, 12], while the continuation of previously prescribed medications can contribute to an increased drug burden. Hence, in this population, a decrease in preventive medications lacking short-term benefit and an increase in medications for symptom control and palliation can be expected [13]. Although in the literature symptom-relief medications generally rise during the final year of life, the reduction in preventive medications is minimal [12]. To optimize medication regimens, re-prescribing—which involves both prescribing medications to address a patient's treatable needs and deprescribing potentially inappropriate medications (PIM)—is essential [14]. Re-prescribing is enhanced by a medication review, which involves a structured evaluation of a patient's medications aimed at optimizing their use and improving quality of life and health outcomes by reducing medication-related problems, while also considering patient preferences [15].

Various tools have been developed to guide clinicians in reviewing medication appropriateness and support deprescribing. However, only a few are tailored specifically for end of life and includes a limited set of medications [16]. Examples include the Screening Tool of Older Persons Prescriptions in Frail adults with limited life expectancy (STOPPFrail [2017[17], updated 2021] [18]), Morin et al. list for individuals with life expectancy of ≤ 3 months (2018) [19] and Elsten EE et al. for patients with a life expectancy of ≤6 months (2024)[20]. However, these tools were not specifically developed for nursing home settings. More recently a re-prescribing tool for nursing home residents with a limited life expectancy (ReNeWAL) was developed (2024)[21]. While these tools provide guidance on the

inappropriateness of medications at the end of life, they do not clearly differentiate their appropriateness for palliative care use. This is evident from the fact that the chronic use of certain medications—for example, proton pump inhibitors (PPIs), steroids, and antipsychotics—are identified as potentially inappropriate by STOPPFrail but are also included in the WHO Essential Medicines List for pain and palliative care [22], as well as in the Lancet Essential Package (LEP) [23], where they are recognized as appropriate for use in palliative care. Moreover, discrepancies exist between these tools regarding the appropriateness of these medications for use at the end of life [16].

Medications previously discontinued as inappropriate during the earlier stages of a life-limiting disease may become relevant for palliative care at the end of life, potentially requiring reinitiation or new initiation. While much attention has been given to identifying PIMs and deprescribing them, there has been less focus on medications that may need to be reinitiated closer to the end of life due to their essential role in palliative care. Deprescribing studies near the end of life, using the STOPPFrail criteria, have reported low deprescribing rates and no significant trends over time [8, 11, 24]. These findings might be influenced by the reinitiation or initiation of medications specifically for palliative purposes. Reinitiation after prior discontinuation could indicate the appropriateness of certain medications in a palliative care context, unsuccessful deprescribing—such as withdrawal symptoms, worsening of the patient's condition, or patient noncompliance—or a gap in the evaluation of medication appropriateness that could lead to the initiation of unnecessary medication. However, the prevalence of reinitiation or initiation of medications near the end of life in the context of palliative care has been less investigated [8]. Accordingly, the study aimed to achieve two objectives: (1) to determine the incidence of initiation and reinitiation of medications deemed inappropriate by STOPPFrail criteria in the last three months of life among nursing home residents dying from life-limiting conditions amenable to palliative care [25], and (2) to identify factors associated with the initiation and reinitiation of these medications in this population.

2. Methods

2.1. Study design and population

We conducted a retrospective cohort study of decedents using routinely collected healthcare reimbursement and administrative data in Belgium. Nursing home residents who died at the age of ≥65 years between January 1, 2015, and December 31, 2019, were identified in the Belgian Statistics Agency's death certificate registration (N =214,978). Residents were included in the cohort if they received at least one reimbursed health care service in a nursing home and died with at least one condition potentially amenable to palliative care listed as a contributing or underlying cause of death (**Supplementary file 5.1**). We excluded decedents who were registered as residents of nursing homes before death but actually received care in a daycare center linked to the nursing home, as well as those missing data on the month and year of death. The study was reported in accordance with the REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement [26].

2.2. Data source and handling

The data sources included databases managed by the InterMutualist Agency (IMA-AIM), which contain data on the insured population in Belgium (>99% of the population), healthcare utilization data, data on all reimbursed medications dispensed at both hospitals and community pharmacies, hospitalization data, and KatZ datasets providing information on the physical and psychological care dependence of nursing home residents [27]. The 18-month IMA data for each decedent prior to death

were deterministically linked at the individual level with data managed by Statistics Belgium, including the death certificate register, census, and fiscal data. **Box1** provides a detailed information on the data source associated with each variable included in our study. More information on the databases, as well as the access and linkage procedures, has been described elsewhere [28].

Box 1: Data managing agencies, associated datasets and variables used in the study

Data managing agency	Data Sets (descriptions)	Key variables /information's provided used to define the predictors or outcomes
IMA-AIM: InterMutualistisch Agentschap	1. Socio-demographic database: All individuals with healthcare insurance.	• Total numbers of nursing home residents registered in the seven health care insurers • Age • Sex • Year of death
	2. National healthcare claims data: All reimbursed healthcare use data from 7 healthcare insurers.	• Total numbers of nursing home residents received reimbursed health care. • Medications dispensed at the hospital pharmacy and the number of days each medication was dispensed prior to death. • Emergency admission • Types of nursing home
	3. Katz-scale database: Evaluations of independence in activities of daily living for patients in outpatient nursing care or staying in nursing homes.	• KatZ scale: physical and psychic dependence
	4. Pharmanet database: All reimbursed medication data dispensed in community pharmacies.	• Medications dispensed at the community pharmacy and the number of days each medication was dispensed prior to death. Combined with medications dispensed at hospital pharmacy used to define number of medications, and the outcome trend for each of the selected medications
	5. Hospitalization database: All hospital admissions.	• Hospital admission • Intensive care unit admission
Statistics of Belgium	Received a linked dataset, which included: • Death Certificate Database • Demographic and Census Database • Fiscal Database	• Provide the total number of individuals aged 65 and above at the time of death, who died between 2015 and 2019, and were registered as residents of nursing homes prior to their death. • Age at the time of death • Underlying cause of death • Contributory/indirect cause of death • Place of death • Highest attained education level

The drugs in the database were classified and recorded based on the World Health Organization's Anatomical Therapeutic Chemical (ATC) classification system [29]. Medication use was tracked using 5th-level ATC codes, representing exact medications. For analysis, these medications were grouped into broader classes aligned with the STOPPFrail criteria. When the criteria specified individual medications, the corresponding 5th-level ATC codes were used to ensure accurate mapping. Additionally, healthcare utilization of the decedent (e.g.; intensive care unit, and emergency admission) was identified in the dataset using nomenclature codes for the services utilized. The underlying and contributing causes of death were recorded in the dataset according to the 10th

revision of the International Classification of Diseases (ICD-10) and identified algorithmically to define the causes of death.

2.3. Identification of medication for the study and classifications

Among the tools for assessing medication appropriateness at the end of life, we selected the medications listed in the first version of the STOPPFrail criteria. Given the publication date of the tools and the data available for our analysis (from 2015 to the end of 2019), we opted for the initial STOPPFrail criteria as our primary reference [17]. Of the 27 criteria [17], we selected 15 medications as their inappropriateness can be determined without detailed, patient-specific clinical data—a necessary limitation given our dataset [30]. Although the STOPPFrail tool provides a list of medications considered inappropriate in the final years of life, some medications are recognized as appropriate for palliative care by other tools, revealing discrepancies. Therefore, in this study we refer to the 15 selected medications simply as "medications" or as "deemed inappropriate by STOPPFrail criteria." For details on the selected medications and comparisons across available tools, refer to **Table 1**.

The selected medications were classified into three categories based on their main use at the end of life as described by literatures: symptomatic management, long-term prevention, and others (**Table 1**). For medications that could be used for dual purposes (symptomatic and preventive), their main use at the end of life was considered. For example, proton pump inhibitors can be used for both symptom management and prevention, such as preventing the side effects of nonsteroidal anti-inflammatory drugs; however, symptom management was considered the main indication [12, 21]. Medications that were not classified as both preventive and symptomatic were categorized as "other". While this classification allowed each medication to appear in only one group, residents could be included in multiple medication groups if they were prescribed drugs from more than one category.

Table 1: Selected medications, their classifications, and appropriateness or inappropriateness according to various tools*

Categorization	Medications [a] (Deemed inappropraite by STOPPFrail)	ATC code[1]	Lucas Morin criteria (last three months)[b]	Late life (Last 6 months)[c]	ReNewal criteria (Consider to START)[d]	WHO Essential palliative medication[e]	Lancet Essential Package (LEP)[f]
Medications for long-term prevention	Lipid modifying agents	C10%	Inadequate	Recommended to deprescribe	/	/	/
	Calcium supplements	A12AX%	Inadequate	/	Vitamin D and calcium supplement	/	/
	Osteoporosis drugs[2]	M05B%, H05AA02	Inadequate	Recommended to deprescribe	Bisphosphonates (and vitamin D and calcium if intake is insufficient)	/	/
	Alpha-blockers	C02CA%, C02LE%	Inadequate	Recommended to deprescribe (C02CA)	Antihypertensive therapy	/	/
	Selective Estrogen Receptor Modulators (SERMS)	G03XC%	/	/	/	/	/
Symptom control medications	Long-term oral NSAIDs ≥ 2 months	M01A%	Often adequate (no duration)	/	/	ibuprofen	Ibuprofen naproxen, diclofenac, meloxicam
	5-alpha reductase inhibitors	G04CA%, G04CB%	Questionable/ inadequate	Recommended to deprescribe (G04)	Alpha-adrenoreceptor antagonists 5-alpha reductase inhibitor	/	/
	Neuroleptic antipsychotics	N05A%	No consensus			haloperidol	haloperidol
	Proton pump inhibitors (PPIs)	A02BC%	No consensus	Recommended to deprescribe	Proton pump inhibitor		Omeprazole
	H2-receptor antagonists	A02BA%	Questionable	Recommended to deprescribe	/	/	/
	Gastrointestinal antispasmodics	A03%	Often adequate	/	/	Hyoscine (butylbromide, hydrobromide), Metoclopramide	Hyoscine butylbromide Metoclopramide
	Long-term oral steroids ≥ 2 months	H02%	Often adequate	/	Regular inhaled corticosteroids	dexamethasone	Dexamethasone
Others	Theophylline	R03D% (R03DA04)	/	/	/	/	/
	Memantine	N06DX01	Often inadequate	/	/	/	/
	Sex hormones	G03% excl. G03XC%	/	Recommended to deprescribe (G03C)	/	/	/

*The table summarizes medication categories deemed inappropriate by STOPPFrail, alongside corresponding recommendations from other deprescribing tools and essential medication lists. Each row represents a medication class or specific drug identified by ATC codes. Columns show how different criteria address these medications, highlighting agreements and discrepancies. A slash (/) indicates no recommendation or not applicable.

[1]ATC; Anatomical Therapeutic Chemical: the % sign indicates all drugs started with the ATC code before the % included. Differentiation between combination and single-agent medications was not possible, as the data were based solely on ATC

codes rather than specific drug names. If a combination product contained at least one active ingredient classified as potentially inappropriate according to the STOPPFrail criteria, it was considered exposure to that inappropriate medication.

[2] Includes anti resorptive/bone anabolic drugs (bisphosphonates, strontium, teriparatide, denosumab)
[a]The 15 selected medication/medication classes deemed to be inappropriate based on STOPPFrail criteria (Screening Tool of Older Persons Prescriptions in Frail adults with limited life expectancy)
[b] The *Morin et al. (2018)* criteria provide a comprehensive classification for medication appropriateness at the end of life, encompassing both new medication initiation and continuation for patients already on treatment. "Often adequate" drug prescribing involves medications that are appropriate and beneficial for symptom management and comfort during the end-of-life period, essential for improving the patient's quality of life and addressing palliative care needs. "Questionable" drug prescribing includes medications for which appropriateness is uncertain, necessitating careful evaluation of potential benefits and risks based on the patient's condition and goals of care. "Often inadequate" drug prescribing refers to medications unsuitable for end-of-life care, often used for long-term chronic disease prevention or treatment, not aligned with the main focus of palliative care. "Not consensus" is applied when there is limited agreement among experts regarding medication appropriateness (if level of agreement was <75%). In the table we indicate the classification based on initiation as of our research interest [31].
[c] *Elsten EE et al.* (2024) provide a list of medications with deprescribing recommendations for patients with a life expectancy of six months or less
[d] Medication Appropriateness for Older Nursing Home Patients With a Limited Life Expectancy, provide both medications to consider to stop and start. To show the discrepancies we provided in the table only medications for consideration to start.
[e]The medication in the table included a medications listed as an essential list for pain and palliative care but deemed inappropriate by STOPPFrail.
[f]a list of medication for Pain and Palliative Care in the Lancet Essential Package (LEP) deemed inappropriate by STOPPFrail developed by the Lancet Commission on Pain and Palliative Care

2.4. Measurement

2.4.1. Outcome

Two primary outcome measures were established:

- Reinitiation of Medications Deemed Inappropriate by STOPPFrail Criteria: This measure tracks medications prescribed 18 to 12 months before death, discontinued (i.e., not prescribed) 12 to 3 months before death, and reintroduced in the last three months of life.
- Initiation of Medications Deemed Inappropriate by STOPPFrail Criteria: This measure examines the start of such medications in the last three months of life, regardless of prior use 18 to 12 months before death.

Outcomes were assessed at an aggregate level for all 15 medications, defining 'at least one medication initiated or reinitiated' after evaluating it at the individual medication level. **Figure. 1** illustrates the timelines and possible drug utilization patterns.

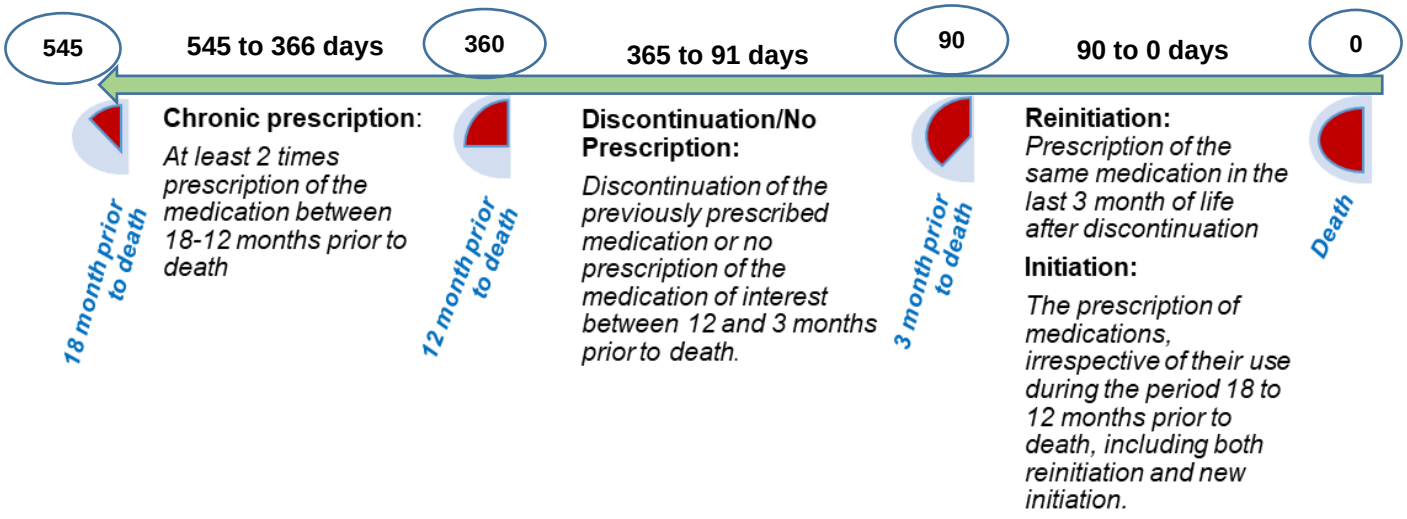


Figure. 1: Pattern of drug utilization from 18 months to death to define initiation and reinitiation: In the last three months of life, the pattern of drug use for the medication of interest can be classified into several categories: continued use, no use, discontinued, and initiated. For this study, the focus is on initiation, which includes both new initiation—where the medication was not prescribed between 18 to 3 months before death and was prescribed during the last 3 months of life—and reinitiation—where the medication was prescribed between 18 to 12 months before death, not prescribed (or discontinued) between 12 to 3 months, and then restarted in the last 3 months of life. Continued use refers to medications that were prescribed both between 12 to 3 months before death and in the last 3 months of life. No use refers to medications that were not prescribed at any point during the last year of life.

2.4.2. Exploratory variables

The dataset provided socio-demographic characteristics of the decedents at the time of death, as well as health care utilization variables.

Socio-demographic characteristics:

- *Gender: Male/female*

- *Age at the time of death was initially provided in 5-year categories starting from 65 years. For analytical purposes, we recategorized these into three groups: Young-Old (65–74 years), Middle-Old (75–84 years), and Oldest-Old (85 years and older)[32].*
- *Educational status was recorded in the database based on the International Standard Classification of Education (ISCED)[33] and was recategorized into no formal education, primary education, secondary education, higher education, and unknown.*
- *Causes of death were identified using codes from the 10th revision of the International Classification of Diseases (ICD-10). Decedents were classified according to their underlying or contributory causes of death, distinguishing those potentially amenable to palliative care from those that were not. According to the publications by Morin et al., life-limiting conditions amenable to palliative care were classified into one of three distinct illness trajectories: (1) cancer – a trajectory of short decline with an evident terminal phase; (2) organ failure – a trajectory of long-term limitations with intermittent acute episodes (e.g., diseases of the cardiovascular system); or (3) prolonged dwindling – a trajectory of progressive loss of physical and cognitive capacities (e.g., Alzheimer's disease)* ***(Supplementary file 5.1)*** *[5]. This classification helps determine the likely time frame for functional decline at the end of life [34]. Based on the underlying causes of death, decedents were further classified as having died from either predictable or unpredictable causes of death. Unpredictable deaths included acute and potentially unpredictable fatal events, such as sepsis, fall-related injuries, suicide, acute myocardial infarction, or stroke with no prior history of ischemic heart disease* ***(Supplementary file 5.2).***

Health care utilization variables:

- *Hospitalizations, emergency department visits, and intensive care unit (ICU) admissions within 3 months prior to death, categorized as either "admitted" or "not admitted"* ***(Supplementary file 5.3).***
- *Chronic medication use: The number of concurrent chronic reimbursed medications recorded 3 months prior to death, including both PIMs and non-PIMs. Medication use was categorized as no polypharmacy (less than five medications), polypharmacy (5–9 medications), and excessive polypharmacy (10 or more medications)* ***(Supplementary file 5.3)****.*
- *Types of nursing home: Based on where the healthcare service was actually delivered to the decedents 3 months prior to death, the type of nursing home was classified as ROB (Rustoorden voor Bejaarden, or 'rest homes'), where nursing and personal care are provided to older persons with low to moderate needs, or RVT (Rust-en VerzorgingTehuizen, or 'rest and nursing homes') for people heavily dependent on care[35]* ***(Supplementary file 5.3)****.*
- *KatZ scale: The physical and psychological dependence of nursing home residents was assessed at different time intervals to determine their functional level and needs in daily living [27]. The results of the Katz evaluation were recorded with Belgian health insurance funds in the context of granting care lump sums. For each resident, their level is categorized (O, A, B, C, D, Cd), See the description of each category in the (****Supplementary file 5.4)****.*

2.5. Statistical analysis

Standard descriptive statistics were used to describe the sociodemographic and healthcare utilization variables. The percentages of categorical variables were tabulated, and the median with the interquartile range (IQR) was reported for number of medications per residents.

The outcome was measured as the incidence proportion, defined as the initiation or reinitiation of at least one medication that was not prescribed or was discontinued between 12 and 3 months prior to death (the at-risk population). The proportion was also estimated by the type of medications (preventive, symptomatic, and others) and for each of the 15 individual medications. We assessed the statistically significant difference between the proportions of initiation or reinitiation of medications prescribed for preventive medications and symptom controls using a Z-test.

A log-binomial regression model was fitted to identify factors associated with the re (initiation) of "at least one medication" deemed PIM by the STOPPFrail criteria. The relative risk (RR) with a 95% confidence interval (CI) was reported as the measure of association. Statistical significance was set a priori ($p \leq 0.05$). Decedents with an unknown highest level of education (n=19,507, 12.29%) were excluded from the models.

We conducted sensitivity analyses for two scenarios: 1) by the type of medication, with separate regression analyses to check if the risk varied for symptomatic and preventive medications, and 2) by excluding residents who died from unpredictable causes to address the challenge of estimating remaining life expectancy and evaluate the robustness of findings. Uncertainty about the remaining life expectancy can hinder medication decisions that take into consideration life expectancy. All analyses were conducted using SAS Enterprise Guide version 8.3 (SAS Institute).

3. Results

3.1. Characteristics of the decedents

Overall, out of 214,978 nursing home residents who died at the age of 65 and above in Belgium from 2015 to 2019, 158,689 (73.82%) died with life-limiting conditions amenable to palliative care and were included in the final analysis (**Figure. 2**).

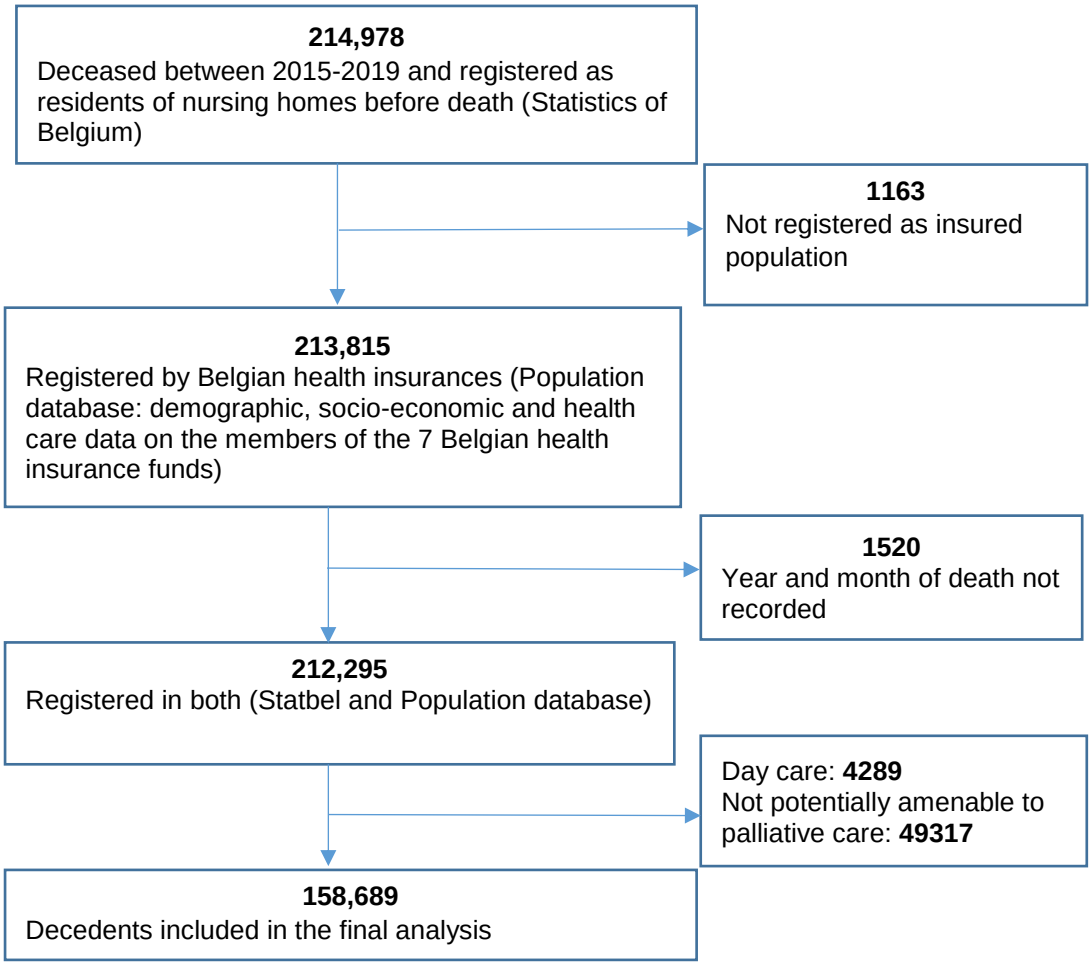


Figure. 2: Study population selection flowchart

Among the included decedents, the majority—103,232 (65.05%)—were female, and 105,648 (66.58%) were aged 85 and above. As depicted in **Table 2**, approximately half of the residents (50.20%) were hospitalized at least once in the last 3 months prior to death, and 51.65% died with organ failure. The majority (84.54%) of residents were on five or more medications, with a median of nine concurrent chronic medications (IQR 6–12) recorded three months prior to death.

Table 2: Characteristics of deceased nursing home residents in Belgium (2015-2019, n=158,689), and the proportions receiving at least one PIM, as well as those who had at least one PIM deprescribed, initiated, or reinitiated.

Socio-demographic and health care utilization variables	Total included in the study[a]	At least one PIM prescribed 2X in the period 18-12 months prior to death[b]	At least one PIM discontinued 12-3 months prior to death (15 PIMs) [b,c]	At least one PIM reinitiated in the last 3 months [b,d]	At least one PIM initiated irrespective of the use prior to 12 months
Total	158,689 (100%)	98,279 (61.93%)	13,724 (13.96%)	2,328 (16.96)	47138 (29.71)
Age					
65-74	10579 (6.67)	7044 (66.58)	1015 (14.41)	204 (20.10)	3507 (33.15)
75-84	42462 (26.76)	27729 (65.30)	4142 (14.94)	761 (18.37)	13462 (31.70)
85 and over	105648 (66.58)	63506 (60.11)	8567 (13.49)	1363 (15.91)	30169 (28.56)
Sex					
Female	103232 (65.05)	64683 (62.66)	8898 (13.76)	1433 (16.10)	27723 (26.86)
Male	55457 (34.95)	33596 (60.58)	4826 (14.36)	895 (18.55)	19415 (35.01)
Educational status					
No formal education	12355 (7.79)	7925 (64.14)	1070 (13.50)	187 (17.48)	3591 (29.07)
Primary education	57633 (36.32)	36724 (63.72)	4998 (13.61)	836 (16.73)	17118 (29.70)
Secondary education	56060 (35.33)	34154 (60.92)	4898 (14.34)	795 (16.23)	16719 (29.82)
Higher education	13134 (8.28)	7556 (57.53)	1092 (14.45)	214 (19.60)	4004 (30.49)
Unknown	19507 (12.29)	11920 (61.11)	1666 (13.98)	296 (17.77)	5706 (29.25)
Years of death					
2015	33411 (21.05)	19801 (59.26)	2817 (14.23)	481 (17.07)	10434 (31.23)
2016	32946 (20.76)	19671 (59.71)	2954 (15.02)	539 (18.25)	9734 (29.55)
2017	33544 (21.14)	21094 (62.88)	2825 (13.39)	476 (16.85)	9949 (29.66)
2018	29699 (18.72)	19010 (64.01)	2545 (13.39)	414 (16.27)	8573 (28.87)
2019	29089 (18.33)	18703 (64.30)	2583 (13.81)	418 (16.18)	8448 (29.04)
Trajectory of illness					
Cancer	27762 (17.49)	16769 (60.40)	2813 (16.78)	585 (20.80)	10970 (39.51)
Organ failure	81964 (51.65)	52178 (63.66)	7170 (13.74)	1238 (17.27)	24791 (30.25)
Prolonged dwindling	48963 (30.85)	29332 (59.91)	3741 (12.75)	505 (13.50)	11377 (23.24)
Predictability of death					
Predictable	147402 (92.89)	91328 (61.96)	12773 (13.99)	2154 (16.86)	43604 (29.58)
Unpredictable	11287 (7.11)	6951 (61.58)	951 (13.68)	174 (18.30)	3534 (31.31)
Types of nursing home[e#]					
ROB	157410 (99.19)	97475 (61.92)	13600 (13.95)	2306 (16.96)	46780 (29.72)
RVT	1279 (0.81)	804 (62.86)	124 (15.42)	22 (17.74)	358 (27.99)
Katz scale[#]					
A	18588 (11.71)	11411 (61.39)	1683 (14.75)	379 (22.52)	7349 (39.54)
B	41970 (26.45)	25966 (61.87)	3786 (14.58)	747 (19.73)	14876 (35.44)
C	27231 (17.16)	17482 (64.20)	2582 (14.77)	410 (15.88)	7847 (28.82)
Cd	59606 (37.56)	36781 (61.71)	4834 (13.14)	636 (13.16)	13622 (22.85)
D	1942 (1.22)	1191 (61.33)	174 (14.61)	29 (16.67)	651 (33.52)
O	5906 (3.72)	3532 (59.80)	524 (14.84)	104 (19.85)	2189 (37.06)
No	3446 (2.17)	1916 (55.60)	141 (7.36)	23 (16.31)	604 (17.53)
Hospitalization *					
No	79031(49.80)	48574 (61.46)	6640 (13.67)	674 (10.15)	14539 (18.40)
Yes	79658 (50.20)	49705 (62.40)	7084 (14.25)	1654 (23.35)	32599 (40.92)
ICU admission*					
No	152352 (96.01)	94166 (61.81)	13150 (13.96)	2206 (16.78)	44699 (29.34)
Yes	6337 (3.99)	4113 (64.90)	574 (13.96)	122 (21.25)	2439 (38.49)

Emergency admission *					
No	84622 (53.33)	52151 (61.63)	7180 (13.77)	832 (11.59)	17517 (20.70)
Yes	74067 (46.67)	46128 (62.28)	6544 (14.19)	1496 (22.86)	29621 (39.99)
Chronic medication use [#]					
< 5	24533 (15.46)	9464 (38.58)	1475 (15.59)	130 (8.81)	5970 (24.33)
5-9	67208 (42.35)	40057 (59.60)	5214 (13.02)	641 (12.29)	17493 (26.03)
10 and above	66948 (42.19)	48758 (72.83)	7035 (14.43)	1557 (22.13)	23675 (35.36)
Number of concurrent use of medications chronically (median with IQR)[#]	9(6-12)	9 (7-13)	10 (6-14)	12 (8-17)	10 (6-13)

[a] Column percentage; [b] Row percentage

[c] Percentage expresses proportion of PIM users within each category for which at least one PIM was discontinued (defined by no recorded prescription between 12-3 months)

[d] Percentage expresses proportion of PIM discontinuer within each category for which at least one PIM was reinitiated

[e] In Belgium, residential care falls into two main categories: ROB, "rest homes", which provide nursing and personal care to older persons whose needs are low to moderate, and RVT, "rest and nursing homes" for people who strongly depend on care.

IQR: Inter quartile range

[#] Recorded at 3 months prior to death

* Recorded in the last 3 months

3.2. Prescription patterns, including discontinuation of medications

During the 18 to 12 months before death, at least one of the 15 medications was prescribed for 98,279 (61.93%) residents (**Table 2**). Specifically, at least one preventive medication was prescribed for 39,243 (24.73%) residents, while symptomatic medications were prescribed for 79,396 (50.03%) residents. Between 12 and 3 months prior to death, at least one chronically prescribed medication was discontinued for 13,724 (13.96%) chronic users. More specifically, a preventive medication was discontinued for 5,529 (14.09%) residents, while symptomatic medications were discontinued for 8,552 (10.77%) residents (**Table 3**).

3.3. Incidence of initiation and reinitiation of medications

In the last 3 months of life, medications were initiated for 47,138 (29.71%) residents after not being prescribed during the 12 to 3 months prior to death. A reinitiation of a previously discontinued medication happened for 2,328 (16.96%) residents. Both initiation and reinitiation happened more often for symptomatic medications than for preventive medications (p-value < 0.001). Specifically, the initiation rate was 6.71% for preventive medications and 25.53% for symptomatic medications, while the reinitiation rate was 11% for preventive medications and 20.29% for symptomatic medications. The rate of both initiation and reinitiation for specific medications varied substantially. The initiation rates ranged from 0% for Selective Estrogen Receptor Modulators (SERMs) to a maximum of 14.07% for antipsychotics. Similarly, the reinitiation rate ranged from 0% for SERMs to 30.37% for gastrointestinal antispasmodics **(Table 3)**.

Table 3: Initiation and reinitiation rates for individual medications and medication categories

Medications	Chronic use n (%)	Discontinuation: n (%)	Reinitiation n (%)	No prescription n (%)[b]	Initiation n (%)
Total (N=158,689)	***98,279 (61.93%)***	***13,724 (13.96%)***	***2,328 (16.96)***	***158,689 (100%)***	***47138 (29.71)***
Preventive medications	**39243 (24.73%)**	**5529 (14.09%)**	**608 (11.00 %)**	**158689 (100%)**	**10644 (6.71%)**
Lipid modifying agents	29431 (18.55%)	2726 (9.26%)	125 (4.59%)	117587 (74.10%)	1259 (1.07 %)
Calcium	7302 (4.60 %)	2206 (30.21%)	443 (20.08%)	134185 (84.56%)	8716 (6.50 %)
Osteoporosis drugs[a]	5438 (3.43%)	716 (13.17%)	40 (5.59 %)	148059 (93.30%)	1008 (0.68 %)
Selective Estrogen Receptor Modulators (SERMS)	108 (0.07%)	13 (12.04%)	0 (0 %)	158550 (99.91%)	1(0%)
Alpha-blockers	171 (0.11%)	22 (12.87%)	1 (4.55 %)	158377 (99.80%)	120 (0.08 %)
Symptom control medications	**79396 (50.03%)**	**8552 (10.77%)**	**1735 (20.29%)**	**158677 (99.99%)**	**40507 (25.53 %)**
Antipsychotics	26529 (16.72%)	1671 (6.30%)	339 (20.29 %)	105191 (66.29%)	14799 (14.07 %)
PPI	49841 (31.41%)	1432 (2.87%)	282 (19.69 %)	79722 (50.24%)	10228 (12.83 %)
Steroids	9062 (5.71%)	1467 (16.19 %)	345 (23.52 %)	128259 (80.82%)	12483 (9.73%)
alpha reductase inhibitors	1706 (1.08%)	518 (30.36%)	142 (27.41%)	150853 (95.06%)	4096 (2.72 %)
NSAIDs	5722 (3.61%)	1972 (34.46%)	186 (9.43%)	138257 (87.12%)	5762 (4.17 %)
H2-receptor antagonists	4769 (3.01%)	523 (10.97%)	19 (3.63 %)	150208 (94.66%)	1799 (1.20 %)
Gastrointestinal antispasmodics	4014 (2.53%)	1485 (37.00%)	451 (30.37%)	128259 (80.82%)	12483 (9.73 %)
Other	**3216 (2.03%)**	**357 (11.10%)**	**10 (2.80%)**	**158689 (100%)**	**538 (0.34)**
Theophylline	2077 (1.31 %)	165 (7.94%)	6 (3.64 %)	155453 (97.96%)	292 (0.19 %)
Sex hormones	614 (0.39%)	93 (15.15%)	3 (3.23 %)	157633 (99.33%)	204 (0.13 %)
Memantine	540 (0.34%)	101 (18.70%)	1 (0.99 %)	157936 (99.53%)	42 (0.03 %)

[a]Anti resorptive/bone anabolic drugs (bisphosphonates, strontium, teriparatide, denosumab)

[b] No prescription" is the denominator for initiation. When considering the total number, 100% represents all residents, meaning that no resident is taking all 15 medications at baseline. At least one medication initiation is based on being "at risk," defined as not using at least one of the 15 medications at baseline. For individual medications, initiation is clearly measured among residents who were not taking that specific medication at baseline.

3.4. Factors associated with initiation and reinitiation

Using regression analysis to control for potential confounders, we identified factors associated with the initiation and reinitiation of medications (**Table 4**). Reinitiation and initiation within the last three months of life was more likely among residents who died from cancer. Hospitalization in the last 3 months of life increased the risk of initiating and reinitiating medications by approximately twofold. Similarly, residents taking 5 or more chronic medications at 3 months prior to death were at a higher risk of reinitiating medications (RR=1.29, 95% CI=1.07-1.55 for those taking 5-9 medications, and RR=1.80, 95% CI=1.49-2.18 for those taking 10 or more). They were also more likely to initiate medications if they were taking 10 or more medications (RR=1.03, 95% CI=1.01-1.06). Being younger-old and middle-old at the time of death (65-84 years) slightly lowered the risk of initiating medications during the last 3 months of life compared with the oldest-old (85 years and above), with RR=0.94 (95% CI=0.91-0.97) for ages 65-74, and RR=0.98 (95% CI=0.96-0.99) for ages 75-84. Similarly, dying later than 2015 decreased the risk of initiation by 6-8%. However, both age at the time of death and the year of death were not associated with reinitiations. In addition, while gender and educational status

were not associated with the reinitiation of medications, the risk of initiation was higher for males (RR=1.20, 95% CI=1.18-1.22) and for those with primary (RR=1.05, 95% CI=1.02-1.08) and secondary education (RR=1.03, 95% CI=1.00-1.06).

Table 4: Factors associated with the initiation and reinitiations of drugs deemed inappropriate by STOPPFrail criteria

Variable	Reinitiation (n=2032, 16.85%)[a]			Initiation (n=41432, 29.77%)[b]		
	%	Univariate RR (95% CI)	Multivariate* RR (95% CI)	%	Univariate RR (95% CI)	Multivariate* RR (95% CI)
Age						
65-74	180 (19.98)	1.26 (1.1-1.45)	1.03 (0.89-1.18)	3102 (33.27)	1.16 (1.13 - 1.20)	**0.94 (0.91, 0.97)**
75-84	667 (18.17)	1.15 (1.05-1.25)	1.01(0.93- 1.10)	11882 (31.70)	1.11 (1.09 - 1.13)	**0.98 (0.96, 0.99)**
85 and over	1185 (15.83)	1.00	1.00	26448 (28.63)	1.00	1.00
Sex						
Female	1246 (16.01)	1.00	1.00	24284 (26.91)	1.00	1.00
Male	786 (18.39)	1.15 (1.06 - 1.25)	1.06 (0.98- 1.15)	17148 (35.04)	1.30 (1.28 - 1.32)	**1.20 (1.18, 1.22)**
Trajectory of illness						
Cancer	522 (20.94)	1.56 (1.40 - 1.76)	**1.18 (1.05-1.32)**	9717 (39.74)	1.70 (1.66 - 1.74)	**1.33 (1.30, 1.37)**
Organ failure	1068 (17.05)	1.27 (1.15 - 1.41)	0.99 (0.90- 1.10)	21620 (30.23)	1.29 (1.27 - 1.32)	**1.08 (1.05, 1.10)**
prolonged dwindling	442 (13.39)	1.00	1.00	10095 (23.37)	1.00	1.00
Educational status						
No formal education	187 (17.48)	1.00	1.00	3591 (29.07)	1.00	1.00
Primary education	836 (16.73)	0.96 (0.83 - 1.11)	0.98 (0.86- 1.14)	17118 (29.70)	1.02 (0.99 - 1.05)	**1.05 (1.02, 1.08)**
Secondary education	795 (16.23)	0.93 (0.80 - 1.07)	0.94 (0.82- 1.02)	16719 (29.82)	1.03 (0.99 - 1.06)	**1.03 (1.00, 1.06)**
Higher education	214 (19.60)	1.12 (0.94- 1.34)	1.14 (0.96- 1.36)	4004 (30.49)	1.05 (1.01 - 1.09)	1.02 (0.98, 1.06)
Types of Nursing home						
ROB	2015 (16.86)	1.00	1.00	41126 (29.78)	1.00	1.00
RVT	17 (15.60)	0.93 (0.60 - 1.43)	0.82 (0.51- 1.22)	306 (27.87)	0.94 (0.85 - 1.03)	0.93 (0.84- 1.01)
Hospitalization						
No	591 (10.15)	1.00	1.00	12777 (18.45)	1.00	1.00
Yes	1441 (23.10)	2.28 (2.08 - 2.49)	**1.89 (1.72- 2.10)**	28655 (40.98)	2.22 (2.18 - 2.27)	**2.08 (2.04, 2.12)**
Chronic medication use						
< 5	113 (8.76)	1.00	1.00	5224 (24.34)	1.00	1.00
5-9	568 (12.37)	1.41 (1.17 - 1.71)	**1.29 (1.07- 1.55)**	15368 (26.09)	1.07 (1.04 - 1.10)	0.98 (0.96-1.01)
10 and above	1351 (21.87)	2.50 (2.08 - 3.00)	**1.80 (1.49- 2.18)**	20840 (35.44)	1.46 (1.42 - 1.50)	**1.03 (1.01, 1.06)**
Years of death						
2015	403 (16.61)	1.00	1.00	9097 (31.36)	1.00	1.00
2016	464 (17.88)	1.08 (0.95 -1.22)	1.05 (0.93- 1.18)	8495 (29.53)	0.94 (0.92 - 0.97)	**0.94 (0.92, 0.96)**
2017	422 (16.76)	1.01 (0.89 - 1.14)	0.96 (0.85- 1.09)	8760 (29.64)	0.95 (0.92 - 0.97)	**0.94 (0.92, 0.96)**
2018	367 (16.29)	0.98 (0.86 - 1.12)	0.94 (0.83- 1.07)	7564 (28.92)	0.92 (0. 90 - 0.95)	**0.92 (0.90, 0.94)**
2019	376 (16.59)	1.00 (0.88 - 1.14)	0.95 (0.84- 1.08)	7516 (29.26)	0.93 (0.91 - 0.96)	**0.93 (0.91, 0.96)**

[a] Among those discontinued their medications between 12 and 3 months prior to death, analysed based on those discontinuers where their educational status is known(N=12058).

[b] Among decedents for whom the medications were not prescribed between 12 and 3 months prior to death, irrespective of medication use in the year preceding their death, analysed based on those discontinuers where their educational status is known (N= 139 182)

*Variables that were clinically relevant and available in the claims data were included in the univariate analyses. All eight variables were retained in the multivariate models: seven showing potential associations, and one (nursing home type) included due to its known clinical relevance. To minimize multicollinearity, highly correlated indicators (e.g., ICU, emergency, and hospital admissions) were consolidated by including only hospital admission. The Katz Index was excluded due to its strong overlap with nursing home type, which was included instead.

In sensitivity analyses, excluding residents who died from unpredictable fatal events (11,287, 7.11%) did not change the factors associated with both initiation and reinitiation, nor did it substantially alter the estimates (**Supplementary file 5.5**). Similarly, sensitivity analyses were conducted based on the type of medications (preventive and symptomatic). Although no new variables were associated with either reinitiation or initiation in the aggregated analysis, the associated factors and their estimates varied by medication type. For preventive medications, reinitiation was more likely among hospitalized residents and those taking five or more medications. Initiation was more likely in residents with organ failure and those who were hospitalized, but less likely among those aged 65–84 years, males, and individuals who died after 2015 **(Supplementary file 5.6)**. For symptomatic medications, reinitiation was more likely among males, cancer patients, hospitalized residents, and those taking five or more medications. Similarly, initiation was more likely in males, cancer cases, individuals with organ failure or primary education, and those who were hospitalized, but less likely in those aged 65–84 years, taking 5–9 medications, and who died after 2015 **(Supplementary file 5.7)**.

4. Discussion

4.1. Key findings

In the last three months of life, 16.96% of nursing home residents who discontinued medications (i.e.; no recorded prescription between 12-3 months) had them reinitiated, while 29.7% of them had medications initiated regardless of their previous use. The proportions differed by the type of medication: both initiation and reinitiation rates were significantly higher for symptomatic medications than for preventive ones (initiation: 25.53% symptomatic vs. 6.71% preventive; reinitiation: 20.29% symptomatic vs. 11% preventive). The risk of initiation and reinitiation was higher among individuals who died from cancer, were hospitalized in the last three months of life, or had 10 or more chronic medication prescriptions recorded at three months. Initiation risk was also higher in males and individuals with primary or secondary education. In contrast, being younger-old and middle-old (65–84 years) and dying after 2015 decreased the risk of initiation.

4.2. Interpretations and implications of the findings

While previous literature has described the high use of medications deemed inappropriate in the last years of life across different settings and patient groups using cross-sectional assessments [24, 36, 37], research on the initiation of new medications and their continued use as death approaches remains limited [8, 25]. Our study strengthens the conclusion that, even at the end of life, there is a high rate of initiation of medications deemed inappropriate [12, 38].

The proportion of medication initiation in our study aligns with a previous Belgian study, which reported a 30% initiation rate among residents with life-limiting diseases at the end of life using the same PIM screening tool [8]. In contrast, our findings indicate a higher initiation rate compared to a

Swedish study, which reported an overall initiation rate of 14% across all settings, with a lower rate of 8.8% in nursing homes during the last three months of life. This discrepancy may be due to differences in the tools used; the Swedish study used the Morin et al. criteria [31], which included a different selection of medications. Although Morin et al. did not classify medications as either symptomatic or preventive; most of the medications considered to have questionable benefits in their study were preventive. In contrast, in the STOPPFrail criteria selected for this study, approximately half were symptom control medications. In general, in the literature, the initiation of symptomatic medications for symptoms amendable to palliative care is considered appropriate, while the initiation of preventive medications is viewed as inappropriate [11, 12, 39]. Our study found that the initiation of symptom control medications was higher, whereas the initiation of preventive medications was lower. Furthermore, when comparing the initiation of preventive medications, our study reported a rate of 6.71% versus 8.8% for the nursing home subgroup in the Swedish study. The inclusion of a broader range of medications in the Swedish study (22 compared to 15 in our study) may also explain the observed small difference.

Our findings also highlight a rather frequent practice of reinitiation after discontinuation. This has been an, overall, overlooked aspect of medication prescribing at the end of life, which offers additional valuable insights into medication management. The relatively high reinitiation rate of medications (16.96%) among residents who discontinued them— particularly for symptomatic medications (20.29%) and preventive medications (11%) — provides key insights into the knowledge around medication management at the end of life. First, our study suggests a need to critically revisit existing guidelines on medication appropriateness with more awareness of potential benefits in palliative care contexts. While, with our data, we could not select those residents who were actually receiving palliative care before death, they were considered as eligible for it based on their illness. The higher reinitiation rate of symptomatic medications (e.g., PPIs, antipsychotics, corticosteroids, gastrointestinal antispasmodics) suggests a greater tendency to use medications for palliative care purposes [40]. The nuance in the classification of these medications as potentially inappropriate is also illustrated by discrepancies between how existing tools [41] such as STOPPFrail [17], Morin et al. [31], the WHO Essential Medicines List [22] consider these medications inappropriate or appropriate at the end of life. Our study contributes with empirical findings to this ongoing debate and emphasizes a need for a more nuanced approach that distinguishes between inappropriate prescribing and justified palliative use of medications. For example, initiating antipsychotics after transitioning to a nursing home has been associated with an increased risk of mortality, underscoring the importance of carefully weighing potential benefits and harms [42]. Similarly, evidence from evaluations of individual clinical data has shown a reported overuse (27.1%) and underuse (38.5%) of PPIs in nursing homes, illustrating the need for more balanced and individualized prescribing practices [43]. Second, our findings suggest the existence of a hitherto overlooked aspect of potentially inappropriate medication practice at the end of life. A notable number of nursing home residents had preventive medications either reinitiated or newly initiated, which are unlikely to offer meaningful benefits given their limited life expectancy, highlighting an ongoing gap in balancing appropriate prescribing in the palliative care context. However, literature reveals a lack of consensus regarding which medications are strictly preventive and, therefore, potentially futile at the end of life [44]. Furthermore, inconsistent recommendations and varying interpretations of guidelines contribute to clinical uncertainty [12, 45], challenging prescribers in effectively using them [41]. In light of the absence of standardization,

prescribing practices for patients at the end of life require a focus on deprescribing as a key component of a connected approach [44].

The findings of the current study, alongside recent deprescribing research conducted on nursing home residents with similar profiles and using the same assessment tool (same medication assessed), further highlight ongoing concerns in prescribing practices at the end of life. Notably, the study found that in the last 4 months of life, only 29.7% of residents had at least one PIM deprescribed, underscoring the low deprescribing rate and continued use of medications deemed inappropriate by STOPPFrail criteria [46]. However, the higher initiation and reinitiation rate of symptomatic medications compared to preventive ones, coupled with low deprescribing rates, suggests an increase in the use of symptomatic medications as death approaches in nursing homes. Previous studies also support this, showing that palliative drugs are frequently prescribed during the final days of life for nursing home residents [12, 40]. This suggests that medications for symptom control require more critical evaluation of their appropriateness. Similarly, the high rate of initiation and reinitiation of preventive medications in the current study, combined with the low deprescribing rate, suggests that residents at the end of life continue to use medications that are clearly futile, necessitating re-prescribing. However, re-prescribing at the end of life requires dual responsibility for prescribers (i.e., estimating the remaining life and evaluating the appropriateness of treatment) [36], with prognostic uncertainty often cited as a key factor contributing to inappropriate treatment [25, 40]. A medication review conducted by a multidisciplinary team could help reduce the use of futile medications [47-50]. However, in the context of nursing homes in Belgium, prescribers—typically general practitioners (GPs) who are primarily responsible for medication management—face significant time constraints, with consultation durations averaging only 20 minutes and in many other European countries, these timeframes are even shorter, ranging from 5 to 20 minutes [51]. Given that nursing home residents often have complex needs including polypharmacy and multimorbidity, providing appropriate medication management within such limited time is a considerable challenge. Additionally, although the literature indicates high palliative care needs among nursing home residents [5], it is often initiated late, typically only two weeks before death [52]. This delay is considered a missed opportunity to optimize medication use. Research has also shown that palliative care reduces inappropriate prescribing and increases deprescribing of unnecessary medications [53, 54]. Therefore, addressing prognostication and the earlier identification of palliative care needs is crucial [40]. For example, in our study, lipid-modifying agents were reinitiated in 4.59% of residents in the last three months of life, while no such medications were used in the last 14 days of life in a hospice setting [55], where prognosis is clearer. This contrast highlights the difficulty of medication management in nursing homes, where predicting decline is more complex. In Belgium, where nursing home residents are primarily managed by GPs, multidisciplinary collaboration involving geriatricians could offer potential benefits. Geriatricians are known to have a broader perspective on polypharmacy and may bring valuable experience and intuition to palliative care and estimating life expectancy. Such collaboration could improve medication management; ensuring treatments are more appropriately tailored to the needs of residents at the end of life.

Three factors were associated with both the initiation and reinitiation of medications. Consistent with a study from Sweden [25], residents who died from cancer had a higher risk of initiating medications. In cancer patients approaching death, the number of medications often increases, leading to a rise in inappropriate prescribing, particularly within symptom-relief drug classes [56]. Similarly, our findings indicated that cancer increases the initiation and reinitiation of symptomatic medications. However, it does not appear to increase the risk of initiating or reinitiating preventive medications. In clinical

practice, the prognosis for cancer is relatively easier to predict compared to other illness trajectories [57]. Knowledge of prognosis may shift treatment goals from curative intent to a focus on quality of life. This may lead to an increased tendency to prescribe symptomatic treatments, which could be inappropriate, such as in the case of cascade treatments, drug interactions, and should therefore be critically evaluated. Additionally, many cancer patients continue to receive preventive medications, even as the use of symptomatic treatments rises and deprescribing rates remain low in this population[46], highlighting the need for greater attention to medication appropriateness. Hospitalization during the last three months of life was also associated with increased medication initiation and reinitiation, aligning with previous findings that hospital stays increases the risk of PIM initiation [58, 59]. This may reflect intensified symptom management near death and the involvement of multiple specialists prescribing within their domains, often overlooking the patient's overall clinical context. Such issues are common in nursing home residents with multiple comorbidities, leading to inappropriate polypharmacy during hospital stays [60] and underscoring the need for post-discharge medication reviews [61]. Additionally, a higher number of chronic medications at three months increased the risk of initiation and reinitiation of medications. This finding is corroborated by studies conducted in nursing home settings [8, 59, 62] as well as in non-setting specific studies [56]. This may be partly explained by for example prescribing of medications to prevent side effects (like PPIs for NSAIDs) and comfort-oriented drugs (e.g., laxatives and opioid), which, in turn, increase the risk of drug-drug interactions and adverse drug reactions, potentially leading to a decline in quality of life [63-65]. The treatment cascade from polypharmacy and inappropriate prescribing [66, 67] may also contribute to medication initiation and reinitiation. At the end of life, while symptom-relief drugs are often prescribed, clinicians may hesitate to deprescribe medications started by others, especially during hospitalization [41], and the continued use of preventive medications remains high [12, 25]. Multidisciplinary collaboration, including consultation with a geriatrician who can assess the patient's overall clinical picture and evaluate the pros and cons of polypharmacy, as well as with clinicians trained in palliative care, could be highly beneficial in these situations.

4.3. Strengths and limitations

To the best of our knowledge, this is the first study to evaluate the reinitiation of medications deemed inappropriate in a nursing home setting at the population level with nationwide coverage, while distinguishing between preventive and symptomatic medications. The selection of individuals who died from conditions potentially amenable to palliative care across different illness trajectories as the study population, along with the investigation of reinitiation and initiation patterns for symptomatic and preventive medications, strengthens the clinical relevance of the findings. In line with other studies utilizing healthcare reimbursement/ dispensing data, several limitations should be considered when interpreting the results. First, the use of the STOPPFrail criteria to assess the appropriateness of medications requires clinical information to understand why the medications were prescribed. As a result, we were unable to apply all of the STOPPFrail criteria, limiting our study to 15 medications selection for which minimal clinical information is needed [30]. However, this limitation could potentially lead to an overestimation of the reinitiation and initiation of medications deemed inappropriate, assuming that all reinitiation and initiation is inappropriate. Secondly, due to the lack of clinical data, the classification of medications as either symptomatic or preventive is approximate [12]. Medications with dual purposes were classified based on existing literature and the contexts in which they are most commonly prescribed. However, acknowledging that their uses are not mutually exclusive, this approach could introduce slight bias in the estimation. Third, dispensation of a medication at the

hospital or community pharmacy is used as a proxy for medication use, but we cannot confirm whether the patients actually took the medication. Fourth, for some drugs prescribed over the counter, the reinitiation and initiation rate might be underestimated (e.g., NSAIDs) if they were dispensed over the counter. Fifth, the prognostic uncertainty experienced by prescribers could be underestimated. Although the study population consists of nursing home residents who died with life-limiting conditions potentially amenable to palliative care, clinicians in the real world may not be able to precisely estimate the date of death [25]. To reduce this uncertainty, we conducted a sensitivity analysis by excluding those whose underlying causes of death were an acute and unforeseen fatal event. Lastly, although the selection of the study population was potentially amenable to palliative care, the pattern of medication use could vary based on who actually received palliative care and when it was started. However, we did not know who received palliative care or not. In the literature, receiving palliative care has been shown to reduce PIMs; however, palliative care physicians have different attitudes towards drug prescriptions in the palliative care context [38], highlighting the need for multidisciplinary medication review decisions.

5. Conclusions

A significant proportion of nursing home residents undergoes a reinitiation or new initiation of medications deemed inappropriate at the end of life according to existing lists and guidelines. Many of these medications were likely prescribed for palliative purposes. Hence, our study on the one hand suggests that existing guidelines on medication appropriateness may need to more explicitly pay attention to palliative care contexts. On the other hand, the finding that a notable number of residents had preventive medications either reinitiated or newly initiated, which are unlikely to provide meaningful benefits in the patients' remaining life, suggests the existence of an inappropriate practice of medication at the end of life that has received little to no attention so far. To address this, the care of nursing home residents can benefit from clear guidelines on medication use in palliative care, consultation with a geriatrician in complex cases, and support from specialist palliative care services, which may help achieve a more balanced approach to medication management. Furthermore, clinicians should be trained to assess medication appropriateness based on care goals, supporting both deprescribing and appropriate prescribing.

References

1. Holmes HM, Hayley DC, Alexander GC*, et al.* Reconsidering medication appropriateness for patients late in life. Arch Intern Med. 2006;166(6):605-9.
2. Liu J, Zhu Y, Tan JK*, et al.* Factors Associated with Frailty in Older Adults in Community and Nursing Home Settings: A Systematic Review with a Meta-Analysis. Journal of Clinical Medicine. 2024;13(8):2382.
3. Taxis K, Kochen S, Wouters H*, et al.* Cross-national comparison of medication use in Australian and Dutch nursing homes. Age Ageing. 2017;46(2):320-3.
4. Collingridge Moore D, Payne S, Keegan T*, et al.* Length of stay in long-term care facilities: a comparison of residents in six European countries. Results of the PACE cross-sectional study. BMJ Open. 2020;10(3):e033881.
5. Morin L, Aubry R, Frova L*, et al.* Estimating the need for palliative care at the population level: a cross-national study in 12 countries. Palliat Med. 2017;31(6):526-36.
6. Jordan RI, Allsop MJ, ElMokhallalati Y*, et al.* Duration of palliative care before death in international routine practice: a systematic review and meta-analysis. BMC Med. 2020;18(1):368.
7. Hertogh CMPM, Ribbe MW. [Palliative care and the health care for the elderly]. Tijdschr Gerontol Geriatr. 2008;39(6):220-3.
8. Paque K, Elseviers M, Vander Stichele R*, et al.* Balancing medication use in nursing home residents with life-limiting disease. Eur J Clin Pharmacol. 2019;75:969-77.
9. Aronson JK. Balanced prescribing–principles and challenges. Br J Clin Pharmacol. 2012;74(4):566-72.
10. Mangin D, Bahat G, Golomb BA*, et al.* International Group for Reducing Inappropriate Medication Use & Polypharmacy (IGRIMUP): Position Statement and 10 Recommendations for Action. Drugs Aging. 2018;35(7):575-87.
11. Paque K, Elseviers M, Vander Stichele R*, et al.* Changes in medication use in a cohort of patients with advanced cancer: The international multicentre prospective European Palliative Care Cancer Symptom study. Palliat Med. 2017;32(4):775-85.
12. Van der Meer HG, Taxis K, Pont LG. Changes in prescribing symptomatic and preventive medications in the last year of life in older nursing home residents. Front Pharmacol. 2018;8:990.
13. Maddison AR, Fisher J, Johnston G. Preventive medication use among persons with limited life expectancy. Progress in palliative care. 2011;19(1):15-21.
14. Wehling M, Petrovic M. Deprescribing or represcribing: not just a semantic dilemma. Eur Geriatr Med. 2022;13(3):529-30.
15. Griese-Mammen N, Hersberger KE, Messerli M*, et al.* PCNE definition of medication review: reaching agreement. Int J Clin Pharm. 2018;40(5):1199-208.
16. Anlay DZ, Paque K, Van Leeuwen E*, et al.* Tools and guidelines to assess the appropriateness of medication and aid deprescribing: An umbrella review. Br J Clin Pharmacol. 2024;90(1):12-106.
17. Lavan AH, Gallagher P, Parsons C*, et al.* STOPPFrail (Screening Tool of Older Persons Prescriptions in Frail adults with limited life expectancy): consensus validation. Age Ageing. 2017;46(4):600-7.
18. Curtin D, Gallagher P, O'Mahony D. Deprescribing in older people approaching end-of-life: development and validation of STOPPFrail version 2. Age Ageing. 2021;50(2):465-71.
19. Morin L, Laroche ML, Vetrano DL*, et al.* Adequate, questionable, and inadequate drug prescribing for older adults at the end of life: a European expert consensus. Eur J Clin Pharmacol. 2018;74(10):1333-42.
20. Elsten EE, Pot IE, Geijteman EC*, et al.* Recommendations for Deprescribing of Medication in the Last Phase of Life: An International Delphi Study. J Pain Symptom Manage. 2024;68(5):443-55. e2.
21. Dijk MMT, A.M. Pouw CK, Hertogh CMPM*, et al.* Medication Appropriateness for Older Nursing Home Patients With a Limited Life Expectancy: From STOPP/START Version 2 to the ReNeWAL Criteria. J Am Med Dir Assoc. 2024:105143.
22. World Health Organization. Web Annex A. World Health Organization Model List of Essential Medicines – 23rd List, 2023. Geneva: World Health Organization; 2023. Contract No.: WHO/MHP/HPS/EML/2023.02.
23. Knaul FM, Farmer PE, Krakauer EL*, et al.* Alleviating the access abyss in palliative care and pain relief—an imperative of universal health coverage: the Lancet Commission report. The Lancet. 2018;391(10128):1391-454.
24. Fournier A, Anrys P, Beuscart J-B*, et al.* Use and Deprescribing of Potentially Inappropriate Medications in Frail Nursing Home Residents. Drugs Aging. 2020;37(12):917-24.
25. Morin L, Wastesson JW, Laroche M-L*, et al.* How many older adults receive drugs of questionable clinical benefit near the end of life? A cohort study. Palliat Med. 2019;33(8):1080-90.
26. Benchimol EI, Smeeth L, Guttmann A*, et al.* The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement. PLoS Med. 2015;12(10):e1001885.
27. IMA. Katz-schaal (Katz scale). Belgian Data Dictionary for Social Protection; [cited 2025 Apr 9]. Available from: https://metadata.ima-aim.be/nl/app/bdds/Kz [
28. Maetens A, De Schreye R, Faes K*, et al.* Using linked administrative and disease-specific databases to study end-of-life care on a population level. BMC Palliat Care. 2016;15:1-10.
29. Norwegian Institute of Public Health. ATC/DDD Index. Available from: https://atcddd.fhi.no/atc_ddd_index/. Accessed August 6, 2024. [
30. Paque K, De Schreye R, Elseviers M*, et al.* Discontinuation of medications at the end of life: A population study in Belgium, based on linked administrative databases. Br J Clin Pharmacol. 2019;85(4):827-37.

31. Morin L, Laroche M-L, Vetrano DL*, et al.* Adequate, questionable, and inadequate drug prescribing for older adults at the end of life: a European expert consensus. Eur J Clin Pharmacol. 2018;74(10):1333-42.
32. Lee SB, Oh JH, Park JH*, et al.* Differences in youngest-old, middle-old, and oldest-old patients who visit the emergency department. Clin Exp Emerg Med. 2018;5(4):249-55.
33. UNESCO Institute for Statistics. International Standard Classification of Education: ISCED 2011 [Internet]. Montreal: UNESCO Institute for Statistics; 2012 [cited 2025 Feb 4]. Available from: http://uis.unesco.org/sites/default/files/documents/international-standard-classification-of-education-isced-2011-en.pdf.
34. Lunney JR, Lynn J, Foley DJ*, et al.* Patterns of Functional Decline at the End of Life. JAMA. 2003;289(18):2387-92.
35. For a healthy Belgium: Care for older people [updated 01 February 2024; cited 2024 April 09]. Available from: https://www.healthybelgium.be/en/health-system-performance-assessment/specific-domains/care-for-the-elderly.
36. Malek Makan A, van Hout H, Onder G*, et al.* Prevalence of potentially inappropriate medications according to STOPP-Frail criteria in nursing home residents, the SHELTER study. BMC Geriatr. 2024;24(1):882.
37. Ham L, Geijteman ECT, Aarts MJ*, et al.* Use of potentially inappropriate medication in older patients with lung cancer at the end of life. J Geriatr Oncol. 2022;13(1):53-9.
38. Pasina L, Recchia A, Nobili A*, et al.* Inappropriate medications among end-of-life patients living at home: an Italian observational study. Eur Geriatr Med. 2020;11(3):505-10.
39. Poudel A, Yates P, Rowett D*, et al.* Use of Preventive Medication in Patients With Limited Life Expectancy: A Systematic Review. J Pain Symptom Manage. 2017;53(6):1097-110.e1.
40. Jansen K, Schaufel MA, Ruths S. Drug treatment at the end of life: an epidemiologic study in nursing homes. Scand J Prim Health Care. 2014;32(4):187-92.
41. Anlay DZ, Peremans L, Cohen J*, et al.* Deprescribing for nursing home residents with limited life expectancy: A qualitative study to identify barriers and enablers for healthcare professionals. Geriatric Nursing. 2025;62:1-11.
42. Harrison SL, Sluggett JK, Lang C*, et al.* Initiation of antipsychotics after moving to residential aged care facilities and mortality: a national cohort study. Aging Clin Exp Res. 2021;33(1):95-104.
43. Wabe N, Urwin R, Meulenbroeks I*, et al.* Over- and Underuse of Proton Pump Inhibitors in Nursing Homes: A Multisite Longitudinal Cohort Study. J Am Med Dir Assoc. 2025;26(2):105393.
44. Todd A, Husband A, Andrew I*, et al.* Inappropriate prescribing of preventative medication in patients with life-limiting illness: a systematic review. BMJ supportive & palliative care. 2017;7(2):113-21.
45. Alhawassi TM, Krass I, Pont LG. Hypertension in Older Persons: A Systematic Review of National and International Treatment Guidelines. J Clin Hypertens (Greenwich). 2015;17(6):486-92.
46. Anlay DZ, Paque K, Van den Eynden B*, et al.* International Deprescribing Guidelines Did Not Impact Actual Practice in Deprescribing of Potentially Inappropriate Medications for Nursing Home Residents: An Interrupted Time Series Analysis. Drugs Aging. 2025.
47. Wouters H, Scheper J, Koning H*, et al.* Discontinuing Inappropriate Medication Use in Nursing Home Residents: A Cluster Randomized Controlled Trial. Ann Intern Med. 2017;167(9):609-17.
48. Lenander C, Bondesson Å, Viberg N*, et al.* Effects of medication reviews on use of potentially inappropriate medications in elderly patients; a cross-sectional study in Swedish primary care. BMC Health Serv Res. 2018;18(1):616.
49. Wauters M, Elseviers M, Vander Stichele R*, et al.* Efficacy, feasibility and acceptability of the OptiMEDs tool for multidisciplinary medication review in nursing homes. Arch Gerontol Geriatr. 2021;95:104391.
50. Anderssen-Nordahl E, Fernández-Liz E, Sabaté Gallego M*, et al.* The impact of a multidisciplinary team intervention on medication prescription in nursing homes in Catalonia. Front Pharmacol. 2024;15:1445141.
51. Irving G, Neves AL, Dambha-Miller H*, et al.* International variations in primary care physician consultation time: a systematic review of 67 countries. BMJ Open. 2017;7(10):e017902.
52. Ten Koppel M, Onwuteaka-Philipsen BD, Van den Block L*, et al.* Palliative care provision in long-term care facilities differs across Europe: Results of a cross-sectional study in six European countries (PACE). Palliat Med. 2019;33(9):1176-88.
53. Marin H, Mayo P, Dersch-Mills D*, et al.* The effect of palliative care consults on deprescribing in palliative cancer patients. J Clin Oncol. 2018;36(34_suppl):92-.
54. Suhrie EM, Hanlon JT, Jaffe EJ*, et al.* Impact of a geriatric nursing home palliative care service on unnecessary medication prescribing. Am J Geriatr Pharmacother. 2009;7(1):20-5.
55. Alwidyan T, McCorry NK, Black C*, et al.* Prescribing and deprescribing in older people with life-limiting illnesses receiving hospice care at the end of life: A longitudinal, retrospective cohort study. Palliat Med. 2024;38(1):121-30.
56. Murphy M, Bennett K, Wright M*, et al.* Potentially inappropriate prescribing in older adults with cancer receiving specialist palliative care: a retrospective observational study. Int J Clin Pharm. 2023;45(1):174-83.
57. Orlovic M, Droney J, Vickerstaff V*, et al.* Accuracy of clinical predictions of prognosis at the end-of-life: evidence from routinely collected data in urgent care records. BMC Palliat Care. 2023;22(1):51.
58. Pérez T, Moriarty F, Wallace E*, et al.* Prevalence of potentially inappropriate prescribing in older people in primary care and its association with hospital admission: longitudinal study. BMJ. 2018;363:k4524.
59. Weinand S, Thürmann PA, Dröge P*, et al.* [Potentially Inappropriate Medication of Nursing Home Residents: An Analysis of Risk Factors Based on National Claims Data (AOK) for 2017]. Gesundheitswesen. 2022;84(5):448-56.
60. Halli-Tierney AD, Scarbrough C, Carroll D. Polypharmacy: Evaluating Risks and Deprescribing. Am Fam Physician. 2019;100(1):32-8.

61. Zhang AD, Zepel L, Woolson S*, et al.* Initiation and Persistence of Antipsychotic Medications at Hospital Discharge Among Community-Dwelling Veterans With Dementia. The American Journal of Geriatric Psychiatry. 2024.
62. Cool C, Cestac P, Laborde C*, et al.* Potentially inappropriate drug prescribing and associated factors in nursing homes. J Am Med Dir Assoc. 2014;15(11):850.e1-9.
63. Kierner KA, Weixler D, Masel EK*, et al.* Polypharmacy in the terminal stage of cancer. Support Care Cancer. 2016;24(5):2067-74.
64. Frechen S, Zoeller A, Ruberg K*, et al.* Drug interactions in dying patients: a retrospective analysis of hospice inpatients in Germany. Drug Saf. 2012;35(9):745-58.
65. Morgan NA, Rowett D, Currow DC. Analysis of drug interactions at the end of life. BMJ Support Palliat Care. 2015;5(3):281-6.
66. Daunt R, McGettigan S, Kelly L*, et al.* Detection of Prescribing Cascades in Multimorbid Older Patients Hospitalized with Acute Unselected Illness. Age Ageing. 2024;53(Supplement_4).
67. O'Mahony D, Rochon PA. Prescribing cascades: we see only what we look for, we look for only what we know. Age Ageing. 2022;51(7).

PART IV

EFFECTS OF DEPRESCRIBING ON QUALITY-OF-LIFE–RELATED OUTCOMES IN NURSING HOME RESIDENTS

Chapter 6

Evolution of health and medication use in a cohort of nursing home residents: a data linkage study

Published:

Anlay DZ**,** de Almeida Mello J, Declercq A, Van Leeuwen E, Paque K, Cohen J, Dilles T. Evolution of Health and Medication Use in a Cohort of Nursing Home Residents: A Data Linkage Study.
J Am Med Dir Assoc. 2026 Jul 2;27(8):106300.
Doi: https://doi.org/10.1016/j.jamda.2026.106300

ABSTRACT

Objectives

Describe the evolution of chronic medication use, potentially inappropriate medications (PIMs), and health outcomes in nursing home (NH) residents, and explore associations between changes in medication use and health outcomes

Design

A retrospective longitudinal data linkage study

Setting and Participants

NH residents in Flanders, insured in Belgium, aged ≥65, with the Belgian version of the interRAI Long Term Care Facility (BelRAI LTCF) assessment between 2016 and 2022.

Methods

Linked data from BelRAI LTCF and national healthcare claims (IMA-AIM). Residents were assessed at baseline (first BelRAI after admission) and 12 months later (±1 month) window. PIM selection was based on a published umbrella review. Health outcomes were measured using validated interRAI scales.

Results

At baseline, 8,713 residents were assessed, of whom 1,691 (19.4%) had a one-year reassessment. At baseline, 94.6% used ≥1 chronic medication, with polypharmacy in 48.4% and excessive polypharmacy in 15%. Over one year, mean chronic medications increased from 5.87 to 6.1, while PIM use declined from 72.7% to 56.0%. Polypharmacy transitions involved 13% of residents moving in and 8% moving out, associated with changes in activity of daily living (ADL) performance and cognitive function. For PIMs, 48.3% continued use, 24.5% discontinued, and 7.8% started, associated with ADL, aggressive behavior, and comorbidity. Across all health domains, 70–88% of residents maintained baseline status. When changes occurred, deterioration was more frequent than improvement, with highest declines in health instability (23.6%), mood (18.3%), and cognition (13.6%), and lowest in pain (9.7%) and ADL (9.2%).

Conclusions and Implications.

Over one year, chronic medication use increased while PIMs decreased. Most health outcomes remained stable, though deterioration was more frequent than improvement. Changes in medication use were associated with changes in health outcomes, and some residents improved, suggesting targeted interventions may help. This innovative data linkage demonstrates strong potential to generate evidence on the causal effects of individual PIMs on health outcomes.

Introduction

Older adults constitute nearly 20% of the population, a proportion expected to increase,[1] driving demand for long-term care and admission to nursing homes (NH).[2] NH residents are a dynamic and vulnerable population with high first-year mortality (up to 42%),[3] underscoring the need for continuous follow-up and quality improvement.[4] Although residents' health generally declines after admission, maintaining quality of life and dignity at end-of-life remains critical. Quality of life is highly valued and closely tied to health outcomes across physical, mental, cognitive, and functional domains, yet these domains remain underassessed in research and are often overlooked in longitudinal studies.[5, 6] Understanding these outcome domains change over time is essential for identifying emerging resident needs, guiding preventive strategies, and informing resource allocation. [7]

Polypharmacy (concurrent use of ≥5 medications),[8] and potentially inappropriate medication (PIM, medications whose risks may outweigh benefits depending on the individual patient context) [9] are common in NH.[4, 10] Polypharmacy is widely used as a quality indicator [11] and is associated with adverse outcomes including frailty, falls, hospitalizations, reduced adherence, and mortality.[12-16] It contributes to PIM exposure [17, 18] and prescribing cascades,[19] further increasing medication burden and harm. Existing evidence remains limited: they examined chronic medication use without assessing PIMs,[20] relied on repeated cross sectional samples rather than individual trajectories,[21] or assessed PIM reduction only within interventional settings,[22] despite the high prevalence of PIMs in NHs, reaching 88%.[23] These limitations highlight the need to monitor individual medication trajectories after admission,[24] as it provides valuable insights into the current medication prescribing patterns for chronic medications and PIMs, including continued use, new use, and deprescribing. However, little is known about how these medication patterns evolve after admission or how changes in medication use (chronic medication and PIMs) relate to changes in resident health.

Medication use transitions and health trajectories are likely to influence each other. Residents with worsening health may increase their use of medicines due to symptom progression or prescribing cascades,[25, 26] while deprescribing often follows a decline in health or a shift in care goals towards comfort. [27, 28] Conversely, as a high medication burden has been linked to declines in certain health domains, such as poorer health- related quality of life, reducing medication burden may help maintain stability or prevent further decline. [29] Examining medication trajectories together with health trajectories is therefore essential to understand how both evolve and how these changes relate to one another after nursing home admission.[30]

Collecting longitudinal data from large cohorts is resource-intensive.[31] Previous studies were constrained by the lack of multidomain, patient centered measures, which limited the ability to examine how medication changes relate to changes in health. In Belgium, the InterMutualist Agency's (IMA-AIM) provides detailed claims data on health care use and medication dispensing,[32] but these data do not capture quality-of-life related patient outcomes.[11] The solution therefore lies in the innovative linkage of different data sources to enrich and complement existing information. In this context, the InterRAI Long Term Care facility assessment, implemented as BelRAI in Belgium, provides standardized multidomain evaluations.[33, 34] Linking BelRAI with IMA-AIM enables longitudinal, multidimensional analyses that have been missing from previous studies and addresses the lack of longitudinal evidence on medication use and quality-of-life related patient outcomes. Therefore, this study aimed to describe the evolution of chronic medication use, PIMs, and quality-of-life related patient outcomes across major health domains between baseline (defined as the first BelRAI

assessment after admission) and one year later, and to explore the association between changes in medication use and changes in these outcomes among NH residents in Flanders, Belgium.

Methods

Study design, settings, and populations

A retrospective cohort study was conducted among NH residents in Flanders, Belgium, using prospectively collected BelRAI LTCF data (2016–2022) linked with IMA-AIM insurance data at each assessment. Residents were assessed at baseline (first BelRAI after admission) and one year later (±1 months window). Only data from NH using BelRAI could be included. At the time of the study, the BelRAI was being implemented, nationally, but was not yet mandatory. Since 2025, it became mandatory in all NHs. The sample in this study consists therefore of the early adopters of the instrument. Residents aged ≥65 at baseline were included, while those receiving only daycare were excluded.

Belgian NHs primarily admit older adults with high care dependency, as extensive home care services allow many to remain at home. About 75% of residents are care-dependent, and over one-third have dementia.[35] Each NH houses ~100 residents, cared for by mixed staff and visited by a median of 30 general practitioners, each independently managing prescribing. Coordination is overseen by a coordinating and consulting Physician.[36]

Data source and handling

Data were drawn from two linked sources: BelRAI LTCF and five IMA-AIM databases. BelRAI LTCF provides standardized, validated outcome measures across key health domains ***(Table 1)***. IMA-AIM contributed: (1) socio-demographics; (2) healthcare utilization including medications dispensed in hospital pharmacies; (3) hospitalizations; (4) Pharmanet (community-dispensed reimbursed medications); and (5) NH admissions and length of stay. For each resident, IMA-AIM data were linked to every BelRAI assessment, creating a comprehensive dataset of medication use and health outcomes enabling longitudinal monitoring.

Medications in the IMA-AIM dataset were recorded using the WHO Anatomical Therapeutic Chemical (ATC) classification system (WHO ATC/DDD Index) at the fifth level for active substances,[37] grouped into broader therapeutic classes when necessary for analysis. Healthcare utilization, including intensive care unit (ICU) stays and emergency department admissions, was identified using nomenclature codes (**Supplementary file 6.1**).

Identification of medication for the study

We identified all prescribed reimbursed medications at each BelRAI assessment, summarizing total use, chronic use, and polypharmacy. Chronic medications were grouped into main anatomical system categories (e.g., cardiovascular, alimentary tract) to analyze patterns and changes over time. PIMs were selected using the umbrella review by Anlay et al., which lists medications considered inappropriate for frail older adults with limited life expectancy, including NH residents,[9] allowing us to select medications consistently classified as inappropriate across different tools. The list was restricted to reimbursed medications in Belgian claims data where inappropriateness could be inferred from chronic use, as dose-based criteria were not available. This process resulted in a final set of 13 medication classes: H2 receptor antagonists, proton pump inhibitors, vitamin D, calcium supplements,

lipid-modifying agents, systemic corticosteroids, long-term oral NSAIDs, anti-resorptive or bone anabolic drugs for osteoporosis, antipsychotics, tricyclic antidepressants, systemic drugs for obstructive airway diseases, systemic antihistamines, and anti-dementia drugs. Details on how inappropriateness was defined for each class, along with corresponding ATC codes, are provided in **Supplementary file 6.2**.

Measurements of variables

Chronic medication use was assessed at two time points: the first BelRAI assessment and 12 months later, based on prescriptions issued in the six months preceding each assessment. Residents were classified as chronic users if they had at least two prescriptions within the 180 days prior to the BelRAI assessment,[38] the interval between consecutive prescriptions did not exceed 90 days, the sum of all intervals including the interval between the last prescription and the BelRAI assessment was at least 90 days, and at least one prescription occurred within three months before the assessment ***(Figure 1)***. Selected PIMs were also assessed at these two points, classified according to criteria specific to each medication.[9]

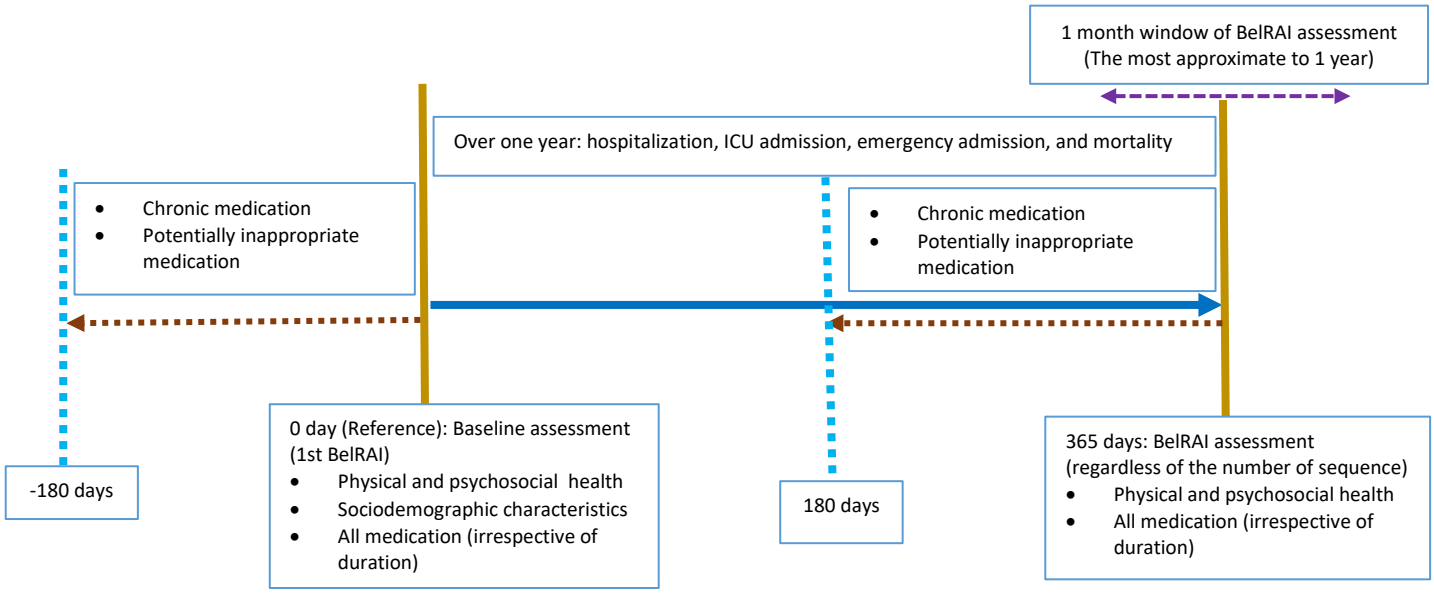


Figure 1: A study diagram with timelines

Health outcomes across physical, psychosocial, mental, and health status domains were evaluated using validated interRAI scales and cut-off scores from previous studies.[7, 39-43] A 12-month interval was chosen because BelRAI assessments are typically conducted every six months, ensuring that all residents would have at least one reassessment. This interval maximized the number of residents with available data, increasing statistical power, and avoided longer follow-up periods that would be less representative (and inclusive) of the original and target cohort due to high attrition from mortality after the first year. The scales, score ranges, and applied cut-offs are presented in ***Table 1***.

Table 1: Measured variables, assessment time points, scoring ranges, and interpretation of cut-off values derived from BelRAI LTCF and IMA-AIM data sources.

Measured health domains and outcome scales	Assessment time	Scored range (Ordinal)	Cut-off value and Interpretation of the cut off	Data source
Physical function				
Activities of Daily Living (ADL) performance (ADL hierarchy [ADLH] scale) [39]	Baseline and 12 months	0-6 ≥3 (extensive assistance for ADL)	0: no existing impairment 1-2: mild impairment ≥3 (moderate to severe impairment): required extensive assistance	BelRAI LTCF
Mood and behavior				
Mood disturbance (Depression Rating Scale [DRS]) [7]	Baseline and 12 months	0-14 ≥3 (daily depressive symptoms)	0: no mood disturbance 1-2: mild mood disturbance ≥3: moderate/severe mood disturbance	BelRAI LTCF
Aggressive behaviour (Aggressive Behavior Scale [ABS])[40]	Baseline and 12 months	0-12	0: No signs of aggression 1-2: Mild aggression 3-4: Moderate aggression ≥5: More severe aggression	BelRAI LTCF
Cognitive function				
Cognitive status (Cognitive Performance Scale [CPS])[41]	Baseline and 12 months	0-6	0-1:intact/Borderline intact 2: Mild impairment ≥3: moderate to severe impairment	BelRAI LTCF
Health status				
Clinical (in)stability (Changes in Health, End-Stage Disease, Signs and Symptoms [CHESS] Scale) [42]	Baseline and 12 months	0-5	0: No health instability 1-2: Minimal/low health instability ≥3: Moderate to severe health instability	BelRAI LTCF
Fall (Risk of falls)	Baseline and 12 months	0-3	0: No fall in last 90 days 1: No fall in last 30 days but fell 31-90 days ago 2: One fall in last 30 days 3: 2+ falls in last 30 days	BelRAI LTCF
Pain (Pain scale) [43]	Baseline and 12 months	0-4 ≥2 (mild daily pain)	0: No pain 1: Less than daily pain 2: Daily pain but not severe 3: Daily severe pain 4: Daily excruciating pain Collapse in to (0, 1-2,3-4)	BelRAI LTCF
Social function				
Level of social engagement (Index of Social Engagement [ISE])	Baseline and 12 months	0-6	0: No engagement 1-2: Low engagement 3-4: Moderate engagement 5-6: High engagement	BelRAI LTCF
Other outcomes				
Co-morbidities/multimorbidity (Based on major diagnosis predefined in interRAI LTCF) **(supplementary file 6.3)**	Baseline and 12 months	0-23	Number of co-morbidities listed in the diagnosis section of the assessment	BelRAI LTCF
Hospitalization	Baseline to 12 months	At least one time admitted to ahospital	0: No 1: Yes	IMA (Hospitalization dataset)
ICU admission	Baseline to 12 months	At least one time admitted in ICU	0: No 1: Yes	IMA (Hospitalization dataset)
Emergency hospital admission	Baseline to 12 months	At least one time admitted in emergency	0: No 1: Yes	IMA (Healthcare claim data)

Long-term medication	Baseline and 12 month	Medications used for more than 3 months	0: 0-4 1: Polypharmacy (5-9) 2: Excessive polypharmacy (10 and above)	IMA (health care and pharmanet)
Death	Baseline to 12 months	Death after first BelRAI assessment	0: No 1: Yes	IMA (Population databases)

Abbreviations: ABC – Aggressive Behaviour Scale; ADLH – Activities of Daily Living Hierarchy Scale; CHESS – Changes in Health, End-Stage Disease, and Signs and Symptoms Scale; CPS – Cognitive Performance Scale; DRS – Depression Rating Scale; ICU – Intensive Care Unit; ISE – Index of Social Engagement

For each health outcome, the transitions between baseline and 12 months were defined on ordinal scales classified as "improved", "no change", or "deteriorated". For PIMs, the transitions were categorized and ordered as not prescribed (no use at either time point), discontinued (stopped use by 12 months), newly prescribed (started use during follow-up), or continued (use at both baseline and 12 months). Polypharmacy transitions were classified as de-escalated (changed from polypharmacy to no polypharmacy), maintained (polypharmacy status remained the same), or escalated (changed from no polypharmacy to polypharmacy). For comorbidities, changes were defined as decreased, stable, or increased in the number of diagnosed conditions. These transition categories were used to explore ordered associations between medication changes and health outcomes.

Data analysis

Analyses were performed using SAS Enterprise Guide 8.3 (SAS Institute Inc., Cary, NC, USA). Sociodemographic characteristics were summarized at baseline for the total cohort and the longitudinal subgroup. Categorical variables were reported as frequencies and percentages; continuous variables as means (SD) or medians (IQR), depending on distribution.

Baseline differences between cross-sectional and longitudinal cohorts were tested using χ^2 for categorical variables. Paired comparisons between baseline and 12 months used paired t-tests (normal continuous), Wilcoxon signed-rank (non-normal continuous), McNemar (dichotomous), and Stuart–Maxwell (categorical with >2 categories) .[44]

Effect sizes were reported as Cohen's g for two-category variables (negligible <0.05, small 0.05–0.14, medium 0.15–0.24, large ≥0.25) [45] and weighted Cohen's kappa for multi-category agreement (slight ≤0.20, fair 0.21–0.40, moderate 0.41–0.60, substantial 0.61–0.80, almost perfect ≥0.81).[46] Because dementia represents a clinically relevant subgroup in nursing homes, we also examined changes in medication use among residents with dementia. These results are presented in the supplementary materials. Trends in chronic medication and PIM use (2016–2022) were tested with the Cochran–Armitage trend test. Associations between medication changes and health outcomes were explored using the Cochran–Mantel–Haenszel (CMH) linear-by-linear statistic for ordinal-by-ordinal relationships, and χ^2 or Fisher's exact tests when a nominal variable (e.g., sex) was involved. Cramer's V was used as the effect size (negligible <0.10, small 0.10–0.29, medium 0.30–0.49, large ≥0.50).[47] To identify the direction of monotone associations, we used the sign of Somers' D (C|R), where positive values indicate higher medication intensification with greater deterioration and negative values indicate the reverse. Significance for each test was set at $p < 0.05$.

Results

Characteristics of study participants

Of 15,992 NH residents with at least one BelRAI assessment, 8,713 residents were assessed cross-sectionally at their first BelRAI assessment, and 1,691 (19.4%) residents were assessed longitudinally one year after the baseline assessment **(Supplementary file 6.4). Table 2** presents the baseline

characteristics of residents assessed cross sectionally and longitudinally. Of the total included residents, 3,801 (43.6%) were aged 75–84 years. Most were female (n = 6,178; 70.9%) and widowed (n = 4,842; 55.6%), and 3,974 (45.6%) had dementia.

Table 2. Baseline sociodemographic characteristics of nursing home residents in Flanders, Belgium (N=8,713)

Baseline characteristics	All residents with first BelRAI LTCF assessment **(N = 8,713)**	Cross-sectionally assessed only (not in the longitudinal) **(N=7022)**	Residents with longitudinal assessment at 12 Months from first BelRAI**(N = 1691)**	P-value Cross-sectional versus longitudinal
Age at baseline				
65-74	1306 (15.0)	1092 (15.55)	214 (12.66)	<.001
75-84	3801 (43.6)	3106 (44.23)	695 (41.10)	
85 and above	3606 (41.4)	2824 (40.22)	782 (46.24)	
Sex				
Male	2535 (29.09)	2092 (29.79)	443 (26.20)	0.003
Female	6178 (70.91)	4930 (70.21)	1248 (73.80)	
Marital status				
Never married	595 (6.83)	471 (6.71)	124 (7.3)	0.26
Married/living with partner	1708 (19.6)	1393 (19.84)	315 (18.63)	
Widowed	4842 (55.57)	3843 (54.73)	999 (59.1)	
Separated (legal/factual)	402 (4.61)	322 (4.59)	80 (4.73)	
Missing	1166 (13.38)	993 (13.29)	173 (10.23)	
Dementia				
Yes	3974 (45.61)	3190 (45.43)	784 (46.36)	0.49
No	4739 (54.39)	3832 (54.57)	907 (53.64)	
Years of baseline assessment				
2016	176 (2.02)	118 (1.68)	58 (3.43)	<.001
2017	328 (3.76)	212 (3.02)	116 (6.86)	
2018	305 (3.50)	197 (2.81)	108 (6.39)	
2019	445 (5.11)	314 (4.47)	131 (7.75)	
2020	499 (5.73)	321 (4.57)	178 (10.53)	
2021	4095 (47.00)	3020 (43.01)	1075 (63.57)	
2022	2865 (32.88)	2840 (40.44)	25 (1.48)*	
NH stay prior to the baseline assessment				
0-3 months	1558 (17.89)	1287 (18.33)	271 (16.03)	0.18
3-6 months	945 (10.85)	757 (10.78)	188 (11.12)	
6-12 months	1153 (13.24)	926 (13.19)	227 (13.42)	
≥ 12 months	5057 (58.03)	4052 (57.70)	1005 (59.43)	

***** Residents whose first BelRAI assessment occurred at the beginning of 2022 had a one-year follow-up within the one-month window and therefore had corresponding IMA data available, as IMA supplied data through the end of 2022. Most residents whose first BelRAI assessment occurred in 2022 were assessed cross-sectionally, as their one-year follow-up extended into 2023 (the impact of data access delay)

Chronic medication and PIM use: Baseline status and one-year changes

At baseline, residents had a median of 8 total medications (IQR 5–12) and a mean of 6 chronic medications (SD 3.8), with 94.6% taking at least one chronic medication. Polypharmacy was present in 48.4% and excessive polypharmacy in 15%. The most common classes were cardiovascular (73.5%),

nervous system (64.9%), and alimentary tract (56.9%). Results for the subgroup of residents with dementia are reported in **Supplementary file 6.5**.

In the longitudinal subgroup, mean chronic medication use increased from 5.87 to 6.1, and prevalence from 94.6% to 96.9%. Significant but negligible increases were observed in cardiovascular (73.1%→76.2%), nervous system (65%→68.6%), alimentary tract (55.9%→58.3%), and blood-forming system drugs (52.6%→56.3%).

At baseline, at least one PIM was used by 74.0% of residents. The most common PIMs were PPIs (45.1%), lipid-modifying agents (24.8%), and antipsychotics (22.0%). In the longitudinal subset, overall PIM use declined (72.7%→56.0%), though patterns varied: PPI (44.2%→48.4%) and antipsychotics (21.9%→26.2%) increased, while calcium (2.5%→1.0%) and anti-dementia drugs (4.9%→3.3%) decreased **(Table 3)**. Detailed transition patterns are provided in the **Supplementary file 6.6**.

Table 3. The use of long-term medication and PIMs in the total baseline population (n = 8,713) and in the longitudinally followed residents (baseline and year 1, n = 1691)

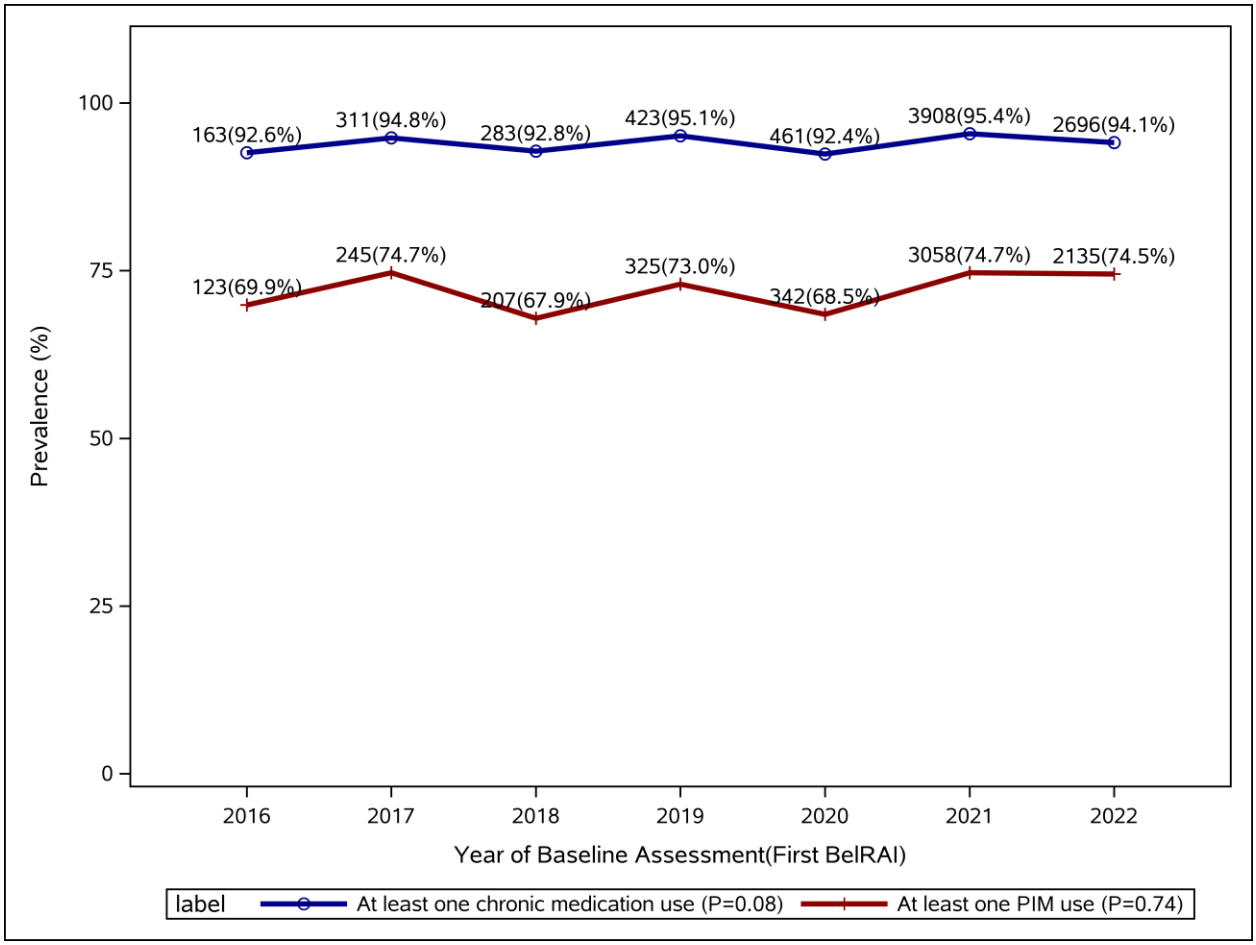
	Total baseline population (N= 8,713)	**Comparative populations (n=1691)**			
		Baseline	**Year 1**	**Effect size ‡**	**P-value**
Total medication (Median[IQR])	8 (5-12)	8 (5-12)	9(6-13)		**<.0001**
Chronic medication (Mean[SD])	6 (3.8)	5.87 (3.5)	6.1 (3.1)		**0.004**
At least one chronic medication (%)	8245 (94.63)	1600 (94.62)	1639 (96.92)	0.023	**0.0002**
Level of Polypharmacy (%)					
No polypharmacy (< 5)	3211 (36.85)	633 (37.43)	550 (32.53)	0.41	**<.0001**
Polypharmacy (5-9)	4220 (48.43)	840 (49.67)	926 (54.76)		
Excessive polypharmacy (≥ 10)	1282 (14.71)	218 (12.89)	215 (12.71)		
Main classes of selected chronic medications (%)					
Alimentary tract (A)	4960 (56.93)	946 (55.94)	986 (58.31)	0.024	**0.014**
Drugs for acid related disorders (A02)	3854 (44.23)	739 (43.70)	835 (49.38)	0.057	**<.0001**
Drugs for functional gastrointestinal disorders (A03)	165 (1.89)	28 (1.66)	23 (1.36)	-0.003	0.369
Vitamins (A11)	219 (2.51)	35 (2.07)	10 (0.59)	-0.015	**<.0001**
*Blood and blood forming (*B*)*	4555 (52.28)	890 (52.63)	952 (56.30)	0.037	**0.0004**
Antithrombotic agents *(*B01*)*	4349 (49.91)	856 (50.62)	929 (54.94)	0.043	**<.0001**
*Cardiovascular system (*C*)*	6404 (73.50)	1236 (73.09)	1289 (76.23)	0.031	**0.0005**
*Genito urinary system and sex hormones (*G*)*	267 (3.06)	59 (3.49)	52 (3.08)	−0.004	0.286
Urologicals *(*G04*)*	238 (2.73)	55 (3.25)	46 (2.72)	−0.005	0.16
*Systemic hormonal preparations, excl. sex hormones and insulins (*H*)*	1204 (13.82)	222 (13.13)	245 (14.49)	0.014	**0.01**
Corticosteroids for systemic use *(*H02*)*	295 (3.39)	44 (2.60)	53 (3.13)	0.005	0.19
*Anti-infective for systemic use (*J*)*	702 (8.06)	125 (7.39)	114 (6.74)	−0.007	0.35
*Antineoplastic and immunomodulating agents (*L*)*	283 (3.25)	42 (2.48)	36 (2.13)	−0.004	0.26
*Musculo-skeletal system (*M*)*	944 (10.83)	171 (10.11)	194 (11.47)	0.014	**0.015**
Anti-inflammatory and anti-rheumatic products *(*M01*)*	138 (1.58)	20 (1.18)	19 (1.12)	−0.001	0.853
*Nervous system (*N*)*	5652 (64.87)	1099 (64.99)	1160 (68.60)	0.036	**0.0003**
Analgesics *(*N02*)*	2367 (27.17)	435 (25.72)	461 (27.26)	0.015	0.106
Antidepressants *(*N06A*)*	2810 (32.25)	585 (34.59)	637 (37.67)	0.068	**0.0002**
*Respiratory system (*R*)*	1149 (13.19)	210 (12.42)	222 (13.13)	0.005	0.376
Drugs for obstructive airway diseases *(*R03*)*	621 (7.13)	114 (6.74)	122 (7.21)	0.007	0.465
Selected PIM (%)					
At least 1 of the PIM	6435 (73.86)	1230 (72.74)	947 (56.00)	−0.167	**<.0001**
H2 receptor antagonist ≥8 weeks (A02BA)	43 (0.49)	16 (0.95)	8 (0.47)	−0.005	**0.011**
Proton pump Inhibitors ≥8 weeks (A02BC)	3929 (45.09)	748 (44.23)	819 (48.43)	0.042	**<.0001**
Vitamin D (A11CC)	160 (1.84)	25 (1.48)	8 (0.47)	−0.010	**0.0007**
Calcium supplement (A12A)	258 (2.96)	43 (2.54)	16 (0.95)	−0.016	**<.0001**
Lipid-modifying agents (C10)	2161 (24.80)	404 (23.89)	393 (23.24)	−0.007	0.377
Systemic corticosteroids ≥ 8 weeks (H02)	378 (4.34)	56 (3.31)	64 (3.78)	0.005	0.317

Long-term oral NSAIDs ≥ 8 weeks (M01A)	186 (2.13)	31 (1.83)	22 (1.30)	−0.005	0.16
Anti-resorptive/bone anabolic drugs for osteoporosis (M05B)	242 (2.78)	45 (2.66)	55 (3.25)	0.006	**0.049**
Antipsychotics ≥12 weeks (N05A)	1917 (22.00)	370 (21.88)	443 (26.20)	0.043	**<.0001**
Tricyclic antidepressants (N06AA)	211 (2.42)	44 (2.60)	50 (2.96)	0.004	0.257
Systemic drugs for obstructive airway diseases (R03DA04, R03DA05, R03DC01,R03DC03)	80 (0.92)	16 (0.95)	12 (0.71)	−0.002	**0.046**
Antihistamines for systemic use (R06A)	562 (6.45)	101 (5.97)	112 (6.62)	0.007	0.139
Anti-dementia drugs (N06D)	452 (5.19)	82 (4.85)	56 (3.31)	−0.016	**0.0002**

‡ For level of polypharmacy the effect size reported as weighetd Kappa (Slight: ≤ 0.20, Fair: 0.21–0.40, Moderate: 0.41–0.60, Substantial: 0.61–0.80, Almost perfect: ≥ 0.81) and for the others *as Cohen's g (negligable < 0.05, small 0.05 - 0.14, medium 0.15 - 0.24, large ≥ 0.25)*

The use of chronic medications, at baseline, increased slightly from 92.6% in 2016 to 94.1% in 2022, while PIM use also rose from 69.9% to 74.5% over the same period; however, no statistically significant overall trend was observed for either **(Figure 2)**.

Figure 2: Trends of at least one chronic medication and PIM use at baseline assessment for nursing home residents (2016-2022)



Health outcomes: Changes between baseline and year one

At baseline, most residents had moderate to severe impairment in ADL (70.1%), cognitive (34.1%), and mood (33.6%), with nearly half showing health instability (49.3%). Mild to severe pain was reported by 33.4%, aggressive behavior by 31.8%, and 80.7% had at least one comorbidity. About one-quarter

(25.6%) experienced at least one fall in the prior three months, while 42% had high social engagement ***(Table 4)***.

Across all domains, 70–88% of residents showed no change over one year (weighted Cohen's kappa: 0.41–0.80), with greatest stability in ADL (88%) and lowest in health instability (70%). Among those who changed, deterioration was more frequent than improvement, particularly in health instability (23.6%), mood (18.3%), and cognition (13.6%), while pain (9.7%) and ADL (9.2%) showed lower deterioration rates. Falls and social engagement exhibited balanced changes (falls: improved 11.4% vs. deteriorated 12.8%; social engagement: improved 12.5% vs. deteriorated 14.2%). Detailed transitions are provided in the **Supplementary file 6.7**.

After one year, moderate/severe ADL impairment rose from 71.5% to 77%, cognitive impairment from 31.5% to 38%, health instability from 4.8% to 9.9%, and mood disturbance from 33.9% to 40.2%. Pain increased from 34.1% to 36.7%, aggressive behavior from 30.8% to 34.7%, and residents with ≥3 comorbidities from 27.5% to 29.6%.

During follow-up, mortality was 19.8%, 20.8% had at least one hospitalization, 0.72% were admitted to ICU, and 27.5% visited the emergency department.

Table 4: Description of physical function, psychosocial, mental health, and health status in the total baseline population (n = 8,713) and in the the longitudinally followed residents (at baseline and year 1, n = 1691).

	Total baseline population (N=8,713)	**Comparative populations (n=1691)**			
		Baseline	**Year 1**	**Weighted Kappa ‡**	**P-value**
Physical function, psychosocial, mental health, and health status					
ADLH scale score	***8180***	***1610***	***1610***		
No impairment	1039 (12.70)	183 (11.37)	142 (8.82)		
Mild impairment	1409 (17.22)	276 (17.14)	228 (14.16)	0.69	**<.0001**
Moderate/Severe impairment	5732 (70.07)	1151 (71.49)	1240 (77.02)		
DRS scale score	**8205**	***1616***	***1616***		
No mood disturbance	2998 (36.54)	567 (35.09)	477 (29.52)		
Mild disturbance	2452 (29.88)	502 (31.06)	490 (30.32)	0.58	***<.0001***
Moderate/Severe disturbance	2755 (33.58)	547 (33.85)	649 (40.16)		
CPS scale score	***8062***	***1592***	***1592***		
Intact/Borderline intact	3130 (38.82)	631 (39.64)	533 (33.48)		
Mild impairment	2183 (27.08)	460 (28.8)	454 (28.52)	0.81	***<.0001***
Moderate/Severe impairment	2749 (34.10)	501 (31.47)	605 (38.00)		
CHESS scale score (Health instability)	***7672***	***1509***	***1509***		
No health instability	3892 (50.73)	828 (54.87)	621 (41.15)		
Minimal/Low instability	3310 (43.14)	609 (40.36)	739 (48.97)	0.48	***<.0001***
Moderate/Severe instability	470 (6.13)	72 (4.77)	149 (9.87)		
ABS scale score	***8211***	***1621***	***1621***		
No aggression	*5598 (68.18)*	*1121 (69.15)*	*1059 (65.33)*		
Mild aggression	*1167 (14.21)*	*231 (14.25)*	*260 (16.04)*	0.57	***<.0001***
Moderate aggression	*798 (9.72)*	*155 (9.56)*	*156 (9.62)*		
Severe aggression	648 (7.89)	114 (7.03)	146 (9.01)		
ISE scale score	***8140***	***1601***	***1601***		
High engagement	*3400 (41.77)*	*699 (43.66)*	*670 (41.85)*		
Moderate engagement	*2178 (26.76)*	*454 (28.36)*	*465 (29.04)*	0.63	0.127
Low engagement	*1628 (20.00)*	*286 (17.86)*	*296 (18.49)*		
No engagement	934 (11.47)	162 (10.12)	170 (10.62)		

Risk of falls scale score	***8157***	***1622***	***1622***		
No fall (90 day)	6048 (74.14)	1232 (75.96)	1211 (74.66)		
Fall 31-90 day ago	888 (10.89)	185 (11.41)	198 (12.21)	0.39	0.830
One fall (30 day)	848 (10.40)	151 (9.31)	154 (9.49)		
2^{+} falls (30 day)	373 (4.57)	54 (3.33)	59 (3.64)		
Pain scale score	***8095***	***1606***	***1606***		
No pain	5392 (66.61)	1058 (65.88)	1016 (63.26)		
Mild pain	2426 (29.97)	495 (30.82)	537 (33.44)	0.63	***0.036***
Severe pain	277 (3.42)	53 (3.30)	53 (3.30)		
Co-morbidity	***8713***	***1691***	***1691***		
No	1679 (19.27)	280 (16.56)	223 (13.19)		
One	2546 (29.22)	505 (29.86)	502 (29.69)	0.8	***<.0001***
Two	2167 (24.87)	441 (26.08)	465 (27.50)		
Three or more	2321 (26.64)	465 (27.50)	501 (29.63)		
Death during the one year follow up[¥]	1727 (19.82)				
System outcomes during the one year follow up					
Hospitalization	1816 (20.84)				
ICU admission	63 (0.72)				
Emergency admission	2392 (27.45)				

[¥]*Total death = 2925 (33.57%);* ‡Slight: ≤ 0.20, Fair: 0.21–0.40, Moderate: 0.41–0.60, Substantial: 0.61–0.80, Almost perfect: ≥ 0.81

Abbreviations: ABC – Aggressive Behaviour Scale; ADLH – Activities of Daily Living Hierarchy Scale; CHESS – Changes in Health, End-Stage Disease, and Signs and Symptoms Scale; CPS – Cognitive Performance Scale; DRS – Depression Rating Scale; ICU – Intensive Care Unit; ISE – Index of Social Engagement

Association between changes in polypharmacy and PIM use with health outcomes

A transition from no polypharmacy to polypharmacy occurred in 13% of residents, while 8% shifted from polypharmacy to no polypharmacy. The increase in the transition in to polypharmacy were significantly associated with deteroration in ADL ($p = 0.02$, Cramer's $V = 0.06$) and cognitive impairment ($p = 0.04$, $V = 0.06$), though effect sizes were negligible.

Regarding PIM patterns, 48.3% of residents had continued PIM use, 24.5% discontinued, 19.5% had no PIMs, and 7.8% were newly prescribed a PIM during follow-up. PIM intensification increased with age (χ^2 $p < 0.0001$, Cramer's $V = 0.10$) and was more common in men than women (χ^2 $p = 0.0001$, $V = 0.11$), with men more often continuing PIMs and women more frequently discontinuing residents experiencing PIM intensification were also more likely to show deterioration in ADL ($p = 0.009$, $V = 0.07$), greater aggression ($p = 0.01$, $V = 0.07$), and increases in comorbidity ($p = 0.008$, $V = 0.07$), although all effect sizes were negligible.

Detailed associations of changes in polypharmacy, overall PIM use (**supplementary file 6.8**), and prevalent specific PIMs (antipsychotics and PPI) with changes in each health outcome are provided in the **supplementary file 6.9**.

Discussion

Key findings

This study leveraged innovative linkage of national health claims and BelRAI data to examine changes in chronic medication use, including PIMs, and their association with quality-of-life related patient outcomes over one year. Of 8,713 residents at baseline, 1,691 (19.4%) were followed longitudinally. The median number of medications increased from 8 to 9, and chronic medication use rose slightly (mean 5.87→6.1; prevalence 94.6%→96.9%). In contrast, PIM use declined overall (72.7%→56.0%), though individual patterns varied, e.g., PPI use increased (44.2%→48.4%), while lipid-modifying agents remained stable (23.9%→23.2%). No significant trend was observed in chronic medication or PIM use

between 2016 and 2022. Most residents (70–88%) maintained their baseline status; when changes in health occurred, deterioration was more common than improvement, particularly high in health instability (23.6%), mood (18.3%), and cognition (13.6%). Polypharmacy transitions (13% into, 8% out of polypharmacy) were associated with ADL and cognition. PIM changes including continuation (48.3%), discontinuation (24.5%), no PIMs (19.5%), and initiation (7.8%) were associated with ADL, aggressive behavior, and comorbidity.

Strength and limitations

The population-level data linkage provides an efficient and scalable approach to track medication use and multidomain health outcomes over time, overcoming the limitations of previous Belgian studies that relied on smaller samples and resource-intensive primary data collection, which limited both comparability and multidomain longitudinal evaluation. [20] However, this study has limitations. First, it was a descriptive analysis to explore changes from baseline to one year. Although we explored associations between medication changes and health status changes with causal intent, the analyses do not establish causal effects. Nevertheless, it offers valuable insights that can guide future causal analyses and serves as an important contribution by presenting clear and interpretable data.[48] Second, only a limited proportion of the cross-sectional population was included in the longitudinal analysis. Residents without a BelRAI assessment at one-year follow-up were excluded to maintain a consistent interval for evaluating changes in medication use and health status. BelRAI implementation in Belgium was still evolving during the study period, and assessments were not consistently completed prior to 2023. Once implementation becomes routine, BelRAI will have strong potential to support longitudinal studies. Despite these constraints and a one-year mortality of 20%, comparable to previous European studies (20–42%),[3, 20, 49] the remaining sample was substantial. As exclusions were primarily due to assessment timing, the risk of major selection or ascertainment bias is likely limited, though mortality is relevant to consider in the analysis of this frail population[50]. Third, the large sample size may yield statistically significant findings that are not clinically meaningful; therefore, effect sizes were reported to indicate the magnitude of observed changes. Fourth, medication data derived from healthcare claims captured medication type and duration but not dosage or over-the-counter use, potentially leading to underestimation of total medication use and PIMs. Fifth, the threshold of five medications used to define polypharmacy reflects a research convention rather than a clinical standard, and some regimens at or above this level may be appropriate for residents with multimorbidity, for example for stroke prophylaxis. Because medication indications were not available in our data, we could not determine whether polypharmacy was appropriate or inappropriate for individual residents. The prevalence of polypharmacy in our study should therefore be interpreted with caution.

Interpretations

High numbers of total and chronic medications and PIM use were observed, with total and chronic medications increasing over one year, while overall PIM use declined only modestly. These findings corroborate with reports of high medication burdens among NH residents internationally.[20, 51, 52] Previous studies reported a mean of 9 total medications [4, 20, 23] and 8 chronic medication,[20] slightly higher than in our study, though still above the mean of 5 medications for Belgian community-dwelling older adults.[53] Despite lower numbers, trajectories mirrored those in a smaller Belgian study where total medications increased from 8.9 to 10.1 and chronic medications from 8 to 8.6.[20] Differences may be contributed by the use of reimbursement data, which excludes non-reimbursed and over-the-

counter drugs (e.g., antacids, NSAIDs), and our shorter follow-up period compared with two years interval in the previous study. However, the most commonly used chronic medication classes remained consistent, including cardiovascular, nervous system, alimentary tract, and blood and blood-forming agents [20, 53]. This similarity is likely because common comorbid conditions in NH residents, consistently reported in international studies [54], largely determine the pattern of chronic medication use . However, unlike prior research, which reported mostly no statistically significant changes between baseline and follow-up for these medication groups [20], our study observed a significant increase over the one-year period. This difference may be explained by the larger sample in our study, approximately five times that of the previous study, which provided greater statistical power to detect even modest changes in medication use.

Our study confirms the high prevalence of PIM use among NH residents [4, 23, 52, 55] and adds real-world evidence on its evolution over time. While interventional studies show reductions in PIM use through medication reviews and deprescribing programs,[56-58] these effects are often localized and short term. Using routinely collected data, we observed a 16.7% absolute reduction in residents using at least one PIM after one year. Comparisons with interventions are difficult due to differences in scope and follow-up, but one study reported a smaller reduction (9.1%) over eight months in the control group,[22] while targeted strategies achieved greater decreases. This suggests that routine care leads to only modest reductions compared with structured interventions. Studies on length of stay and PIM use report conflicting results, though all confirm high prevalence.[59, 60]

Although a small reduction in PIM use was observed among residents with at least one PIM at baseline, overall patterns in Belgian NHs between 2016 and 2022 show no meaningful change, with consistently high rates. Another study reported a small but statistically significant reduction in PIM use, although the change was unlikely to be clinically meaningful.[52] This persistence highlights the need for stronger deprescribing efforts, as initiation may not be the main issue, but ongoing monitoring is often lacking. Previous research on deprescribing trends also shows no change or a decrease,[61] indicating substantial work remains to reduce PIM use. Although several efforts have aimed to improve medication appropriateness in Belgian NHs, [58, 62, 63, 64 ,65 ,66, 67] these have not translated into meaningful reductions in PIM use in our cohort. More scalable and sustained deprescribing strategies are needed to strengthen impact.

Despite reductions in PIMs within individual trajectories, residents experienced significant changes in most health domains, with deterioration more common than improvement. Declines in physical, cognitive, and psychosocial domains align with international long-term care studies,[7, 68, 69] and reflect the high frailty and limited life expectancy of Belgian NH residents, whose average stay is less than two years).[3] In such circumstances, although overall health status is not expected to improve substantially, reducing PIMs remains important because the different dimensions of quality of life can still be maintained and, in some cases, improved. Deprescribing may enhance day-to-day wellbeing even if it does not halt broader decline. The dual dynamic of modest PIM reductions alongside deterioration suggests that prescribing improvements alone may not yield measurable clinical gains, reinforcing the need for broader supportive interventions. While we observed associations between transitions in polypharmacy and PIM use with changes in certain health outcomes, these findings should be interpreted cautiously. Previous study reported the association between polypharmacy and a 1 year declines in cognition among NH residents, but they did not examine simultaneous changes in medication use and health over time.[70] Our descriptive analysis therefore provides only initial

insights, and further work focusing on individual medications and applying causal methods is needed to generate clinically meaningful findings. Our findings also confirm interrelations between domains, such as cognitive and physical decline,[69] underscoring the need for a multidimensional approach. Although declines were common, many residents remained stable, and some improved,[7, 68, 69] suggesting targeted efforts could help preserve or enhance valued health domains.

Conclusions and Implications

By linking BelRAI and IMA-AIM data, this study provides real-world insight into medication use and health trajectories among NH residents in Belgium, characterized by a substantial burden of chronic medication and PIM use. Over one year, chronic medication use increased, while reductions in PIM use were small. Between 2016 and 2022, both chronic medication and PIM use remained high with no meaningful trend change, indicating persistent use over time. Most residents maintained baseline health status, but when changes occurred, deterioration was more common than improvement, often across interrelated domains, underscoring the multidimensional nature of health in this population. Exploratory analyses showed that changes in polypharmacy and PIMs use were associated with changes in certain health domains. Although causality cannot be inferred, these findings suggest that medication patterns may influence resident health. To better understand these relationships, future studies should evaluate individual medications and apply causal methods. With the current study, this innovative data linkage demonstrates strong potential to generate evidence that can improve care and outcomes for NH residents. Overall, the observed high medication burden and declines across multiple health domains underscores the need for multidisciplinary interventions that support deprescribing, and promote person-centered care to improve well-being in NH residents.

References

1. Statbel en het Federaal Planbureau. Bevolkingsvooruitzichten 2023-2070 [updated February 13, 2024; cited 2024 April 08]. Available from: https://www.plan.be/databases/data-35-nl-bevolkingsvooruitzichten_2022_2070.
2. KCE Report 376: Performance of the Belgian health system – report 2024.
3. Collingridge Moore D, Payne S, Keegan T, *et al.* Length of stay in long-term care facilities: a comparison of residents in six European countries. Results of the PACE cross-sectional study. BMJ Open. 2020;10(3):e033881.
4. Paque K, Elseviers M, Vander Stichele R, *et al.* Associations of potentially inappropriate medication use with four year survival of an inception cohort of nursing home residents. Arch Gerontol Geriatr. 2019;80:82-7.
5. van Leeuwen KM, van Loon MS, van Nes FA, *et al.* What does quality of life mean to older adults? A thematic synthesis. PLoS One. 2019;14(3):e0213263.
6. Andersson ÅG, Dahlkvist L, Kurland L. Patient-centered outcomes and outcome measurements for people aged 65 years and older—a scoping review. BMC Geriatr. 2024;24(1):528.
7. Mulla RT, Hirdes JP, McAiney C, *et al.* Factors Associated with Mood Transitions among Older Canadian Long-Term Care Residents: A Multistate Transition Model. J Am Med Dir Assoc. 2025;26(7):105612.
8. Nicholson K, Liu W, Fitzpatrick D, *et al.* Prevalence of multimorbidity and polypharmacy among adults and older adults: a systematic review. The Lancet Healthy Longevity. 2024;5(4):e287-e96.
9. Anlay DZ, Paque K, Van Leeuwen E, *et al.* Tools and guidelines to assess the appropriateness of medication and aid deprescribing: An umbrella review. Br J Clin Pharmacol. 2024;90(1):12-106.
10. Morin L, Laroche ML, Texier G, *et al.* Prevalence of Potentially Inappropriate Medication Use in Older Adults Living in Nursing Homes: A Systematic Review. J Am Med Dir Assoc. 2016;17(9):862.e1-9.
11. For a healthy Belgium: Care for older people [updated 01 February 2024; cited 2024 April 09]. Available from: https://www.healthybelgium.be/en/health-system-performance-assessment/specific-domains/care-for-the-elderly.
12. Davies LE, Spiers G, Kingston A, *et al.* Adverse Outcomes of Polypharmacy in Older People: Systematic Review of Reviews. J Am Med Dir Assoc. 2020;21(2):181-7.
13. Boateng I, Pascual CR, Grassby P, *et al.* The impact of polypharmacy on health outcomes in the aged: A retrospective cohort study. PLoS One. 2025;20(2):e0317907.
14. Fried TR, O'Leary J, Towle V, *et al.* Health outcomes associated with polypharmacy in community-dwelling older adults: a systematic review. J Am Geriatr Soc. 2014;62(12):2261-72.
15. Gutiérrez-Valencia M, Izquierdo M, Cesari M, *et al.* The relationship between frailty and polypharmacy in older people: A systematic review. Br J Clin Pharmacol. 2018;84(7):1432-44.
16. Lavrador M, Cabral AC, Castel-Branco M, *et al.* Chapter 17 - Polypharmacy and medication adherence. In: Oliveira PJ, Malva JO, editors. Aging: Academic Press; 2023. p. 435-53.
17. Samara Ea, Nazzal Z, Naghnaghia S, *et al.* Potentially inappropriate medication uses and associated factors among elderly primary health care clinics attendees: A call to action. PLoS One. 2023;18(8):e0290625.
18. Alhawassi TM, Alatawi W, Alwhaibi M. Prevalence of potentially inappropriate medications use among older adults and risk factors using the 2015 American Geriatrics Society Beers criteria. BMC Geriatr. 2019;19(1):154.
19. Rochon PA, Gurwitz JH. The prescribing cascade revisited. The Lancet. 2017;389(10081):1778-80.
20. Ivanova I, Wauters M, Stichele RV, *et al.* Medication use in a cohort of newly admitted nursing home residents (Ageing@NH) in relation to evolving physical and mental health. Arch Gerontol Geriatr. 2018;75:202-8.
21. De Wolf J, Dilles T, Vander Stichele R, *et al.* Evolution of Drug Utilization in Nursing Homes in Belgium. Clin Pharmacol Biopharm. 2014;3(124):2.
22. Fournier A, Anrys P, Beuscart J-B, *et al.* Use and deprescribing of potentially inappropriate medications in frail nursing home residents. Drugs Aging. 2020;37(12):917-24.
23. Anrys PM, Strauven GC, Foulon V, *et al.* Potentially inappropriate prescribing in Belgian nursing homes: prevalence and associated factors. J Am Med Dir Assoc. 2018;19(10):884-90.
24. Lion S, Evrard P, Foulon V, *et al.* Drug–drug interactions in nursing home residents: analysis from the COME-ON trial. Age Ageing. 2023;52(1).
25. Chen Z, Liu Z, Zeng L, *et al.* Research on prescribing cascades: a scoping review. Front Pharmacol. 2023;Volume 14 - 2023.
26. Piggott KL, Mehta N, Wong CL, *et al.* Using a clinical process map to identify prescribing cascades in your patient. BMJ. 2020;368:m261.
27. Reeve E, Gnjidic D, Long J, *et al.* A systematic review of the emerging definition of 'deprescribing' with network analysis: implications for future research and clinical practice. Br J Clin Pharmacol. 2015;80(6):1254-68.
28. Scott IA, Hilmer SN, Reeve E, *et al.* Reducing Inappropriate Polypharmacy: The Process of Deprescribing. JAMA Internal Medicine. 2015;175(5):827-34.
29. Aljeaidi MS, Haaksma ML, Tan ECK. Polypharmacy and trajectories of health-related quality of life in older adults: an Australian cohort study. Qual Life Res. 2022;31(9):2663-71.
30. Anderson TS, Ayanian JZ, Curto VE, *et al.* Changes in the Use of Long-Term Medications Following Incident Dementia Diagnosis. JAMA Internal Medicine. 2023;183(10):1098-108.
31. Barker RO, Hanratty B, Kingston A, *et al.* Changes in health and functioning of care home residents over two decades: what can we learn from population-based studies? Age Ageing. 2021;50(3):921-7.
32. InterMutualist Agency. IMA-AIM.[cited 2025 Oct 13]. Available from: https://ima-aim.be/ [

33. InterRAI. Worldwide. Available from: https://interrai.org/applications/status-and-outcome-scales/ [Accessed 09 Jan 2026].
34. de Almeida Mello J, Wellens NI, Hermans K, *et al.* The Implementation of Integrated Health Information Systems - Research Studies from 7 Countries Involving the InterRAI Assessment System. Int J Integr Care. 2023;23(1):8.
35. Devos C, Cordon A, Lefèvre M, Obyn C, Renard F, Bouckaert N, Gerkens S, Maertens de Noordhout C, Devleesschauwer B, Haelterman M, Léonard C, Meeus P. Performance of the Belgian health system – report 2019. Health Services Research (HSR) Brussels: Belgian Health Care Knowledge Centre (KCE). 2019. KCE Reports 313. D/2019/10.273/34.
36. Van Leeuwen E, Anthierens S, van Driel ML, *et al.* General practitioners' perspectives on discontinuation of long-term antidepressants in nursing homes. Eur J Gen Pract. 2022;28(1):23-31.
37. Norwegian Institute of Public Health. ATC/DDD Index. Available from: https://atcddd.fhi.no/atc_ddd_index/. Accessed August 6, 2024.
38. Paque K, De Schreye R, Elseviers M, *et al.* Discontinuation of medications at the end of life: A population study in Belgium, based on linked administrative databases. Br J Clin Pharmacol. 2019;85(4):827-37.
39. Egbujie BA, Turcotte LA, Mulla RT, *et al.* Patterns of Transient and Terminal Transitions in Activities of Daily Living Performance Levels among Long-Term Care Residents: A Multistate Markov's Model Analysis of Population-Based Longitudinal Data in Canada. J Am Med Dir Assoc. 2025;26(6):105565.
40. Perlman CM, Hirdes JP. The aggressive behavior scale: a new scale to measure aggression based on the minimum data set. J Am Geriatr Soc. 2008;56(12):2298-303.
41. Morris JN, Fries BE, Mehr DR, *et al.* MDS Cognitive Performance Scale©. J Gerontol. 1994;49(4):M174-M82.
42. Hirdes JP, Frijters DH, Teare GF. The MDS-CHESS scale: a new measure to predict mortality in institutionalized older people. J Am Geriatr Soc. 2003;51(1):96-100.
43. Fries BE, Simon SE, Morris JN, *et al.* Pain in U.S. Nursing Homes: Validating a Pain Scale for the Minimum Data Set. The Gerontologist. 2001;41(2):173-9.
44. Sun X, Yang Z, editors. Generalized McNemar's test for homogeneity of the marginal distributions. SAS Global forum; 2008.
45. Cohen, J. (1988). Statistical Power Analysis for the Behavioral Sciences (2nd ed.). Routledge. https://doi.org/10.4324/9780203771587.
46. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics. 1977;33(1):159-74.
47. Mohammed looti (2025). Interpret Cramer's V (With Examples). PSYCHOLOGICAL STATISTICS. Retrieved from https://stats.arabpsychology.com/interpret-cramers-v-with-examples/ [
48. Loeb S, Dynarski S, McFarland D, *et al.* Descriptive Analysis in Education: A Guide for Researchers. NCEE 2017-4023. National Center for Education Evaluation and Regional Assistance. 2017.
49. Vetrano DL, Collamati A, Magnavita N, *et al.* Health determinants and survival in nursing home residents in Europe: Results from the SHELTER study. Maturitas. 2018;107:19-25.
50. Hussain J, Peters TJ, Johnson M, *et al.* Missing data in palliative and end of life care trials. Guidance on how to reduce, handle and report incomplete data. 2022.
51. Kummer I, Reissigová J, Lukačišinová A, *et al.* Polypharmacy and potentially inappropriate prescribing of benzodiazepines in older nursing home residents. Ann Med. 2024;56(1):2357232.
52. Cateau D, Bugnon O, Niquille A. Evolution of potentially inappropriate medication use in nursing homes: Retrospective analysis of drug consumption data. Res Social Adm Pharm. 2021;17(4):701-6.
53. Wauters M, Elseviers M, Vaes B, *et al.* Polypharmacy in a Belgian cohort of community-dwelling oldest old (80+). Acta Clin Belg. 2016;71(3):158-66.
54. Moore KL, Boscardin WJ, Steinman MA, *et al.* Patterns of chronic co-morbid medical conditions in older residents of U.S. nursing homes: differences between the sexes and across the agespan. J Nutr Health Aging. 2014;18(4):429-36.
55. Drusch S, Le Tri T, Ankri J, *et al.* Potentially inappropriate medications in nursing homes and the community older adults using the French health insurance databases. Pharmacoepidemiol Drug Saf. 2023;32(4):475-85.
56. Wouters H, Scheper J, Koning H, *et al.* Discontinuing Inappropriate Medication Use in Nursing Home Residents: A Cluster Randomized Controlled Trial. Ann Intern Med. 2017;167(9):609-17.
57. Khawagi W, Alshehri A, Alghuraybi Z, *et al.* Prevalence and Predictors of Potentially Inappropriate Prescribing in Older People Receiving Home Health Care in Saudi Arabia According to the American Geriatrics Society Beers Criteria 2019. Healthcare. 2024;12.
58. Wauters M, Elseviers M, Vander Stichele R, *et al.* Efficacy, feasibility and acceptability of the OptiMEDs tool for multidisciplinary medication review in nursing homes. Arch Gerontol Geriatr. 2021;95:104391.
59. Sönnerstam E, Gustafsson M, Lövheim H. Potentially inappropriate medications in relation to length of nursing home stay among older adults. BMC Geriatr. 2022;22.
60. Chen LL, Tangiisuran B, Shafie A, *et al.* Evaluation of potentially inappropriate medications among older residents of Malaysian nursing homes. Int J Clin Pharm. 2012;34:596-603.
61. Anlay DZ, Paque K, Van den Eynden B, *et al.* International Deprescribing Guidelines Did Not Impact Actual Practice in Deprescribing of Potentially Inappropriate Medications for Nursing Home Residents: An Interrupted Time Series Analysis. Drugs Aging. 2025.
62. Anrys P, Strauven G, Boland B, *et al.* Collaborative approach to Optimise MEdication use for Older people in Nursing homes (COME-ON): study protocol of a cluster controlled trial. Implementation Science. 2016;11(1):35.

63. Azermai M, Wauters M, De Meester D*, et al.* A quality improvement initiative on the use of psychotropic drugs in nursing homes in Flanders. Acta Clin Belg. 2017;72(3):163-71.
64. Belgisch Centrum voor Farmacotherapeutische Informatie (BCFI). Goed en veilig gebruik van geneesmiddelen: deprescribing; [cited 2025 Jul 14]. Available from: https://www.bcfi.be/nl/chapters/1?frag=9991233&matches=deprescribing [
65. Damiaens A, Frisson A, Foulon V. Process Optimization Of the Medicines' pAthway in nursing Homes. https://www.isrctn.com/ISRCTN17231220 2023 [
66. (FAMHP); FAfMaHP. Flash Vig-news: the benzodiazepine withdrawal programme now has a permanent place in pharmaceutical care. 09 Jul 2025. Available from: https://www.famhp.be/en/news/flash_vig_news_the_benzodiazepine_withdrawal_programme_now_has_a_permanent_place_in. Accessed 29 Oct 2025.
67. (RIZIV) Rvz-ei. Nieuwe indicatoren: doelmatig voorschrijven van protonpompinhibitoren bij overtollig maagzuur [Internet]. 16 Dec 2024. Available from: https://www.riziv.fgov.be/nl/pers/nieuwe-indicatoren-doelmatig-voorschrijven-van-protonpompinhibitoren-bij-overtollig-maagzuur. Accessed 2025 Nov 18. [
68. Morris JN, Howard EP, Schachter E*, et al.* Cognitive Change Among Nursing Home Residents: CogRisk-NH Scale Development to Predict Decline. J Am Med Dir Assoc. 2023;24(9):1405-11.
69. Egbujie BA, Turcotte LA, Mulla RT*, et al.* Patterns of Transient and Terminal Transitions in Activities of Daily Living Performance Levels among Long-Term Care Residents: A Multistate Markov's Model Analysis of Population-Based Longitudinal Data in Canada. J Am Med Dir Assoc. 2025;26(6):105565.
70. Vetrano DL, Villani ER, Grande G*, et al.* Association of Polypharmacy With 1-Year Trajectories of Cognitive and Physical Function in Nursing Home Residents: Results From a Multicenter European Study. J Am Med Dir Assoc. 2018;19(8):710-3.

Chapter 7

The effect of deprescribing proton pump inhibitors on quality-of-life related patient outcomes among nursing home residents: a target trial emulation

Anlay DZ, *Paque K, de Almeida Mello J, Declercq A, Van Leeuwen E, Dilles T, Cohen J. (in submission at Lancet Healthy Longevity)The effect of deprescribing proton pump inhibitors on quality-of-life related patient outcomes among nursing home residents: a target trial emulation (submitted)*

Abstract

Background: Long-term use of proton pump inhibitors (PPIs), often considered inappropriate, is common among nursing home residents, while deprescribing rates remain low. Although concerns about prolonged use of PPI have increased, previous studies have largely overlooked quality-of-life–related patient outcomes, which are particularly relevant for this population. Evidence on the impact of PPI deprescribing on these outcomes remains limited.

Objective: To investigate the effect of discontinuing long term proton pump inhibitor therapy on multiple quality-of-life–related patient outcomes, hospitalization, and mortality in nursing home residents

Methods: We emulated a two-arm pragmatic randomized trial using linked Belgian national data from interRAI Long Term Care Facility assessments and health insurance claims. Residents aged 65 or older with at least 3 months of continuous PPI use before baseline (first assessment) were eligible. The intervention was deprescribing, defined as no active supply of PPI at baseline with last dispensing ending within 30 days prior to baseline assessment. The comparator was continued use. Outcomes were assessed over 12 months, with six quality-of-life–related measures (activities of daily living, cognition, depressive symptoms, pain, falls, and self-reported health) as the primary outcomes, and all-cause mortality and number of hospitalizations as the secondary outcomes. Inverse probability of treatment weighting was used to balance confounders, and average treatment effects were then estimated using marginal structural models, applying weighted generalized estimating equations (wGEE) for the six quality-of-life–related patient outcomes. Negative binomial models were applied for hospitalization, and restricted mean survival time was used for mortality.

Results

A total of 3,604 residents (1,393 deprescribed; 2,211 continued) were included. Across 12 months of follow up while residents remained alive, trajectories of all 6 quality-of-life–related patient outcomes were similar in the two groups, with no statistical significant differences. Deprescribing was associated with lower hospitalization rate, with an incidence rate ratio of 0.81 (95 % CI: 0.69 to 0.94). Survival patterns varied over time: by 180 days, the deprescribed group accumulated 4.41 more days alive (95% CI: +1.97 to +6.85), whereas by 360 days they accumulated 16.01 fewer days alive (95% CI: -22.78 to -9.23).

Conclusions

In this emulated target trial, deprescribing long term PPI therapy did not change quality-of-life–related patient outcomes but was associated with a lower hospitalization rate. Survival patterns differed over time, showing a modest early advantage for deprescribing that reversed later in follow-up.

Introduction

Proton pump inhibitors (PPIs) suppress gastric acid secretion by inhibiting the gastric H^+/K^+ ATPase [1], and they are among the most frequently prescribed medications in nursing home residents worldwide, with prevalence estimates ranging from 27% to 79.7% [2-9]. Most indications for PPIs require only short-term use (<8 weeks), either for treatment of acid-related conditions (e.g., gastro esophageal reflux disease(GERD), peptic ulcer disease, *Helicobacter pylori* eradication, dyspepsia) or for gastroprotection during temporary exposure to bleeding risk–increasing drugs (BRIDs), such as nonsteroidal anti-inflammatory drug (NSAIDs), antiplatelets, or anticoagulants, as well as after bariatric surgery or endoscopic ulcer therapy [10, 11]. Long-term PPI therapy (>8 weeks) is appropriate only for selected conditions, including severe esophagitis, Barrett's esophagus, chronic use of BRIDs with high bleeding risk like a documented history of gastrointestinal bleeding [12]. However, studies suggest that approximately two-thirds of PPI prescriptions are continued beyond the duration recommended by guidelines, often without a clear long-term indication [13]. For example, 11% of PPI therapy continues after the offending NSAID is stopped.

Hence, discontinuation of PPI can be a manner to avoid low value care and can lead to cost savings [14] but also improve patient outcomes. Although PPIs have a favorable safety profile for short term use, prolonged exposure has been associated with important adverse effects. While most evidence is observational and cannot firmly establish causality, studies consistently report links between long term PPI use and several negative outcomes[15]. These risks are particularly relevant for nursing home residents, who often have multiple chronic conditions, frailty, and heightened susceptibility to medication-related complications [16]. Reported risks include vitamin B12 deficiency, chronic kidney disease, osteoporotic fractures, respiratory and gastrointestinal infections such as Clostridioides difficile and community acquired pneumonia, and dementia [15-17]. PPIs have also been reported to contribute to loss of muscle function [18], increased risk of hospitalization [18], and higher all-cause mortality in older adults [16]. Despite these potential harms, PPIs remain a major target for medication optimisation in older individuals due to high rates of overuse, occasional underuse in high risk patients, financial burden, and contribution to polypharmacy (concurrent use of five or more chronic medications) [15, 19].

Current guidelines recommend periodic review of ongoing PPI use and deprescribing when appropriate, defined as the planned and supervised reduction or cessation of potentially inappropriate medications (PIMs) [20].The long-term use of PPIs is rarely necessary, and deprescribing is usually recommended after 4-8 weeks [21]. Different strategies of PPI deprescribing have been reported, including abrupt stopping or dose reduction, "intermittent" or "on-demand" use, where intermittent use involves a fixed short course (typically 2 to 8 weeks) and on-demand use involves taking PPIs only until symptoms resolve, and switching to H2 receptor antagonists, particularly for non-erosive reflux disease or functional dyspepsia[12]. However, rebound acid hypersecretion may occur even with gradual tapering [22]. Safely deprescribing PPIs is assumed to reduce inappropriate polypharmacy, improve health related outcomes, and reduce healthcare costs. Despite efforts to raise awareness of inappropriate PPI use and despite deprescribing guidelines, prescribing rates have continued to rise [23]. Overall deprescribing rates remain low. For example, in France general adult population discontinuation remained around 12% between 2017 to 2020 [24]. In Belgian nursing homes, PPIs are the most common PIMs, and are the least often deprescribed PIM at 9.45% [3].

While deprescribing of inappropriate long-term PPI therapy in older adults receives increasing attention, also in research, hitherto an important remaining knowledge gap is that the effect of deprescribing PPIs on clinical outcomes relevant to frail nursing home residents remains uncertain [23]. Their extensive use underscores the need to understand any risks linked to long term continuation vs discontinuation of PPI treatment [25]. However, most existing studies have only been able to describe process outcomes, such as discontinuation success, recurrence of symptoms after discontinuation, or gastrointestinal safety. Evidence about effects on quality of life related outcomes that matter most for frail nursing home residents is lacking, for instance in health domains such as physical function, cognition, and psychosocial well-being [26]. But evidence about the influence of PPI deprescribing on overall health outcomes is also limited. PPIs may alter the activity of insulin like growth factor 1, a key regulator of mobility and physical functioning [27], and studies show a 12 -18 % reduction in serum vitamin B12 after 12 months of therapy, as well as reductions in calcium and parathyroid hormone, which may contribute to cognitive decline, bone fragility, and falls [28]. On the other hand, concerns about symptom recurrence after deprescribing may contribute to or worsen depressive symptoms [29]. Hence, evidence about PPI deprescribing on health outcomes including falls, depressive symptoms and mortality is highly relevant but lacking [30].

The reason for this evidence gap is partly the well-described problem that (deprescribing) trials, for practical and ethical reasons, often do not include people with cognitive impairment [31-33] or vulnerable nursing home residents, leading to the populations of most interest being excluded from the findings [34], hence limiting the validity of the findings. Therefore, innovative use of real-world observational data can offer a promising additional source of causal evidence [35, 36]. While causal interpretation from observational studies is challenging, mostly because of bias due to confounding [37], approaches like target trial emulation provide a rigorous framework for causal evidence from observational data. They apply principles of randomized trials to longitudinal observational data and use inverse probability of treatment weighting (IPTW) to address confounding by balancing baseline characteristics between treatment and comparison groups [38]. Using this framework, the present study investigates the effect of discontinuing long term PPI use on quality-of-life related patient outcomes in nursing home residents. Specifically, we compare discontinuation with continued use in relation to quality-of-life related patient outcomes (primary outcome), hospitalization, and mortality (secondary outcomes).

Methods

Study design: target trial specification and emulation

We designed an emulated two-arm pragmatic randomized clinical trial using a target trial emulation framework to estimate the causal effect of proton pump inhibitor (PPI) deprescribing on multiple quality-of-life related patient outcomes among nursing home residents. Leveraging linked administrative and clinical assessment data, we specified the key components of the hypothetical randomized trial and emulated each element in the observational big data [39]. A concise comparison of the target trial protocol and its emulation is provided in **(Table 1)**. This study was conducted in accordance with the REMROSE-D guidance (Reporting and Methodological Recommendations for Observational Studies estimating the Effects of Deprescribing medications) [40] and reported following the TARGET guideline (Transparent Reporting of Observational Studies Emulating a Target Trial) [41].

Data source

We linked data from two national sources to construct the cohort for the emulated target trial. First, the BelRAI Long Term Care Facility (LTCF) dataset represents the Belgian version of the international interRAI LTCF assessment [42], a standardized multidomain instrument used to monitor residents' health and care needs. At each BelRAI assessment, validated outcome scales are automatically generated, including measures of physical function (Activities of Daily Living Hierarchy Scale), cognitive function (Cognitive Performance Scale), social engagement (Social Engagement Scale), mood and behavior (Aggressive Behavior Scale; Depression Rating Scale), and health status (Changes in Health, End-Stage Disease, Signs and Symptoms [CHESS] Scale, Falls Risk Scale, and Pain Scale). BelRAI LTCF also contains diagnostic information and comorbidities (for example dementia and cancer) [43]. These assessments served as the basis for baseline covariates and longitudinal outcome measurements in the emulation. We included all residents whose first BelRAI assessment (defined as the baseline assessment in this manuscript) occurred between 2016 and 2022. In Flanders, the region covered by these data, BelRAI assessments are now mandatory. A baseline assessment is expected to be completed within four days of admission following a three-day observation period, with subsequent assessments conducted every six months or after major clinical changes. Because the system is still being rolled out, the actual intervals between assessments vary across residents. At each assessment, outcome scales are automatically computed from items entered by health care professionals.

Second, national health insurance claims data from IMA-AIM provided sociodemographic variables (age, sex, date of death), health care utilization (for example hospitalizations), and comprehensive medication dispensing records from hospital and community pharmacies, including dispensing dates and World Health Organization Anatomical Therapeutic Chemical (ATC) codes. These data also included nursing home admission and length of stay information [44, 45]. IMA-AIM data were linked to each BelRAI assessment using an encrypted social security identifier, enabling determination of PPI use, chronic exposure (at least three months before baseline), and timing of discontinuation relative to each BelRAI assessment.

We had access to two years of IMA-AIM medication and health care utilization data prior to the first BelRAI assessment, with data available through the end of 2022. This ensured complete capture of covariates, medication exposures, and all information corresponding to the outcomes of interest, while allowing us to establish the temporal relation between covariates, medication use, and outcome assessments throughout follow-up.

Eligibility criteria

We included nursing home residents aged ≥65 years who had a valid baseline BelRAI LTCF assessment, which served as time zero and provided all baseline covariates required for the emulated target trial. To ensure chronic PPI exposure before treatment assignment, residents were required to have ≥3 months of continuous PPI dispensing before baseline. A 30-day pre-baseline grace period was applied to classify residents who had recently discontinued PPI therapy, providing a window short enough to ensure that discontinuation remained relevant to baseline measures but long enough to capture a meaningful number of deprescribers, while recognising that deprescribing will usually not have occurred exactly on the day of the BelRAI assessment (**Figure 1**).

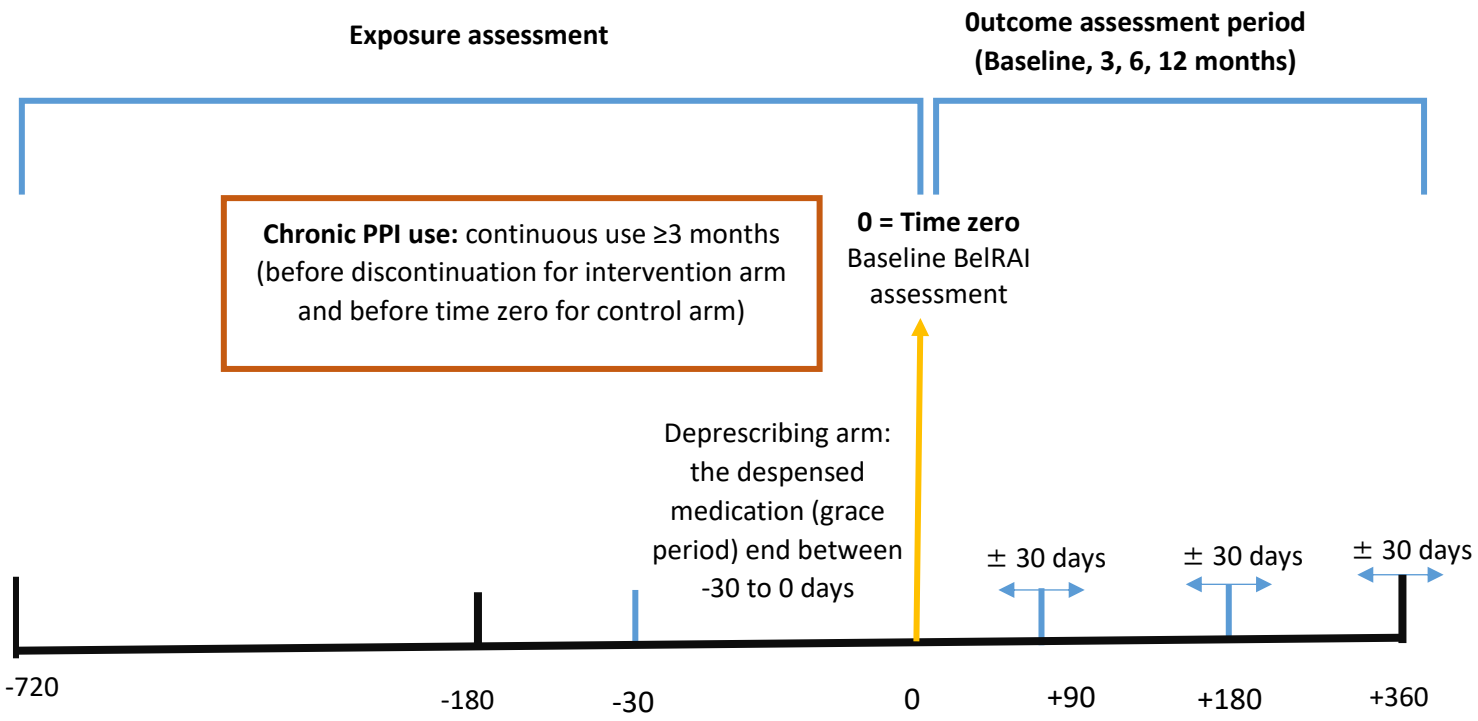


Figure 1: Target trial emulation timeline for exposure and outcome assessment

Residents who were on chronic PPI but for whom their last PPI supply ended more than 30 days before baseline were excluded, placing them outside the grace period and therefore incompatible with the assignment of deprescribing strategy. Residents receiving day care services only were also excluded because they do not undergo routine BelRAI LTCF assessments needed for longitudinal follow up and do not represent long stay nursing home residents.

Treatment strategies

In the emulation, residents were classified into two treatment strategies at time zero, defined by the baseline BelRAI assessment. The first strategy involved deprescribing PPI therapy, defined as no active PPI supply on the baseline date and a most recent dispensing with an estimated end date, based on dispensing date and prescription intervals, within the 30 day grace period before baseline (intervention). The second strategy involved continuing PPI therapy, defined as an active PPI supply covering the baseline date and no discontinuation in the preceding three months (control).

Table 1: Summary of a target trial protocol and its emulation to estimate the effect of PPI deprescribing versus continuation on multiple patient relevant outcomes in nursing home residents

Target trial Protocol component	**Target trial**	**Emulation in observational data**
Eligibility criteria (Population)	**Inclusion:** Residents aged ≥65 years who are chronic PPI users for ≥3 months at randomization. **Exclusion:** Individuals who are no longer using PPI or who discontinued long before randomization.	**Similar to target trial** **Inclusion**: Residents aged ≥65 with ≥3 months of continuous PPI dispensing before the baseline BelRAI assessment (Time Zero). A 30-day pre-baseline grace period was used to classify residents who had recently discontinued PPI. **Exclusion:** Residents whose last PPI supply ended >30 days before baseline (out of grace period). **Sensitivity analysis:** Excluded residents with intermittent/on-demand PPI use after baseline discontinuation to evaluate the robustness of the deprescribing definition.
Treatment strategy	**Strategy 1** Deprescribing PPI at time zero (Intervention). **Strategy 2** Continuing PPI at time zero (control).	Same conceptual strategies. Residents were classified at baseline based on dispensing data: **Deprescribing:** No active PPI supply at baseline and last PPI supply ended ≤30 days before baseline. **Continuation:** Active PPI supply on baseline date.
Treatment assignment	Randomization to deprescribing or continuation groups at time zero, and residents were not blinded to their treatment assignment.	Random assignment to deprescribing or continuing PPI was emulated using inverse probability of treatment weights (IPTW) based on baseline covariates and confounders chosen a priori from the linked clinical and health claims data. We then stablized weight to approximate random allocation at baseline.
Outcomes	Primary outcomes: Trajectory of six quality of life related patient outcomes (extensive assistance of ADL, extensive cognitive impairment, daily depressive symptoms, daily pain, fall, self-reported health) Secondary outcomes: All-cause mortality Number of hospitalizations	Same outcomes as the target trial. We define extensive assistance of ADL (activities of daily living hierarchy scale ≥3), extensive cognitive impairment (cognitive performance scale ≥3), daily depressive symptoms (depression rating scale ≥3), daily pain (pain scale ≥2), fall (interRAI Falls Scale ≥1), self-reported health (poor self-rated health ≥2) All-cause mortality (time to death within 12 months) Number of hospitalizations: total admissions accumulated while alive up to 12 months
Follow-up (Start and end)	Residents followed from randomization until death, loss to follow-up, or 12 months, whichever occurred first. The six patient-centred outcomes measured at 0, 3, 6, and 12 months, with mortality and hospitalization outcomes accumulating throughout the 12-month period.	Same as the target trial. Time zero was defined as the baseline BelRAI assessment, when all eligibility criteria were satisfied and treatment assignment was defined. Residents were followed for 12 months, with the six patient-centred outcomes measured at 0, 3, 6, and 12-month aligned time points, mortality analysed as time to death, and hospitalizations counted until death or 12 months (administrative censoring).
Causal contrast	Intention-to-treat effect of assignment to deprescribing vs continuation.	The same
Statistical analysis	Intention-to-treat analysis	We applied an intention-to-treat analysis. IPTWs were derived using a multivariable logistic regression model. Population-average treatment effects were then estimated using marginal structural models:

	IPTW-weighted generalized estimating equations (GEE) for the six quality of life related patient outcomes, reporting odds ratios (ORs); IPTW-weighted negative binomial regression for hospitalization counts, reporting incidence rate ratios (IRRs); and for all-cause mortality, restricted mean survival time (RMST) was calculated as the area under the IPTW-adjusted Kaplan–Meier survival curve, reported as RMST differences and RMST ratios.

Outcomes and follow-up

We evaluated eight outcomes over twelve months: six quality-of-life–related patient outcomes (primary) and hospitalization and all-cause mortality (secondary). The primary outcomes were derived from validated interRAI scales within BelRAI LTCF assessments; although originally ordinal, they were recoded as binary outcomes for analysis. These included the Activities of Daily Living Hierarchy Scale (range 0 to 6; ≥3 indicates extensive assistance of ADL) [46], the Cognitive Performance Scale (range 0 to 6; ≥3 indicates significant cognitive impairment) [47], the Depression Rating Scale (range 0 to 14; ≥3 indicates daily depressive symptoms) [48], the Pain Scale (range 0 to 4; ≥2 indicates daily pain) [49], the Fall Risk Scale (range 0 to 3; 0 indicates no fall and ≥1 indicates at least one fall in the last 90 days), and the single item self-reported health (range 0 to 3; ≤1 indicates good health and ≥2 indicates poor health). The items used to derive these scales are listed in **Supplementary file 7.1.** Because we are estimating a treatment effect for which the time since baseline is clinically meaningful, follow-up assessments were aligned to fixed time points at 3, 6, and 12 months using a ±1-month window (Figure 1). This window accommodates variation in actual BelRAI assessment dates and prevents unnecessary missing data that would arise if assessments had to occur exactly at those time points.

In this emulated target trial, death was treated as the intercurrent event that truncated follow up. We used a 'while alive' strategy as a primary estimand, meaning that outcome values were analysed only during the period a resident remained alive (until death or 12 months for residents who remained alive). This approach is appropriate in nursing homes, where residents are generally frail, often have multiple chronic conditions, and commonly have substantial palliative and end of life care needs, with median survival frequently less than two years [50]. In this context, quality-of-life–related patient outcomes are meaningful only while a resident is alive.

Two additional outcomes were obtained from the IMA-AIM data sources. All-cause mortality captured any death occurring from baseline through 12 months; time to death was recorded in days, with survivors administratively censored at day 360, corresponding to the end of follow-up. Hospitalization was measured as the total number of hospital admissions accumulated from baseline until death or, for those who remained alive, until 12 months of follow-up.

Covariates used for the inverse probability of treatment weights

Baseline covariates were obtained from the linked data. Socio-demographic factors included age, sex, marital status, living situation, social engagement [51], smoking, and alcohol use. Health and morbidity-related covariates included mental health, clinical stability measured by the CHESS score[52], dementia, cancer, palliative care status, and an overall comorbidity count (27 list of diseases recorded in BelRAI).

Medication related covariates included the total number of chronic medications and the number of fall risk increasing drugs (FRIDs) based on the STOPPFall criteria (including 14 drug lists)[53]

(Supplementary file 7.2). Additional specific medications included antidepressants, antipsychotics, analgesics, and NSAIDs. A proxy for long term PPI indications was captured from bleeding related risk factors, including prior bleeding events and concomitant NSAID, anticoagulant, or antiplatelet use [10, 11]. We also included duration of PPI use before baseline and type of PPI at time zero as certain PPIs have been found to cross the blood–brain barrier, demonstrating that they directly affect the brain [54, 55].

Health care utilization and system factors included hospitalizations in the previous three months, the number of general practitioner consultations, the calendar year of the first BelRAI assessment, and the duration from nursing home admission to the baseline assessment. In addition, to minimise selection bias due to differential depletion of people who are susceptible [56], baseline values of the outcome measures were included as covariates in the adjustment set. The quality of life related patient outcomes in this study reflect residents' current health status rather than incident events, and individuals often enter follow up with varying levels of impairment. BelRAI assessments document residents' current status at each evaluation, and treatment groups may therefore differ in baseline levels of impairment. Adjusting for baseline outcome values ensures that longitudinal trajectories are not distorted by these underlying differences and prevents selection bias arising when one group begins follow up with fewer individuals still susceptible to further deterioration.

We used a causal directed acyclic graph (DAG) to identify the minimum sufficient adjustment set of confounders **(Supplementary file 7.3)**. Following principles of outcome-wide longitudinal designs for causal inference, we applied the same comprehensive set of baseline covariates across all outcomes. In addition to the minimum set identified by the DAG, this broader adjustment set was selected to avoid collider or mediator bias while providing stronger confounding control. Using one consistent covariate set avoids outcome specific variable selection, reduces bias, and ensures comparability across the different health domains evaluated in the emulated target trial [57]. This approach is also consistent with recommendations for claims-based research, where including many pre-exposure covariates, similar to high dimensional propensity score methods, can improve confounding adjustment [58]. The detailed description of each variables level is provided in the **Supplementary file 7.4.**

Statistical analysis

The main analysis compared the effect of PPI deprescribing (intervention group) with continuation (control group) on eight outcomes within the emulated target trial, using an intention-to-treat approach. Descriptive statistics were used to summarise baseline characteristics, reported as frequencies and percentages for categorical variables and as means with standard deviations (SD) for continuous variables.

The probability of receiving treatment (i.e., deprescribing PPI) was predicted using a multivariable binary logistic regression model to obtain the propensity score, with deprescribing status at time zero as the outcome and conditional on the covariates.

We applied the inverse probability of treatment weighting (IPTW) approach to construct a weighted pseudo-population in which treatment assignment was independent of measured baseline confounders. After weighting, the deprescribing and continuation groups had similar covariate distributions, allowing the emulated population to approximate the balance expected in a pragmatic

randomised trial [38, 59]. We applied stabilised weights to mitigate selection bias, reduce the influence of extreme weights, and improve precision [60].

To evaluate whether the exchangeability assumption was achieved, we assessed covariate balance after applying the stabilised IPTW using the standardised mean difference (SMD). An SMD below 0.1 was considered evidence of adequate balance between the deprescribing and continuation groups [61].

For the six patient-centered outcomes, the stabilised IPTW were incorporated into marginal structural models employing GEE with a binomial distribution and logit link, along with an autoregressive correlation structure of order 1 (AR(1)). The models for each outcome, in addition to applying the weights, included terms for follow-up time, treatment assignment, and a time-by-treatment interaction to assess whether trajectories differed between the deprescribing and continuation strategies across follow-up (the primary contrast of interest). Average treatment effect odds ratios with 95% confidence intervals were reported to estimate the effect of deprescribing under the causal-inference framework.

Hospitalization counts were modeled using IPTW weighted negative binomial regression with a log link to accommodate overdispersion (variance exceeding the mean)[62]. We included the log of time at risk while alive, measured in days and capped at 360, as an offset to account for differences in follow-up due to censoring at death or at the end of the 12-month follow up period. Results were presented as incidence rate ratios (IRRs) comparing deprescribing with continuation for the while alive hospitalization rate over 12 months.

For all-cause mortality, the proportional hazards assumption was violated (crossing Kaplan–Meier curves and failure of Schoenfeld residual tests)[63, 64]. Therefore, restricted mean survival time (RMST) was used as a robust and clinically interpretable alternative. RMST was defined as the area under the IPTW-adjusted survival curve up to a prespecified restriction time (τ), which represents the maximum follow-up window over which survival time is averaged. We calculated the RMST from baseline to 90, 180, 270, and 360 days, corresponding to clinically meaningful time horizons and the maximum period with reliable follow-up data, allowing the effect of the treatment to be reflected at different points in time rather than relying on a single summary measure. RMST results were expressed as RMST differences and RMST ratios. An RMST difference reflects the absolute number of additional (or fewer) days lived, on average, up to τ under deprescribing compared with continuation.

To complement the while-alive estimand, we conducted supplementary sensitivity analyses reflecting alternative strategies for handling outcome data truncated by death [65]. First, we used a composite approach in which death was incorporated directly into the outcome as the worst possible value. Second, we implemented a hypothetical strategy by imputing post-death values under a scenario in which all residents were assumed to remain alive. Third, we performed principal-stratum analyses restricted to residents who survived at each follow-up assessment, allowing comparison of trajectories among survivors only [66]. Together, these analyses provided insight into how assumptions about post-death outcomes influence the estimated effect of deprescribing and the robustness of the primary findings.

We conducted a sensitivity analysis by re-defining the intervention at time zero as sustained discontinuation (N = 145), excluding intermittent or on-demand PPI use, and applying the same analytical procedure.

To evaluate how robust the observed findings were to unmeasured confounding, we reported E-values, which quantify the strength an unmeasured confounder would need to explain the observed effects [67]. All estimates were reported with 95% CI, and two-sided p-values less than 0.05 were considered statistically significant.

Statistical analyses were conducted using SAS software, version 9.4 (SAS Institute, Cary, NC, USA).

Missing data

Missing covariates and outcomes were imputed using SAS PROC MI with fully conditional specification (FCS), applying the appropriate method based on variable type. Binary and ordinal variables were imputed using FCS LOGISTIC, multinomial variables using FCS DISCRIMINATE, and count variables using FCS predictive mean matching (PMM) [68]. All variables were included in their most detailed form during imputation to retain information, and variables from imputed dataset were subsequently categorized as required for IPTW estimation and for the outcome models. *See* ***Supplementary file 7.4*** for detailed description how to handle each variables for imputation and modeling in the propensity score model.

Because outcome data were missing to varying degrees, and the primary analysis used a while-alive estimand, we applied an "impute-then-delete" approach [66]. All outcome values up to 12 months were first imputed to address intermittent missingness; afterwards, any imputed values occurring after death were deleted. This ensured complete information for residents who were alive at each time point while maintaining consistency with the while-alive strategy, in which post-death outcomes are undefined.

Results

Participant's selection and characteristics

A total of 3,604 nursing home residents entered the emulated target trial, of whom 1,393 (38.65 %) were classified into the intervention group and 2,211 (61.35 %) into the control group (see **Figure 2**).

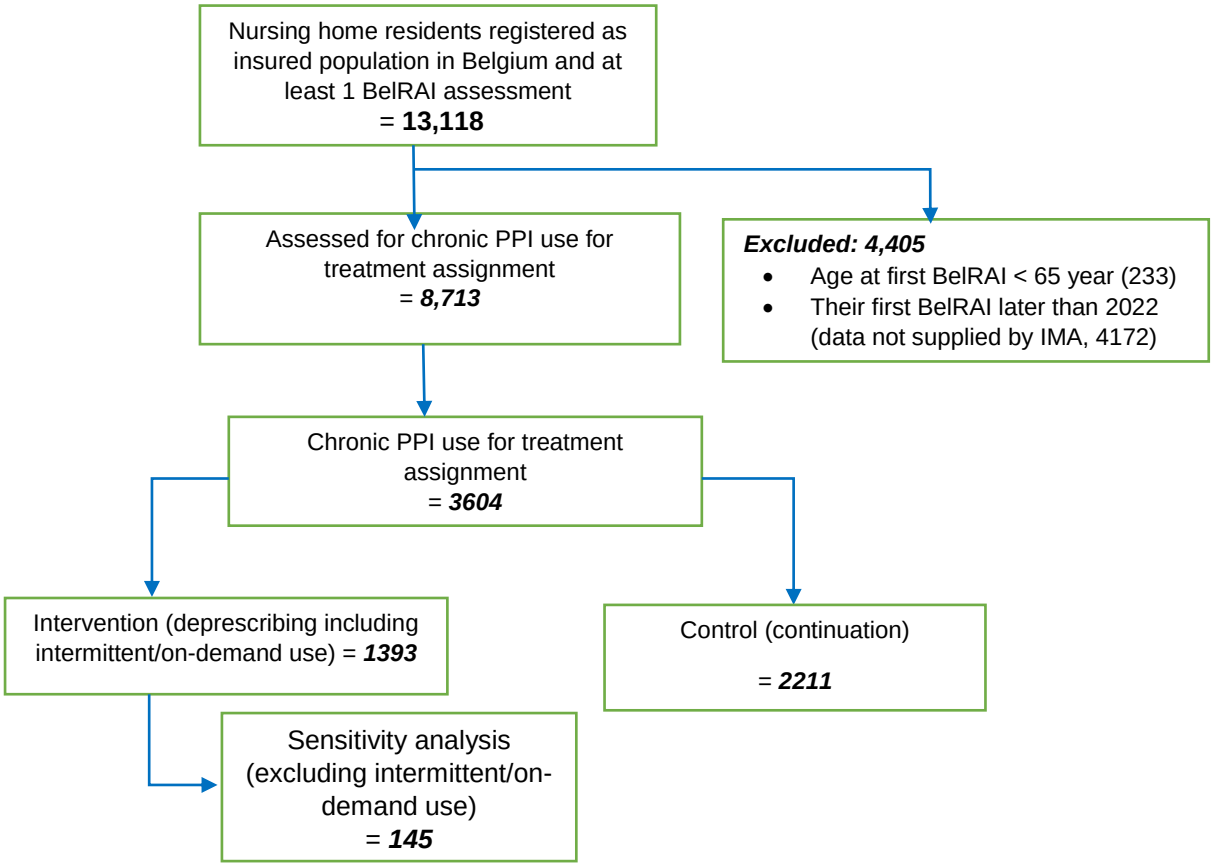


Figure 2: Flow diagram illustrating the selection process of participants from the linked BelRAI and IMA-AIM data.

Table 2 summarizes the baseline characteristics of residents included in the emulated trial. At treatment assignment, 1,505 residents (41.8%) were aged ≥85 years, with 38.0% in the intervention group and 44.1% in the control group. Female residents comprised the majority of the cohort (N=2,633, 73.1%; 71.5% intervention, 74.0% control).

Three or more morbidities were present in 1,135 residents (31.5%; 30.3% intervention, 32.2% control), and dementia diagnosis was recorded in 1,490 residents (41.3%; 41.4% intervention, 41.3% control).

Residents received a mean of 7.79 ± 3.74 chronic medications (7.88 ± 4.14 intervention, 7.74 ± 3.46 control) and 2.65 ± 1.67 fall-risk–increasing drugs (2.56 ± 1.72 intervention, 2.70 ± 1.64 control).

Gastrointestinal bleeding risk was algorithmically identified in the linked data in 74 residents (2.1%), with 2.2% in the intervention group and 2.6% in the control group. At the initiation of the treatment strategy, most residents were on pantoprazole, used by 2,960 residents (82.1%; 80.7% intervention,

83.0% control), and the majority had used PPIs for 12–24 months prior to baseline, documented in 2,897 residents (80.4%; 79.8% intervention, 80.8% control).

In the 3 months prior to baseline, 672 residents (18.6%; 20.4% intervention, 17.5% control) had at least one hospitalization, and 2,106 residents (58.4%; 56.2% intervention, 53.6% control) had at least one general practitioner consultation.

At baseline, 2,645 residents (73.4%; 73.0% intervention, 74.1% control) required extensive assistance with activities of daily living, and 1,318 residents (36.6%; 35.4% intervention, 37.3% control) had daily depressive symptoms. Extensive cognitive impairment was present in 1,070 residents (29.7%; 31.1% intervention, 28.8% control), and 910 residents (25.2%; 27.4% intervention, 23.9% control) had experienced a fall in the 90 days prior to deprescribing. Daily pain was reported by 619 residents (17.2%; 17.4% intervention, 17.0% control), and 2,219 residents (61.6%; 60.5% intervention, 62.3% control) rated their health as poor.

Table 2: Baseline characteristics of nursing home residents included in the target trial emulation, stratified by treatment assignment (PPI discontinuation versus continuation), before and after applying stabilised IPTW.

Variable	Level	Over all cohort (N=3604)		Unweighted (actual number of individuals)			Weighted (pseudo-population)		
		Before imputation	After imputation	Intervention N (%)	Control N (%)	SMD	Intervention N (%)	Control N (%)	SMD
Total		3604	3604	1393 (38.65%)	2211 (61.35%)		1398(38.77%)	2208(61.23%)	
Socio-demographic									
Age	65-74	538 (14.93%)	538(14.93%)	229(16.4%)	309(14.0%)	0.069	205(14.7%)	327(14.8%)	0.004
	75-84	1561 (43.31%)	1561(43.31%)	634(45.5%)	927(41.9%)	0.072	591(42.3%)	950(43.0%)	0.016
	>=85	1505 (41.76%)	1505(41.76%)	530(38.0%)	975(44.1%)	0.123	602(43.1%)	931(42.2%)	0.019
Sex	Male	971 (26.94%)	971 (26.94%)	397(28.5%)	574(26.0%)	0.057	382(27.3%)	596(27.0%)	0.007
	Female	2633 (73.06%)	2633 (73.06%)	996(71.5%)	1637(74.0%)	0.057	1016(72.7%)	1612(73.0%)	0.007
Marital status	Married/partner	599 (16.63 %)	694 (19.3%)	286(20.6%)	408(18.4%)	0.053	271 (19.4%)	424(19.2%)	0.005
	Never married	247 (6.85%)	276 (7.7%)	103(7.4%)	173(7.8%)	0.016	106 (7.6%)	168(7.6%)	0.002
	Separated	174 (4.83 %)	204 (5.7%)	75(5.4%)	129(5.8%)	0.019	79 (5.7%)	126(5.7%)	0.003
	Widowed	2103 (58.35%)	2429 (67.4%)	928(66.6%)	1501(67.9%)	0.027	942 (67.4%)	1490(67.5%)	0.002
	Missing	481 (13.35 %)							
Living situation	a lone	2058 (57.10%)	214659.5%)	834(59.9%)	1312(59.4%)	0.011	831(59.4%)	1314(59.5%)	0.003
	live with others	1385 (38.43%)	145840.5%)	559(40.1%)	899(40.6%)	0.011	568(40.6%)	893(40.5%)	0.003
	Missing	161 (4.47%)							
Social engagement	High	1459 (40.48%)	1538 (42.7%)	536(38.5%)	1002(45.3%)	0.139	593(42.4%)	941(42.6%)	0.005
	Moderate	871 (24.17 %)	915 (25.4%)	366(26.3%)	549(24.8%)	0.033	359(25.7%)	561(25.4%)	0.006
	Low	701 (19.45 %)	735 (20.4%)	316(22.7%)	419(19.0%)	0.092	280(20.0%)	447(20.2%)	0.006
	No	392 (10.88 %)	416 (11.5%)	175(12.6%)	241(10.9%)	0.052	166(11.9%)	258(11.7%)	0.007
	Missing	181 (5.02 %)							
Smoking	No	593 (16.45 %)	619 (17.2%)	215(15.4%)	404(18.3%)	0.076	242(17.3%)	380(17.2%)	0.002
	Yes	2845 (78.94%)	2985 (82.8%)	1178(84.6%)	1807(81.7%)	0.076	1156(82.7%)	1828(82.8%)	0.002
	Missing	166 (4.61 %)							
Alcohol use	No	1120 (31.08%)	1180 (32.74%)	455(32.6%)	725(32.8%)	0.007	465(33.3%)	727(32.9%)	0.008
	Yes	2311 (64.12%)	2424 (67.26%)	938(67.4%)	1486(67.2%)	0.007	933(66.7%)	1481(67.1%)	0.008
	Missing	173 (4.80 %)							
Health and morbidity									
CHESS: health instability	No	1552 (43.06%)	1721 (47.7%)	628(45.1%)	1093(49.4%)	0.087	665(47.6%)	1053(47.7%)	0.002
	Minimal/low	1486 (41.23%)	1618 (44.9%)	650(46.6%)	968(43.8%)	0.057	626(44.8%)	990(44.8%)	0.002
	Moderate/severe	209 (5.8%)	264 (7.3%)	115(8.2%)	149(6.7%)	0.057	107(7.6%)	165(7.5%)	0.007
	Missing	357 (9.91%)							
Dementia	No	2114 (58.66%)	2114 (58.66%)	816(58.6%)	1298(58.7%)	0.003	823(58.9%)	1296(58.7%)	0.005
	Yes	1490 (41.34%)	1490 (41.34%)	577(41.4%)	913(41.3%)	0.003	575(41.1%)	912(41.3%)	0.005
Cancer	No	3027 (83.99%)	3209 (89.1%)	1248(89.6%)	1961(88.7%)	0.029	1247(89.2%)	1966(89.0%)	0.004
	Yes	357 (9.91 %)	395 (11.0%)	145(10.4%)	250(11.3%)	0.029	151(10.8%)	242(11.0%)	0.004
	Missing	220 (6.10 %)							
Mental health	No	3079 (85.43%)	3209 (89.1%)	1254(90.0%)	1955(88.4%)	0.051	1240(88.7%)	1963(88.9%)	0.008
	Yes	381 (10.57 %)	395 (11.0%)	139(10.0%)	256(11.6%)	0.051	158(11.3%)	245(11.1%)	0.008

	Missing	144 (4 %)							
Palliative care	No	3228 (89.57%)	3474 (96.4%)	1342(96.3%)	2132(96.4%)	0.012	1348(96.4%)	2129(96.4%)	0.002
	Receiving /planned	106 (2.94%)	130 (3.6%)	51(3.7%)	79(3.6%)	0.012	50(3.6%)	79(3.6%)	0.002
	Missing	270 (7.49 %)							
Parkinson disease	No	3129 (86.82%)	3320 (92.1%)	1277(91.7%)	2043(92.4%)	0.027	1284(91.8%)	2032(92.0%)	0.008
	Yes	266 (7.38 %)	284 (7.9%)	116(8.3%)	168(7.6%)	0.027	114(8.2%)	176(8.0%)	0.008
	Missing	209 (5.80 %)							
Number of morbidities	0	634 (17.59%)	634 (17.59%)	240(17.2%)	394(17.8%)	0.016	243(17.4%)	386(17.5%)	0.002
	1	964 (26.75%)	964 (26.75%)	388(27.9%)	576(26.1%)	0.041	376(26.9%)	591(26.8%)	0.003
	2	871 (24.17%)	871 (24.17%)	343(24.6%)	528(23.9%)	0.017	336(24.0%)	533(24.1%)	0.003
	>=3	1135 (31.49%)	1135 (31.49%)	422(30.3%)	713(32.2%)	0.042	444(31.7%)	698(31.6%)	0.002
Medication burden & treatment context									
FRIDs	Mean ± SD	2.65 ± 1.67	2.65 ± 1.67	2. 56 ± 1.72	2. 70 ± 1.64	0.084	2. 64 ± 1.71	2. 65 ± 1.64	0.005
Chronic medications	Mean ± SD	7.79 ± 3.74	7.79 ± 3.74	7. 88 ± 4.14	7. 74 ± 3.46	0.038	7. 79 ± 3.90	7. 79 ± 3.60	0.001
Analgesics	No	2271 (63.01%)	2271 (63.01%)	860(61.7%)	1411(63.8%)	0.043	880(63.0%)	1392(63.1%)	0.002
	Yes	1333 (36.99%)	1333 (36.99%)	533(38.3%)	800(36.2%)	0.043	518(37.0%)	816(36.9%)	0.002
Antidepressants	No	2120 (58.82%)	2120 (58.82%)	866(62.2%)	1254(56.7%)	0.111	819(58.6%)	1295(58.7%)	0.002
	Yes	1484 (41.18%)	1484 (41.18%)	527(37.8%)	957(43.3%)	0.111	579(41.4%)	913(41.3%)	0.002
Antipsychotics	No	2771(76.89 %)	2771(76.89 %)	1077(77.3%)	1694(76.6%)	0.017	1075(76.9%)	1696(76.8%)	0.002
	Yes	833 (23.11%)	833 (23.11%)	316(22.7%)	517(23.4%)	0.017	323(23.1%)	512(23.2%)	0.002
NSAIDs	No	3530 (97.95%)	3530 (97.95%)	1363(97.8%)	2167(98.0%)	0.011	1371(98.1%)	2164(98.0%)	0.005
	Yes	74 (2.05 %)	74 (2.05 %)	30(2.2%)	44(2.0%)	0.011	27(1.9%)	44(2.0%)	0.005
Intervention related factors: PPI indication & GI bleeding risk									
Bleeding risk	No	3335 (92.54%)	3516 (97.6%)	1362(97.8%)	2154(97.4%)	0.025	1363(97.5%)	2154(97.5%)	0.003
	Yes	74 (2.05%)	88 (2.4%)	31(2.2%)	57(2.6%)	0.025	35(2.5%)	54(2.5%)	0.003
	Missing	195 (5.41%)							
Duration PPI use(months)	3-6	137 (3.8%)	137 (3.8%)	63(4.5%)	74(3.3%)	0.061	54(3.8%)	84(3.8%)	0.001
	6-9	118 (3.3%)	118 (3.3%)	56(4.0%)	62(2.8%)	0.067	48(3.4%)	73(3.3%)	0.007
	9-12	123 (3.4%)	123 (3.4%)	46(3.3%)	77(3.5%)	0.010	50(3.6%)	75(3.4%)	0.010
	12-24	2,897 (80.4%)	2,897 (80.4%)	1111(79.8%)	1786(80.8%)	0.026	1118(80.0%)	1774(80.3%)	0.009
	>=24	329 (9.1%)	329 (9.1%)	117(8.4%)	212(9.6%)	0.042	128(9.1%)	202(9.1%)	0.002
Types of PPI	Pantoprazole	2960 (82.13%)	2960 (82.13%)	1124(80.7%)	1836(83.0%)	0.061	1150(82.3%)	1815(82.2%)	0.002
	Omeprazole	435 (12.07%)	435 (12.07%)	189(13.6%)	246(11.1%)	0.074	168(12.0%)	265(12.0%)	0.001
	Other PPIs	209 (5.80%)	209 (5.80%)	80(5.7%)	129(5.8%)	0.004	80(5.8%)	128(5.8%)	0.001
Health care utilization & system factors									
Time from admission to assessment (months)	<6	677 (18.8%)	677 (18.8%)	326(23.4%)	351(15.9%)	0.190	259(18.5%)	410(18.6%)	0.002
	6-12	480 (13.3%)	480 (13.3%)	189(13.6%)	291(13.2%)	0.012	184(13.1%)	292(13.2%)	0.003
	12-24	582 (16.1%)	582 (16.1%)	231(16.6%)	351(15.9%)	0.019	230(16.5%)	360(16.3%)	0.004
	>=24	1,865 (51.7%)	1,865 (51.7%)	647(46.4%)	1218(55.1%)	0.174	725(51.9%)	1145(51.9%)	0.001
Hospitalization	No	2846 (78.97%)	2932 (81.4%)	1108(79.6%)	1824(82.5%)	0.075	1131(80.9%)	1794(81.3%)	0.010
	Yes	628 (17.43%)	672 (18.6%)	285(20.4%)	387(17.5%)	0.075	268(19.1%)	414(18.7%)	0.010
	Missing	130 (3.61%)							
Number of GP consultation	0	1498 (41.56%)	1637 (45.4%)	611(43.8%)	1026(46.4%)	0.051	631(45.2%)	1002(45.4%)	0.004
	1	1460 (40.51%)	1610 (44.7%)	625(44.9%)	985(44.6%)	0.009	625(44.7%)	983(44.5%)	0.004
	2	210 (5.83%)	237 (6.6%)	107(7.7%)	130(5.9%)	0.072	96(6.9%)	148(6.7%)	0.006
	>=3	103 (2.86%)	120 (3.3%)	50(3.6%)	70(3.2%)	0.022	46(3.3%)	75(3.4%)	0.007
	Missing	333 (9.24%)							
Years of first BelRAI assessment	2016-2019	423 (11.74%)	423 (11.74%)	103(7.4%)	320(14.5%)	0.228	172(12.3%)	261(11.8%)	0.014
	2020-2022	3181 (88.26%)	3181 (88.26%)	1290(92.6%)	1891(85.5%)	0.228	1226(87.7%)	1947(88.2%)	0.014
Outcome status at the baseline									
Extensive assistance of ADL	No	902 (25.0%)	959 (26.6%)	598 (27.0%)	361 (25.9%)	0.025	360 (25.7%)	582 (26.4%)	0.014
	Yes	2,525 (70.1%)	2645 (73.4%)	1613 (73.0%)	1032 (74.1%)	0.025	1038(74.3%)	1626(73.6%)	0.014
	Missing	177 (4.91%)							
Daily depressive symptoms	No	2,188 (60.7%)	2286 (63.4%)	900 (64.6%)	1386 (62.7%)	0.040	881(63.0%)	1400(63.4%)	0.009
	Yes	1,252 (34.7%)	1318 (36.6%)	493 (35.4%)	825 (37.3%)	0.040	518 (37.0%)	808 (36.6%)	0.009
	Missing	164 (4.55%)							
Extensive cognitive impairment	No	2,363 (65.6%)	2534 (70.3%)	960 (68.9%)	1574 (71.2%)	0.050	983 (70.3%)	1553(70.3%)	0.001
	Yes	1,014 (28.1%)	1070 (29.7%)	433 (31.1%)	637 (28.8%)	0.050	415 (29.7%)	655 (29.7%)	0.001
	Missing	227 (6.30%)							
Fall (in the prior 90 days)	No	2571 (71.34%)	2694 (74.8%)	1011(72.6%)	1683 (76.1%)	0.081	1038(74.2%)	1645(74.5%)	0.007
	Yes	857 (23.78%)	910 (25.2%)	382 (27.4%)	528 (23.9%)	0.081	361 (25.8%)	562 (25.5%)	0.007
	Missing	176 (4.88%)							
Daily pain	No	2,838 (78.8%)	2985 (82.8%)	1150(82.6%)	1835(83.0%)	0.013	1149(82.2%)	1827(82.8%)	0.016

	Yes	557 (15.5%)	619 (17.2%)	243(17.4%)	376(17.0%)	0.013	250(17.8%)	381(17.2%)	0.016
	Missing	209 (5.80%)							
Self-reported health	Good health	1,154 (32.0%)	1385(38.43%)	550(39.5%)	835(37.7%)	0.036	530(37.9%)	844(38.2%)	0.007
	Poor health	1,811 (50.2%)	2219 (61.57%)	843(60.5%)	1376(62.3%)	0.036	869(62.1%)	1364(61.8%)	0.007
	Missing	639 (17.73 %)							

After applying stabilised IPTW, the weighted pseudo-population consisted of approximately 3,606 residents, representing the reweighted distribution under the treatment strategies. All SMD were below 0.1, indicating good covariate balance, as shown in the Love plot (**Figure 3**). The distribution of the weighted pseudo-population is presented in **Table 2**, and details of the propensity score model used to estimate the weights are provided in the ***Supplementary file 7.5***.

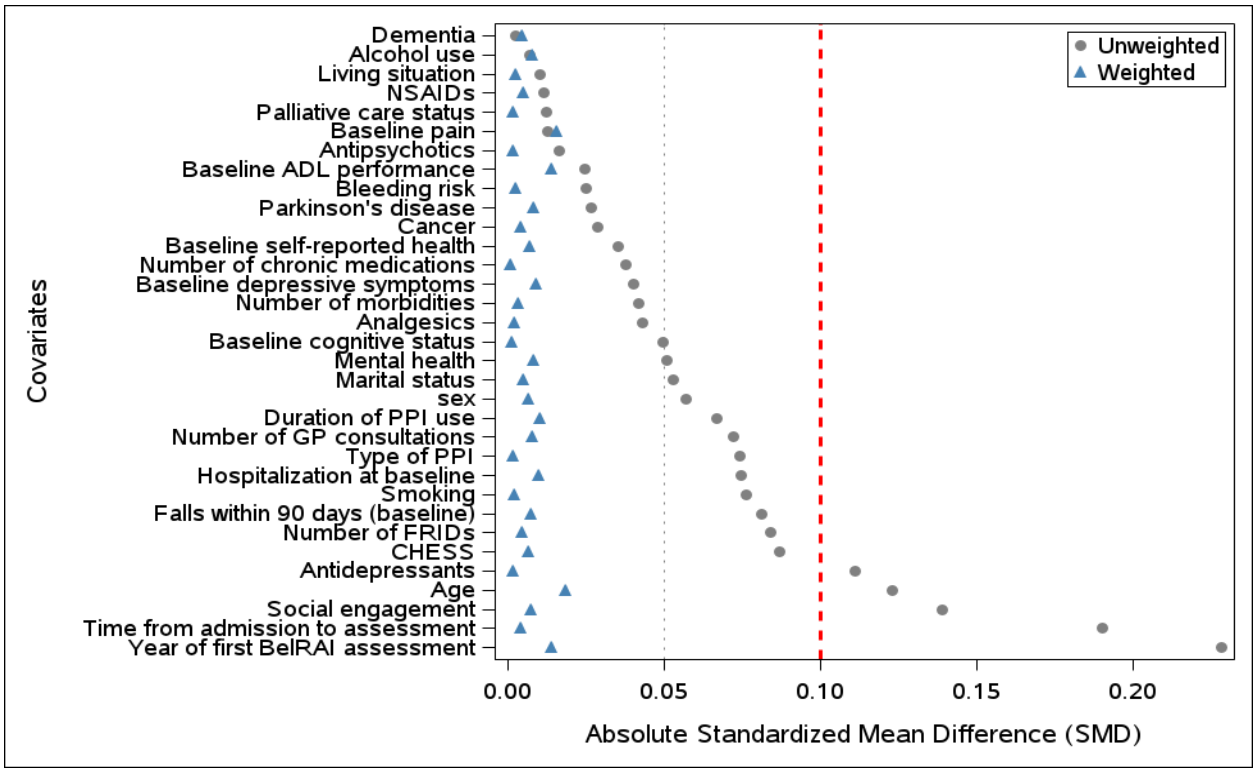


Figure 3: Love plot showing absolute standardized mean differences before and after stabilized weighting

Mortality and follow up

Over 12 months, 770 residents (21.4 %) died, with a median time to death of 154.5 days (IQR, 71–258). Deaths accumulated early and steadily (3 months: 240 residents, 6.7 %; 6 months: 437 residents, 12.1 %; 12 months: 770 residents, 21.4 %), resulting in an increasing proportion of truncated outcomes at each assessment window. The distribution of observed, missing, and truncated outcome statuses across visits for all six quality of life related outcomes is summarised in ***supplementary file 7.6.***

Effect of deprescribing in quality of life related patient outcomes

Across follow-up while residents were alive (until death or the 12-month end of follow-up quality of life related patient outcomes remained similar between groups. Extensive assistance for ADL changed from 74.3% at baseline to 74.6% in the intervention group versus 73.6% to 75.3% in the control group. Significant cognitive impairment changed from 29.7% to 31.8% versus 29.7% to 32.4%. Daily

depressive symptoms changed from 37.0% to 40.1% versus 36.6 % to 38.8 %. Daily pain changed from 17.8% to 16.7% versus 17.2% to 18.2 %. Falls changed from 25.8 % to 25.1 % versus 25.5% to 24.5%. Poor self-reported health changed from 62.1% to 62.2% versus 61.8 % to 63.7 %. Across all six outcomes, changes in outcome trajectories were non-significant, and odds ratios indicate no significant differences between PPI deprescribing and continuation **(Table 3).**

Table 3: Prevalence of quality of life related patient outcomes at each follow-up by treatment assignment and the estimated average treatment effect on outcome trajectories, reported as odds ratios with 95% confidence intervals.

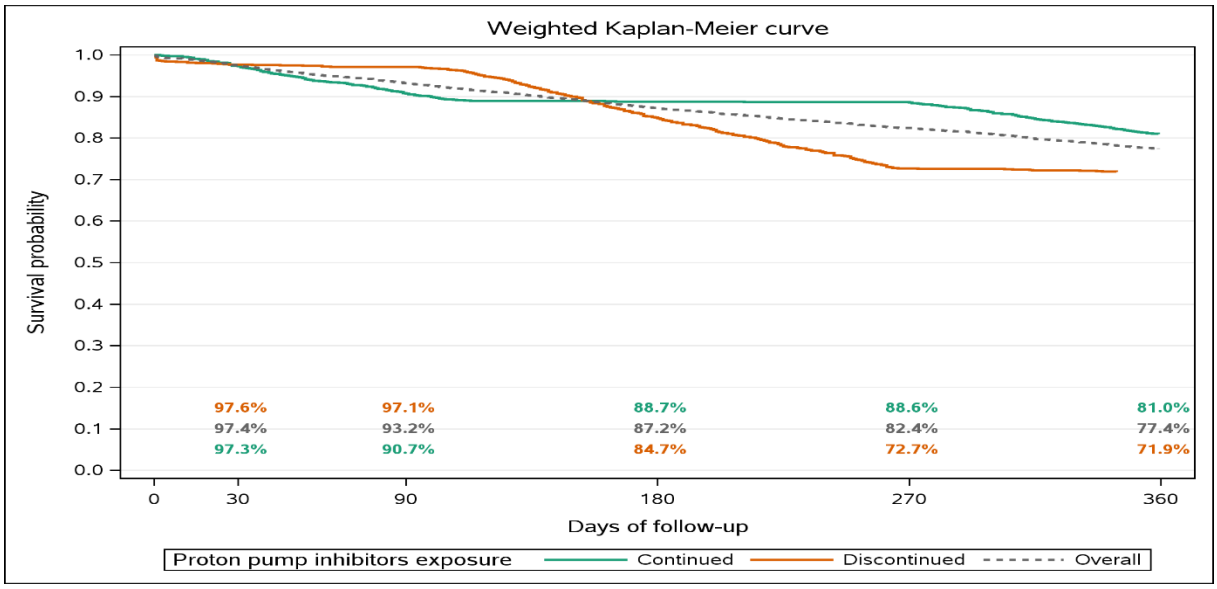
Outcomes	3 months		6 months		12 months		Treatment effect on outcome trajectories: (Time*PPI exposure)	
	Deprescribed (%)	Continued (%)	Deprescribed (%)	Continued (%)	Deprescribed (%)	Continued (%)	OR (95% CI)	P-value
Extensive assistance for ADL	74.0 (71.4-76.5)	73.3 (71.3-75.4)	74.5 (72.0-77.1)	73.8 (71.8-75.9)	74.6 72.0-77.1)	75.3 (73.3-77.2)	0.992 (0.982, 1.002)	0.1224
Significant cognitive impairment	29.6 (27.0-32.3)	29.3 (27.2-31.5)	30.8 (28.1-33.4)	30.4 (28.3-32.6)	31.8 (29.1-34.6)	32.4 (30.2-34.6)	0.996 (0.986, 1.005)	0.3650
Daily depressive symptoms	37.4 (34.4-40.5)	36.8 (34.5-39.1)	38.6 (35.6-41.6)	38.4 (36.0-40.8)	40.1 (37.0-43.2)	38.8 (36.5-41.1)	1.004 (0.990–1.018)	0.6015
Daily Pain	16.2 (14.0-18.5)	17.3 (15.5-19.1)	16.8 (14.4-19.2)	17.3 (15.4-19.2)	16.7 (14.3-19.1)	18.2 (16.4-20.1)	0.996 (0.978–1.013	0.6335
Fall	25.1 (22.0-28.2)	25.2 (22.7-27.7)	25.9 (22.7-29.1)	25.2 (22.4-28.0)	25.1 (22.1-28.2)	24.5 (22.0-27.0)	1.004 (0.983–1.028)	0.7238
Self-Reported Health	60.1 (56.1–64.2)	61.1 (58.2-63.9)	62.6 (59.4–65.9)	63.9 (61.0-66.7)	62.2 (59.1–65.3)	63.7 (61.0–66.4)	1.002 (0.981–1.024)	0.8448

Effect of deprescribing on all-causes of mortality and number of hospitalization

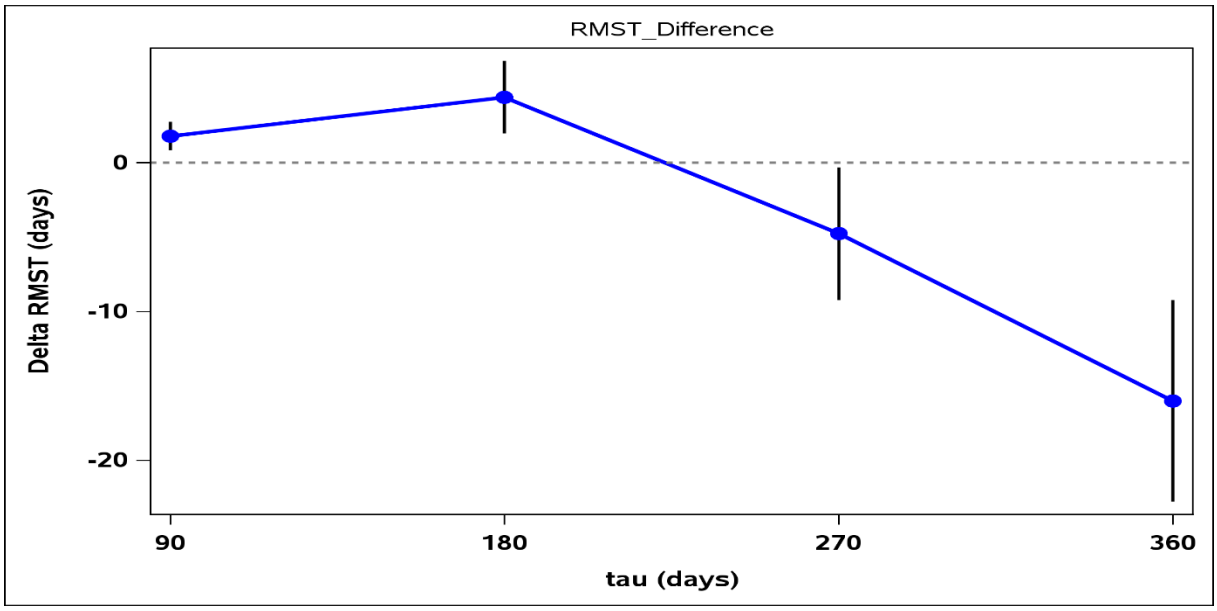
At 12 months, 18.7% of residents in the control group (413 deaths among 2,211 individuals) and 25.6% in the intervention group (357 deaths among 1,393 individuals) had died. Restricted mean survival time (RMST) estimates showed clear variation across the pre-specified time horizons. At $\tau = 90$ days, the deprescribed group accumulated 1.80 more days alive than the continued group, indicating a difference of 1.80 days in average survival time over the 0–90-day interval. At $\tau = 180$ days, the RMST difference was +4.41 days, at $\tau = 270$ days it shifted to −4.77 days, and by $\tau = 360$ days, it reached −16.0 days. RMST ratios followed the same pattern, being slightly above 1.0 at 90 and 180 days and below 1.0 at 270 and 360 days. The overall survival patterns are shown in **Figure 4 A** (Kaplan–Meier curves), and the RMST differences over the different time are visualized in **Figure 4 B**. Full numerical results are provided in **Supplementary file 7.7**.

The risk of experiencing at least one hospitalization, while residents were alive (up until death or the 12-month end of follow-up), was 26.2% (95% CI 24.3–28.1) in the continued group and 21.5% (95% CI 19.2–23.9) in the deprescribed group. In the weighted negative-binomial model restricted to person-time alive, the deprescribed group had 19% fewer hospitalizations per unit of person-time

compared with the continued group (IRR = 0.81, 95% CI 0.69–0.94). The corresponding E-value was 1.78 for the point estimate and 1.32 for the confidence-limit estimate, indicating that an unmeasured confounder would need to be associated with both treatment assignment and hospitalization rate by these magnitudes to fully explain the observed effect. This suggests that unmeasured confounding is unlikely to change these findings. The yearly hospitalization rate was 0.416 in the continued-therapy group compared with 0.335 in the deprescribed group, which clinically corresponds to approximately 42 hospitalizations per 100 residents alive per year for those continuing PPIs versus 34 per 100 residents per year among those who had deprescribed (see **Supplementary file 7.8** for the detailed estimates).



A



B

Figure 4: A) Kaplan–Meier curves for all-cause mortality by treatment strategy (Deprescribed vs Continued). B) Difference in restricted mean survival time (ΔRMST, Deprescribed − Continued) with 95% CIs at τ=3, 6, 9, and 12 months (IPTW-weighted; MI-pooled). Positive values favour deprescribing.

Result of sensitivity analysis

For primary outcome: Across most sensitivity analyses, including re-defining exposure to sustained discontinuation (by excluding intermittent or on-demand use of PPI), as well as the hypothetical and principal stratum estimands, the results remained consistent with the main analysis and showed no statistically significant differences between the intervention and control for any of the six primary outcomes. However, under the composite estimand, which treats death as the worst possible outcome, effect estimates differed. Except for ADL which showed no significant difference, all other composite outcomes showed significantly higher composite risk in the deprescribed group, with OR ranging from 1.03 to 1.06 and p values less than 0.001. See the **Supplementary file 7.9** for detailed estimates for each estimand.

Secondary outcomes: In the sensitivity analysis limited to residents with sustained deprescribing, excluding those with intermittent or on-demand PPI use, the results were broadly consistent with the main findings. In this restricted cohort, survival consistently favored continued therapy across all follow-up periods **Supplementary file 7.7 and Supplementary file 7.10**. The effect on the number of hospitalizations was consistent with the primary analysis, with residents in the sustained deprescribed group experiencing fewer hospitalizations than those who continued therapy. Detailed estimates are provided in the supplementary file **Supplementary file 7.8.**

Discussions

Key findings

In this emulated target trial of 3,604 nursing home residents, PPI deprescribing did not meaningfully change the trajectories of quality of life related patient outcomes when assessed while residents remained alive or by 12-month follow-up. The six primary outcomes—extensive assistance for ADL, significant cognitive impairment, daily pain, daily depressive symptoms, falls, and self-reported health—showed no evidence of statistical and clinically relevant differences between groups. Survival patterns, however, varied over time with a significant advantage for the deprescribing group upto 180 days from baseline but a reversal after that. Deprescribing was associated with 19% fewer hospitalizations per person-time, corresponding to an IRR of 0.81 (95% CI 0.69–0.94).

Strength and limitations

A key strength of this study is the explicit emulation of a target trial, following core design principles that enhance causal interpretation in an observational setting. To our knowledge, this is the first target trial emulation to evaluate the effect of PPI deprescribing on multiple quality of life related patient outcomes in a nursing home population, a group largely excluded from conventional clinical trials. The use of validated interRAI assessments, combined with advanced methods such as IPTW and multiple imputation, enabled careful control of measured confounding and missing data. The relatively large cohort and structured 12 month follow up further strengthened the precision and applicability of the findings, providing robust evidence relevant to routine long term care practice.

Nonetheless, the interpretation of our findings should take into account some potential limitations inherent to the use of administrative data, including misclassification bias, residual confounding by indication and follow-up time. First, deprescribing pathways tapering (dose reduction) could not be fully captured because deprescribing is not formally coded in Belgian medication systems and PPI prescriptions lack dose-change nomenclature. As a result, some brief tapering at time zero may have

been classified as continuation, although this effect is likely small because tapering usually lasts only a few weeks (mostly full discontinuation by 4-8 weeks)[13]. Second, individual clinical indications for long term PPI therapy could not be verified and only proxy measures were available. Although most long term use in older adults occurs without a documented indication [13, 14, 69], some residual confounding by indication cannot be excluded. This problem of potential residual confounding, despite the target trial design, is a reason why causal inference is still limited. However, the target trial design and the relative consistency across supplementary analyses, strengthen the robustness of the findings. Third, although follow up was limited to one year, which restricts the assessment of longer term effects, this timeframe is still reasonably appropriate for frail nursing home residents with limited life expectancy, and the while alive strategy ensures the estimates remain clinically meaningful. Fourth , the primary outcomes were analysed using binary clinical thresholds, which may reduce sensitivity to detect small changes, as the underlying interRAI scales are ordinal. Small shifts within the lower severity categories are unlikely to be clinically meaningful in this frail population, where mild fluctuations are expected and seldom influence care decisions. Furthermore, although interRAI assessments are validated instruments, they are completed by different health professionals [42], which may introduce some measurement variability; however, this variability is expected to be random rather than systematic, and therefore unlikely to bias the results in a particular direction.

Interpretation of findings

Our findings suggest no influence of deprescribing on quality-of-life related patient outcomes. Although no studies have evaluated comparable outcomes specifically in nursing home residents, related evidence from deprescribing interventions in other settings provides a useful context for interpreting our findings. In particular, evidence from the C-SENIoR trial (Deprescribing Intervention of PPIs on Community-Dwelling Older Adults), a pragmatic non-randomised controlled trial conducted in Portuguese primary care, demonstrated that the intervention substantially reduced long-term PPI use over six months. However, despite this marked reduction in PPI exposure, health-related quality of life—assessed as a secondary outcome across domains including mobility, self-care, usual activities, depression/anxiety, and pain/discomfort—did not differ significantly between the intervention and usual care groups [31]. Although the quality-of-life dimensions assessed in C-SENIoR are not identical to the interRAI quality-of-life related patient outcomes evaluated in our study, they capture related constructs, particularly activities of daily living, mood, and pain. The absence of significant change in the outcomes in the context of reduced PPI use is therefore consistent with our findings. Across the different analytic approaches applied in this study, including the sustained discontinuation definition and the hypothetical and principal stratum estimands, the direction of effects remained consistent and aligned with the primary findings of the while-alive estimand, supporting the robustness of the results. The only departure was observed with the composite approach, where death is assigned the worst possible value; because mortality was slightly higher in the deprescribing group later in follow-up and overall, this approach favoured continuation and is therefore less suitable for isolating effects on quality-of-life related patient outcomes. In this context, our findings strengthen the evidence that deprescribing should be considered when there is no clear long-term indication for PPI therapy, as it does not appear to adversely affect quality-of-life related patient outcomes and should not discourage its rational use [25]. However, our dataset did not include verified clinical indications; instead, we relied on proxy indicators for long-term acid suppression needs. Although these proxies reflect real-world prescribing patterns, they are not perfect substitutes for confirmed clinical indications. Interpretation should therefore be differentiated: for residents with a strong, evidence-based

indication, continuation of therapy remains appropriate, as high-risk groups were not specifically identified in the evaluation. A systematic review of interventional studies also reported heterogeneous effects of PPI deprescribing on quality of life as a secondary outcome, with most trials showing no significant difference compared with continued daily therapy; however, continued use appeared more beneficial in patients with more severe disease, while discontinuation was associated with improved quality of life in some cases [70]. For those without a clear indication—likely a substantial proportion of long-term users—our results provide reassurance that deprescribing appears safe with respect to functional, cognitive, mood, and fall-related outcomes, while reducing hospitalizations, medication burden, and, thus, system-level costs [71].

Our finding of no evidence for a detrimental cognitive effect of deprescribing is also consistent with previous findings from other populations and contributes to the ongoing debate on whether PPI use affects cognitive impairment [32, 72]. Previous studies comparing long-term users with non-users have reported inconsistent associations, with some suggesting increased cognitive impairment [34, 73] while others found no relationship [33, 74]. A major source of these discrepancies is that the contradicting work relied largely on claims data, where cognitive measures are often incomplete or misclassified and confounding control is limited [33]. In contrast, our study used validated cognitive assessment instruments and a target-trial emulation framework informed by causal diagrams, enabling more complete capture of baseline dementia and other confounders. This approach reduces misclassification bias and yields more reliable estimates of cognitive trajectories. Moreover, many earlier studies excluded individuals with cognitive impairment at baseline [31-33] or nursing home residents[34]—leading to limited generalizability of the findings to nursing home residents, among whom cognitive impairment is common. By including this population, our study provides a more pragmatic and clinically relevant assessment suggesting that PPI use has limited influence on cognitive change in one of the most vulnerable groups.

Our finding of increased risk of hospitalization with continued PPI use also corroborates previous evidence [69, 75]. Most prior research across diverse older adult populations shows that continued or inappropriate PPI use is associated with a higher risk of hospitalization or readmission. In a prospective longitudinal cohort nested within a multinational European randomized trial of older adults with multimorbidity (OPERAM), persistent PPI use increased the hazard of rehospitalization over one year by 31%. Although OPERAM did not directly compare deprescribing with continuation, its design and findings support our observation that reducing sustained PPI use may help lower the hospitalization burden [76]. Similar associations were reported in the Italian registry (REPOSI)–based inpatient study, where inappropriate PPI use was linked to a 27% higher one-year rehospitalization risk and a substantially greater risk of adverse outcomes when therapy continued without a clear indication [75]. Evidence from large administrative cohorts also demonstrates that unnecessary continuation is associated with significantly higher rehospitalization rates, up to 34% [77]. Collectively, this evidence consistently suggests that continued PPI use may contribute to a greater hospitalization burden, which aligns with the lower hospitalization risk observed with deprescribing in our nursing home cohort.

Our findings about an influence of PPI deprescribing on mortality are, much like the existing research, inconsistent. Several studies report higher mortality when PPIs are continued without a valid indication. In a German cohort study continuation of PPI beyond the recommended period after discharge was linked to an almost 20% increase in 2 year mortality [77], and in Australia among older adults discharged to residential aged care facilities, continued therapy was associated with a 54 %

higher risk of death or readmission within one year [69]. Other studies, however, have found no significant association [76], which illustrates the broader uncertainty in the literature. Within this context, our mortality findings should be interpreted with caution. The timing dependent survival pattern in our study fits within the broader uncertainty reported in the literature and should be interpreted as such. However, the early advantage of deprescribing during the first six months may also suggest that deprescribing may offer a short term mortality benefit in frail residents approaching the end of life when clear indications for long term use are absent, but a disadvantage to those not near the end of life.

Conclusions

By applying a causal target trial emulation to real world data from nursing home residents, our study adds novel and important evidence about the possible influences of proton pump inhibitor deprescription in nursing home patients. Our findings, when interpreted alongside existing evidence from other populations, suggest that deprescribing long-term PPI therapy may not meaningfully alter trajectories of quality-of-life related patient outcomes, including function, cognition, mood, pain, falls, and self-reported health, but may offer advantage in terms of reducing hospitalizations. The influence on survival (early advantage and later attenuation) is less clear.

These findings support routine medication review in nursing homes as a manner to de-implement low value care. For residents without a clear ongoing indication, continuation of PPIs, while a highly prevalent practice in nursing home residents, is unlikely to improve key quality-of-life related patient outcomes but deprescribing it may reduce hospitalization burden, alongside medication burden and cost. Future research could evaluate the effect of PPI deprescribing according to confirmed clinical indications to better distinguish residents with and without clear long-term need.

References

1. Forte JG, Lee HC. Gastric Adenosine Triphosphatases: A Review of their Possible Role in HCL Secretion. Gastroenterology. 1977;73(4, Part 2):921-6.
2. Rane PP, Guha S, Chatterjee S*, et al.* Prevalence and predictors of non-evidence based proton pump inhibitor use among elderly nursing home residents in the US. Research in Social and Administrative Pharmacy. 2017;13(2):358-63.
3. Anlay DZ, Paque K, Van den Eynden B*, et al.* International Deprescribing Guidelines Did Not Impact Actual Practice in Deprescribing of Potentially Inappropriate Medications for Nursing Home Residents: An Interrupted Time Series Analysis. Drugs Aging. 2025.
4. Pasina L, Novella A, Elli C*, et al.* Overuse of proton pump inhibitors in nursing homes: An Italian multicenter observational study. Pharmacoepidemiol Drug Saf. 2020;29(4):461-6.
5. Hendrix I, Page AT, Korhonen MJ*, et al.* Patterns of High-Dose and Long-Term Proton Pump Inhibitor Use: A Cross-Sectional Study in Six South Australian Residential Aged Care Services. Drugs - Real World Outcomes. 2019;6(3):105-13.
6. Wabe N, Urwin R, Meulenbroeks I*, et al.* Over- and Underuse of Proton Pump Inhibitors in Nursing Homes: A Multisite Longitudinal Cohort Study. J Am Med Dir Assoc. 2025;26(2):105393.
7. Plácido AI, Aguiar A, Piñeiro-Lamas M*, et al.* Assessment of potentially inappropriate medications using the EU (7)-PIM list, in a sample of Portuguese older adults' residents in nursing homes. Risk Manag Healthc Policy. 2022:1343-52.
8. Doell A, Walus A, To J*, et al.* Quantifying Candidacy for Deprescribing of Proton Pump Inhibitors among Long-Term Care Residents. Can J Hosp Pharm. 2018;71(5):302-7.
9. Patterson Burdsall D, Flores HC, Krueger J*, et al.* Use of Proton Pump Inhibitors With Lack of Diagnostic Indications in 22 Midwestern US Skilled Nursing Facilities. J Am Med Dir Assoc. 2013;14(6):429-32.
10. Andrawes M, Andrawes W, Das A*, et al.* Proton Pump Inhibitors (PPIs)-An Evidence-Based Review of Indications, Efficacy, Harms, and Deprescribing. Medicina (Kaunas). 2025;61(9).
11. Gwee KA, Goh V, Lima G*, et al.* Coprescribing proton-pump inhibitors with nonsteroidal anti-inflammatory drugs: risks versus benefits. J Pain Res. 2018;11:361-74.
12. Farrell B, Pottie K, Thompson W*, et al.* Deprescribing proton pump inhibitors. Can Fam Physician. 2017;63(5):354.
13. Turner JP, Thompson W, Reeve E*, et al.* Deprescribing proton pump inhibitors. Aust J Gen Pract. 2022;51(11):845-8.
14. Chau SH, Sluiter RL, Hugtenburg JG*, et al.* Cost-Utility and Budget Impact Analysis for Stopping the Inappropriate Use of Proton Pump Inhibitors After Cessation of NSAID or Low-Dose Acetylsalicylic Acid Treatment. Drugs Aging. 2020;37(1):67-74.
15. Bolt J, Thompson W, Inglis C. Appropriate Use of Proton Pump Inhibitors in Older Adults: Concerns and Solutions. Drugs Aging. 2025.
16. Ben-Eltriki M, Green CJ, Maclure M*, et al.* Do proton pump inhibitors increase mortality? A systematic review and in-depth analysis of the evidence. Pharmacol Res Perspect. 2020;8(5):e00651.
17. Maes ML, Fixen DR, Linnebur SA. Adverse effects of proton-pump inhibitor use in older adults: a review of the evidence. Ther Adv Drug Saf. 2017;8(9):273-97.
18. Vinke P, Wesselink E, van Orten-Luiten W*, et al.* The Use of Proton Pump Inhibitors May Increase Symptoms of Muscle Function Loss in Patients with Chronic Illnesses. Int J Mol Sci. 2020;21(1).
19. Schubert ML. Adverse effects of proton pump inhibitors: fact or fake news? Curr Opin Gastroenterol. 2018;34(6):451-7.
20. Scott IA, Hilmer SN, Reeve E*, et al.* Reducing inappropriate polypharmacy: the process of deprescribing. JAMA Intern Med. 2015;175(5):827-34.
21. Lee C, Lo A, Ubhi K*, et al.* Outcome after Discontinuation of Proton Pump Inhibitors at a Residential Care Site: Quality Improvement Project. Can J Hosp Pharm. 2017;70(3):215-23.
22. Namikawa K, Björnsson ES. Rebound Acid Hypersecretion after Withdrawal of Long-Term Proton Pump Inhibitor (PPI) Treatment-Are PPIs Addictive? Int J Mol Sci. 2024;25(10).
23. Wilsdon TD, Hendrix I, Thynne TR*, et al.* Effectiveness of Interventions to Deprescribe Inappropriate Proton Pump Inhibitors in Older Adults. Drugs Aging. 2017;34(4):265-87.
24. Gendre P, Mocquard J, Artarit P*, et al.* (De)Prescribing of proton pump inhibitors: what has changed in recent years? an observational regional study from the French health insurance database. BMC Prim Care. 2022;23(1):341.
25. Thompson W, Pottegård A. Adverse effects of proton pump inhibitors. BMJ. 2026;392:s95.
26. Shrestha S, Poudel A, Steadman K*, et al.* Outcomes of deprescribing interventions in older patients with life-limiting illness and limited life expectancy: A systematic review. Br J Clin Pharmacol. 2020;86(10):1931-45.
27. Doi T, Shimada H, Makizako H*, et al.* Insulin-Like Growth Factor-1 Related to Disability Among Older Adults. J Gerontol A Biol Sci Med Sci. 2016;71(6):797-802.
28. Shahid MS, Ahmed N, Kamal Z*, et al.* A Systematic Review of Long-Term Use of Proton Pump Inhibitors (PPIs) in Older Adults on Polypharmacy: Do PPIs Deplete Nutrients? Cureus. 2025;17(8):e90888.
29. Thompson W, Black C, Welch V*, et al.* Patient Values and Preferences Surrounding Proton Pump Inhibitor Use: A Scoping Review. Patient. 2018;11(1):17-28.
30. Wilsdon TD, Hendrix I, Thynne TRJ*, et al.* Effectiveness of Interventions to Deprescribe Inappropriate Proton Pump Inhibitors in Older Adults. Drugs Aging. 2017;34(4):265-87.

31. Romano S, Rodrigues AT, Guerreiro JP*, et al.* Effectiveness of a Collaborative Deprescribing Intervention of Proton Pump Inhibitors on Community-Dwelling Older Adults: The C-SENIoR Pragmatic Non-randomised Controlled Trial. Drugs Aging. 2025;42(12):1169-83.
32. Khan Z, Mehan S, Saifi MA*, et al.* Proton Pump Inhibitors and Cognitive Health: Review on Unraveling the Dementia Connection and Co-morbid Risks. Curr Alzheimer Res. 2024;20(11):739-57.
33. Goldstein FC, Steenland K, Zhao L*, et al.* Proton Pump Inhibitors and Risk of Mild Cognitive Impairment and Dementia. J Am Geriatr Soc. 2017;65(9):1969-74.
34. Haenisch B, von Holt K, Wiese B*, et al.* Risk of dementia in elderly patients with the use of proton pump inhibitors. Eur Arch Psychiatry Clin Neurosci. 2015;265(5):419-28.
35. Moriarty F, Thompson W, Boland F. Methods for evaluating the benefit and harms of deprescribing in observational research using routinely collected data. Res Social Adm Pharm. 2022;18(2):2269-75.
36. Wastesson JW, Kamgang KS, Lundby C*, et al.* Studying Deprescribing Using Routinely Collected Healthcare Data: Old Challenges and New Opportunities. Basic Clin Pharmacol Toxicol. 2025;137(5):e70131.
37. Hernán M, Robins J. Causal inference: What if. boca raton: Chapman & hill/crc.(2020). Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations. 2020.
38. Chesnaye NC, Stel VS, Tripepi G*, et al.* An introduction to inverse probability of treatment weighting in observational research. Clin Kidney J. 2022;15(1):14-20.
39. Hernán MA, Robins JM. Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available. Am J Epidemiol. 2016;183(8):758-64.
40. Hayes KN, Niznik JD, Gnjidic D*, et al.* The Reporting and Methodological Recommendations for Observational Studies Estimating the Effects of Deprescribing Medications (REMROSE-D) ISPE-Endorsed Guidance. Pharmacoepidemiol Drug Saf. 2025;34(11):e70255.
41. Cashin AG, Hansford HJ, Hernán MA*, et al.* Transparent Reporting of Observational Studies Emulating a Target Trial-The TARGET Statement. JAMA. 2025;334(12):1084-93.
42. de Almeida Mello J, Wellens NI, Hermans K*, et al.* The Implementation of Integrated Health Information Systems - Research Studies from 7 Countries Involving the InterRAI Assessment System. Int J Integr Care. 2023;23(1):8.
43. InterRAI. Worldwide. Available from: https://interrai.org/applications/status-and-outcome-scales/ [Accessed 09 Jan 2026]. [
44. Maetens A, De Schreye R, Faes K*, et al.* Using linked administrative and disease-specific databases to study end-of-life care on a population level. BMC Palliat Care. 2016;15:1-10.
45. InterMutualist Agency. IMA-AIM.[cited 2025 Oct 13]. Available from: https://ima-aim.be/ [
46. Egbujie BA, Turcotte LA, Mulla RT*, et al.* Patterns of Transient and Terminal Transitions in Activities of Daily Living Performance Levels among Long-Term Care Residents: A Multistate Markov's Model Analysis of Population-Based Longitudinal Data in Canada. J Am Med Dir Assoc. 2025;26(6):105565.
47. Morris JN, Fries BE, Mehr DR*, et al.* MDS Cognitive Performance Scale©. J Gerontol. 1994;49(4):M174-M82.
48. Mulla RT, Hirdes JP, McAiney C*, et al.* Factors Associated with Mood Transitions among Older Canadian Long-Term Care Residents: A Multistate Transition Model. J Am Med Dir Assoc. 2025;26(7):105612.
49. Fries BE, Simon SE, Morris JN*, et al.* Pain in U.S. Nursing Homes: Validating a Pain Scale for the Minimum Data Set. The Gerontologist. 2001;41(2):173-9.
50. Collingridge Moore D, Payne S, Keegan T*, et al.* Length of stay in long-term care facilities: a comparison of residents in six European countries. Results of the PACE cross-sectional study. BMJ Open. 2020;10(3):e033881.
51. Gilbart EE, Hirdes JP. Stress, Social Engagement and Psychological Well-Being in Institutional Settings: Evidence Based on the Minimum Data Set 2.0. Canadian Journal on Aging / La Revue canadienne du vieillissement. 2000;19(S2):50-66.
52. Hirdes JP, Frijters DH, Teare GF. The MDS-CHESS scale: a new measure to predict mortality in institutionalized older people. J Am Geriatr Soc. 2003;51(1):96-100.
53. Seppala LJ, Petrovic M, Ryg J*, et al.* STOPPFall (Screening Tool of Older Persons Prescriptions in older adults with high fall risk): a Delphi study by the EuGMS Task and Finish Group on Fall-Risk-Increasing Drugs. Age Ageing. 2020;50(4):1189-99.
54. Cheng F, Ho Y-F, Hung L*, et al.* Determination and pharmacokinetic profile of omeprazole in rat blood, brain and bile by microdialysis and high-performance liquid chromatography. J Chromatogr A. 2002;949(1-2):35-42.
55. Rojo LE, Alzate-Morales J, Saavedra IN*, et al.* Selective interaction of lansoprazole and astemizole with tau polymers: potential new clinical use in diagnosis of Alzheimer's disease. Journal of Alzheimer's Disease. 2010;19(2):573-89.
56. Stovitz SD, Banack HR, Kaufman JS. 'Depletion of the susceptibles' taught through a story, a table and basic arithmetic. BMJ Evidence-Based Medicine. 2018;23(5):199-.
57. VanderWeele TJ, Mathur MB, Chen Y. Outcome-wide longitudinal designs for causal inference: a new template for empirical studies. 2020.
58. Schneeweiss S, Rassen JA, Glynn RJ*, et al.* High-dimensional propensity score adjustment in studies of treatment effects using health care claims data. Epidemiology. 2009;20(4):512-22.
59. Stürmer T, Wyss R, Glynn RJ*, et al.* Propensity scores for confounder adjustment when assessing the effects of medical interventions using nonexperimental study designs. J Intern Med. 2014;275(6):570-80.
60. Pezzi A, Cavo M, Biggeri A*, et al.* Inverse probability weighting to estimate causal effect of a singular phase in a multiphase randomized clinical trial for multiple myeloma. BMC Med Res Methodol. 2016;16(1):150.

61. Austin PC, Stuart EA. Moving towards best practice when using inverse probability of treatment weighting (IPTW) using the propensity score to estimate causal treatment effects in observational studies. Stat Med. 2015;34(28):3661-79.
62. Lee KH, Pedroza C, Avritscher EBC*, et al.* Evaluation of negative binomial and zero-inflated negative binomial models for the analysis of zero-inflated count data: application to the telemedicine for children with medical complexity trial. Trials. 2023;24(1):613.
63. Royston P, Parmar MKB. Restricted mean survival time: an alternative to the hazard ratio for the design and analysis of randomized trials with a time-to-event outcome. BMC Med Res Methodol. 2013;13(1):152.
64. Uno H, Claggett B, Tian L*, et al.* Moving beyond the hazard ratio in quantifying the between-group difference in survival analysis. J Clin Oncol. 2014;32(22):2380-5.
65. Hussain J, Peters TJ, Johnson M*, et al.* Missing data in palliative and end of life care trials. Guidance on how to reduce, handle and report incomplete data. 2022.
66. Pham TM, Kahan BC, Lopes A*, et al.* Estimating treatment effects in trials with outcome data truncated by death: A case study on aligning estimators with estimands. Clin Trials. 2025;22(6):676-86.
67. VanderWeele TJ, Ding P. Sensitivity Analysis in Observational Research: Introducing the E-Value. Ann Intern Med. 2017;167(4):268-74.
68. SAS Institute Inc. SAS/STAT® User's Guide. Cary (NC): SAS Institute Inc.; 2025. Available from: https://documentation.sas.com/api/docsets/statug/v_039/content/mi.pdf?locale=en.
69. Roberts G, Pegoli M, Grzeskowiak L*, et al.* Hospital admission as a deprescribing triage point for patients discharged to Residential Aged Care Facilities. Age Ageing. 2021;50(5):1600-6.
70. Rossi A, Perrella L, Scotti S*, et al.* Approaches to Deprescribing Proton Pump Inhibitors in Clinical Practice: A Systematic Review. J Clin Med. 2024;13(20).
71. Xie M, You JHS. Deprescribing of proton pump inhibitors in older patients: A cost-effectiveness analysis. PLoS One. 2024;19(10):e0311658.
72. Batchelor R, Gilmartin JF, Kemp W*, et al.* Dementia, cognitive impairment and proton pump inhibitor therapy: A systematic review. J Gastroenterol Hepatol. 2017;32(8):1426-35.
73. Gomm W, von Holt K, Thomé F*, et al.* Association of proton pump inhibitors with risk of dementia: a pharmacoepidemiological claims data analysis. JAMA neurology. 2016;73(4):410-6.
74. Booker A, Jacob LE, Rapp M*, et al.* Risk factors for dementia diagnosis in German primary care practices. Int Psychogeriatr. 2016;28(7):1059-65.
75. Elli C, Novella A, Pasina L*, et al.* Proton pump inhibitors and 1-year risk of adverse outcomes after discharge from internal medicine wards: an observational study in the REPOSI cohort. Intern Emerg Med. 2025;20(4):1119-26.
76. Aubert CE, Blum MR, Gastens V*, et al.* Prescribing, deprescribing and potential adverse effects of proton pump inhibitors in older patients with multimorbidity: an observational study. CMAJ Open. 2023;11(1):E170-e8.
77. Palmowski L, von Busch A, Unterberg M*, et al.* Timely Cessation of Proton Pump Inhibitors in Critically Ill Patients Impacts Morbidity and Mortality: A Propensity Score-Matched Cohort Study. Crit Care Med. 2024;52(2):190-9.

PART V

DATA ACCESS AND STRUCTURAL CHALLENGES IN BIG DATA HEALTHCARE RESEARCH

Chapter 8

Structural challenges in accessing and using big data in health care: a case study based on palliative care research

Published:
Anlay DZ, Paque K, Sabbe K, Miranda R, Dilles T, Cohen J. Structural challenges in accessing and using big data in health care: A case study based on palliative care research.
Int J Med Inform. 2026 Jul 6;220:106593.
doi: https://doi.org/10.1016/j.ijmedinf.2026.106593

ABSTRACT

Background

Big data holds transformative potential for health research, yet accessing and utilizing it remains challenging. Based on firsthand experience, this study identifies structural challenges and proposes ways to improve data accessibility and usability.

Methods

Using a case study within the PhD project DepEnD (Deprescribing at the End of Life), we analysed two data requests at the national level: Cohort 1, linking Belgian health insurance data with data from Statistics Belgium, and Cohort 2, with the Belgian Resident Assessment Instrument (BelRAI). We conducted document analysis included email correspondence, meeting minutes, and data application and approval documents. The entire trajectory from data request preparation to acquisition and use was mapped and illustrated with timelines. Challenges related to access and use were analyzed thematically.

Results

We reviewed 111 emails, 19 meeting minutes, 20 documents submitted to the Belgian Information Security Committee (ISC), and 2 ISC-authorized documents. The process from document preparation to data access took 3.5 years for Cohort 1 and 20 months for Cohort 2. Delays stemmed from multiple parties involved in data sharing and authorization. These challenges fell into five key themes: 1) bureaucratic, procedures and regulations with substantial human dependency; 2) limited personnel capacity; 3) data quality and accuracy issues; 4) operational and technical problems; and 5) lack of clear responsibility and coordination throughout the data-sharing lifecycle

Conclusions

Accessing big data was not as straightforward as anticipated; the process involved significant delays, complexity, and high costs. These challenges compromised timelines, narrowed research scope, led to inefficient use of public funds, and risked the completion of time-bound projects. Streamlining access is therefore essential and should be a priority. Based on observed challenges, we propose solutions focusing on strengthening data infrastructures, harmonizing data access procedures through clear protocols, building adequate personnel capacity, establishing jointly agreed timelines, and enabling fast, transparent communication among stakeholders.

Keywords

Big Data, Data Access Challenges, Data Sharing, European Health Data Space, Health Data Linkage, Palliative Care

1. INTRODUCTION

Big data is widely presented as a major driver of healthcare transformation [1]. Advances in artificial intelligence, machine learning, and large-scale analytics can support clinicians, providers, and policymakers by enabling earlier disease detection, improving therapeutic decision-making, predicting outcomes, advancing personalized medicine, and enhancing health outcomes [2-4]. This promise stems from the ability to generate insights from large, diverse, and frequently updated datasets [5].

In palliative and end-of-life research, big data can provide insights into complex issues and overcome challenges such as difficulties in recruiting participants by enabling analyses of large linked cohorts. Researchers can evaluate healthcare use, sociodemographic factors, and health expenditures, forecast future palliative care needs, explore family network structures, and study symptom prevalence near the end of life [1]. Big data also allows investigation of real-world questions difficult to address in randomized trials [6], including medication effectiveness and safety across the drug lifecycle [7]. Overall, it offers rapid, high-impact insights with relatively limited effort, motivating many researchers, including PhD candidates, to use large, diverse datasets for interdisciplinary questions.

Despite its promise, big data research presents substantial challenges. Researchers must ensure data quality and integrity, protect privacy, and manage large, complex datasets [8-10]. Practical obstacles include long turnaround times, inconsistent access procedures, and difficulties in data linkage [11, 12], which depend on coordination among multiple parties and clear communication. Structural issues, particularly within data holders, can delay projects and disrupt timelines. Given the limited funding periods of many research projects, including doctoral programs that typically last four years in most European countries, such delays can jeopardize the feasibility of the research.

Having conducted several palliative care projects using big data and experienced firsthand the challenges of accessing and using such data, we aim to provide a counterbalance to inflated expectations held by researchers, funders, and the wider public regarding achieving its potential. Using prospective documentation from two recent projects, we describe practical difficulties in data access and use. By critically analyzing these challenges, we propose recommendations for researchers, data holders, and governments to mitigate common obstacles and support secure and efficient health data sharing across Europe [13].

2. METHODS

We used a case study design based on documented experiences from the DepEnD (Deprescribing at the end of life) project. Data were analysed using an adapted READ approach (Ready materials, Extract data, Analyse data, Distil the findings), applied to the access procedures for two data cohorts.

2.1. Description of the project and data requests

This study draws on two data requests from a PhD project aimed at generating evidence on deprescribing of medications in older adults with limited life expectancy using linked administrative and clinical data. Cohort 1 was a decedent cohort (2014–2019) for interrupted time series analysis, and Cohort 2 a prospective cohort of nursing home residents (2016–2022) identified via the BelRAI assessment system for longitudinal and causal analyses of medication effects in real-world settings.

2.2. Data collection

We used retrospective document analysis [14] to describe practical challenges in accessing data for both Cohorts. Primary sources included working documents such as meeting minutes with data holders and research teams, email correspondence among stakeholders (including the Belgian Health Care Knowledge Center (KCE) for small cell risk analysis (SCRA)), and approved Information Security Committee (ISC) documents (see **Table 1** for key terms). Meeting minutes captured agreed methods for data delivery and linkage procedures, as well as challenges encountered, project implications, and solutions implemented. Emails, recorded in Microsoft Word (®Microsoft 2023) tables with dates, senders, recipients, and content, provided real-time insight into data access requests, permissions, and issue resolution. For each cohort, we extracted time intervals for key stages, including initial contact with the data holders, ISC application and approval, data delivery, error identification, and the communication and redelivery of corrected data.

Table 1: Definitions and operationalization of key terms

Term	Definition
European Health Data Space (EHDS)	An EU initiative establishing a common framework for secure, high-quality sharing and secondary use of health data across Member States, promoting interoperability and streamlined access procedures [13].
Health Data Agency (HDA)	The national Health Data Access body/ authority responsible for regulating and facilitating access to health data, ensuring compliance with the EHDS framework and national legislation [15].
Information Security Committee (ISC)	A regulatory body responsible for reviewing, approving, and overseeing secure access and use of sensitive health and administrative data for research, ensuring compliance with national data protection and ethical standards [16, 17].
Small cell risk analysis (SCRA)	It is an analysis of the risk that a dataset for secondary use contains small cells, where aggregated information could re-identify one or a few individuals, and is often required by the Information Security Committee before transferring linked data to the user.
Data access delay	Any extension beyond the first project year allocated for database creation and access was considered a delay.
Data mapping	Matching fields from one data source to another, forming the basis for integration, transformation, and linkage [18].
Data quality	Suitability of data for secondary use (EHDS Article 2(2)(z) [13]).
Data holders	Agencies providing data for research (EHDS Regulation, Article 2(2)(t) [13]).
Data host	The data holder responsible for securely storing, managing, and granting access to linked data from multiple holders.

2.3. Data analysis

The research team reviewed all meeting minutes and email correspondence for both cohorts to gain a comprehensive understanding of the data access process. Key steps were identified and plotted on timelines to compare the actual sequence and duration against the planned one-year timeframe for data access, highlighting delays. Challenges and their implications were systematically coded and

thematized. Delivered variables on the remote SAS server were compared to the ISC-approved list to identify discrepancies and resolutions. Themes were discussed in research group meetings to incorporate team members' perspectives, and an independent co-author with data access experience provided additional objectivity. Preliminary results and interpretations were then verified with data holders to ensure consistency and alignment with their experiences. Reflexive consideration of the data holders' perspective informed co-created recommendations for researchers, data holders, and governments, ensuring solutions were practical, relevant, and feasible.

3. RESULTS

In total, we reviewed and analyzed 111 emails (56 for Cohort 1, 55 for Cohort 2), 19 meeting minutes (average 1.5 hours, range 1–2 hours), and two ISC-authorized documents, along with 20 documents submitted for ISC approval (10 per cohort).

3.1. Requested data sources and involved parties

Access to personal data required approval from the ISC, which authorizes and defines good practices for electronic exchange of personal data in Belgium, including social security and health domains [16, 17]. Cohort 1 includes data from IMA-AIM and Statistics Belgium, while Cohort 2 incorporates IMA-AIM and Pyxima **(Table 2)**. Other partners include the Trusted Third Party (TTP, eHealth) for secure data linkage and KCE for SCRA to ensure privacy compliance. The PhD project was conducted collaboratively between Vrije Universiteit Brussel (VUB) and the University of Antwerp (UA), with both institutions involved in the contractual agreements and every step of the data access procedure. Researchers adhered to the internal regulations of both universities governing good research conduct.

Table 2: Data Cohorts, involved data holders, and associated datasets

Cohort	Data managing agency	Data Sets
Cohort 1	1.IMA-AIM (InterMutualistic Agency)	6. ***Population database:*** Contains demographic, socio-economic and health care data on the members of the 7 Belgian health insurance funds. 7. ***National healthcare claims data:*** Contains information on the health care provided to the members of the seven Belgian health insurance funds in the context of compulsory health insurance. 8. ***Katz-scale database:*** Evaluations of independence in activities of daily living for patients in outpatient nursing care or staying in nursing homes. 9. ***Pharmanet database:*** All reimbursed medication data dispensed in community pharmacies, provided to the members of the seven Belgian health insurance funds in the context of the compulsory health insurance 10. ***Hospitalization database:*** All hospital admissions, data on hospital stays registered by the seven Belgian health insurance funds
	2. Statbel (Statistics of Belgium, the Belgian Statistical Office)	1. ***Death certificate database:*** Causes and place of death. 2. ***Demographic and Census Database:*** Includes educational level. 3. ***Fiscal database:*** includes net taxable income.
Cohort 2	1. IMA-AIM	The same dataset with cohort 1
	2. Pyxima	**1. Belgian Resident Assessment Instrument Long-Term Care Facilities (BelRAI LTCF) V1-3.0:** provides assessments across clinical, functional, medical, and psychosocial domains, as well as validated scales and triggers for clinical actions, measured longitudinally.

The procedure for accessing and using the data involves multiple steps and stakeholders, from preparing ISC application documents to obtaining journal manuscript approval. An overview of the process and required documents is provided in **Table 3**.

Table 3: Procedure, required documents for accessing and utilizing linked data and the different actors responsible at each steps*

Phases/steps	Responsible Actors	Key Activities
1. Document preparation for ISC application	The researchers as an applicant is the main responsible person (involving the VUB and UAntwerpen) with a counselling role of data holders. in our case IMA-AIM acts as data processor (and does data hosting for our projects), assures smooth document preparation before submission to ISC.	1.1. Contact the data holders and the data host, and arrange mutual meetings or email exchanges to clarify and operationalize the research questions and methods, thereby ensuring a common understanding. 1.2. Prepare variable summary and justification (description, motivation, coding/level), in collaboration with the data holder (via document sharing for comment and corrections, email, and meetings) 1.3. Draft and finalize cooperation agreement between the requesting universities and the data host 1.4. Review and collect additional required documents, including the Information Security and Privacy Policy (involving VUB, UAntwerpen, and IMA-AIM) and the Principles and Practices of Good Research (as required by the universities), for submission. 1.5. Complete Data Protection Impact Assessment (DPIA) for each cohort 1.6. Exploration of collaborative partners by the data host (e.g.; designate an approved partner for small cell risk analysis [to be conducted after privacy approval and before data access], Trusted Third Parties (TTPs) for data linkage) 1.7. Obtaining internal approval from each data holders 1.8. Filling in the form of the ISC application
2. From document submission to ISC approval	ISC, with potential clarifications from Researchers	2.1. Verify application completeness. 2.2. Legal review of submitted documents. 2.3. Request clarifications or meetings with researchers if needed.
3. From approval to initial data access	Researchers, all data holders, data host, eHealth, Belgian Health Care Knowledge Center [KCE]	3.1. The researcher notify the deliaration of ISC to data holders and data host to initiate the data flow for linkage 3.2. TTPs initiate data linkage - Data flow procedures detailed in **Supplementary file 8.1** (for both Cohort 1 and Cohort 2); full linkage process published elsewhere [19] 3.3. Small cell risk analysis (the researcher creates categorical variables and prepares their categories/levels in an Excel file to facilitate the analysis, in our case conducted by the KCE as a partner). 3.4. Finalized and signed contractual (collaborative) agreement, reviewed by the legal offices of each university, and then signed by the project promoters, rectors of both universities, and the data holders. 3.5. VPN SSL access to the Intermutualist Agency's (IMA) secure information network - Includes signing of user agreement and receipt of access token 3.6. Data made available to the researcher via secure remote server hosted by IMA 3.7. Payment of invoice to data hosts
4. From initial data access to completion of data exploration and validation	Data Host, Researchers	4.1. The data host notifies the researcher about the availability of the linked data on the server, provides a description of the dataset name, and recommends checking the datasets for correctness in terms of the agreed delivery. 4.2. Researcher explore and validate datasets
5. *Notifying data validation results:* if no errors are found, confirm accordingly; if errors are identify, report them to	Researcher, data holders, data host and eHealth	5.1. Researcher report errors or missing variables in the data set based on the list of variables approved by ISC 5.2. Data holders supplement the missing variables/records 5.3. eHealth executed the linkage in accordance with the supplement. 5.4. The data host notifies the researcher when the data is made available on the server.

	data holders for correction and redelivery of the data			
6.	*After accessing corrected data*	Researchers, data host	6.1. 6.2. 6.3.	Researcher check the modified delivery and notify the host for correctiness again Analysis and write up based on the data Submit manuscript to data host for review before journal submission - Ensure appropriate use and referencing of data

***Note:** The order of steps may not always be fixed. For example, in Step 1, as long as all required documents are completed for the ISC application, a flexible approach can be followed. In practice, some steps should precede others—such as discussing with the data holder before preparing the data request, since the data holder has better knowledge of the dataset, checking metadata, and accounting for evolving changes. Additionally, not all steps will apply in every case. For instance, if the first data delivery is correct, no redelivery will be needed. Moreover, in projects which only use aggregated non-personal data (that do not need to be linked on individual level), the data access procedure is much faster as no ISC approval is necessary. The steps presented here are based on the actual process we experienced.

3.2. Tracking the Data Access Journey

The procedure from document preparation, in consultation with data holders, to access to corrected and linked datasets took 3.5 years for Cohort 1 and 20 months for Cohort 2. In both cohorts, the longest step was the linkage procedure, from ISC approval to first data access, taking 22 months for Cohort 1 and 10 months for Cohort 2. The interval from ISC application to approval was under three months for both data requests. **Figure 1** shows six key milestones in the data access and utilization procedure and the duration between each.

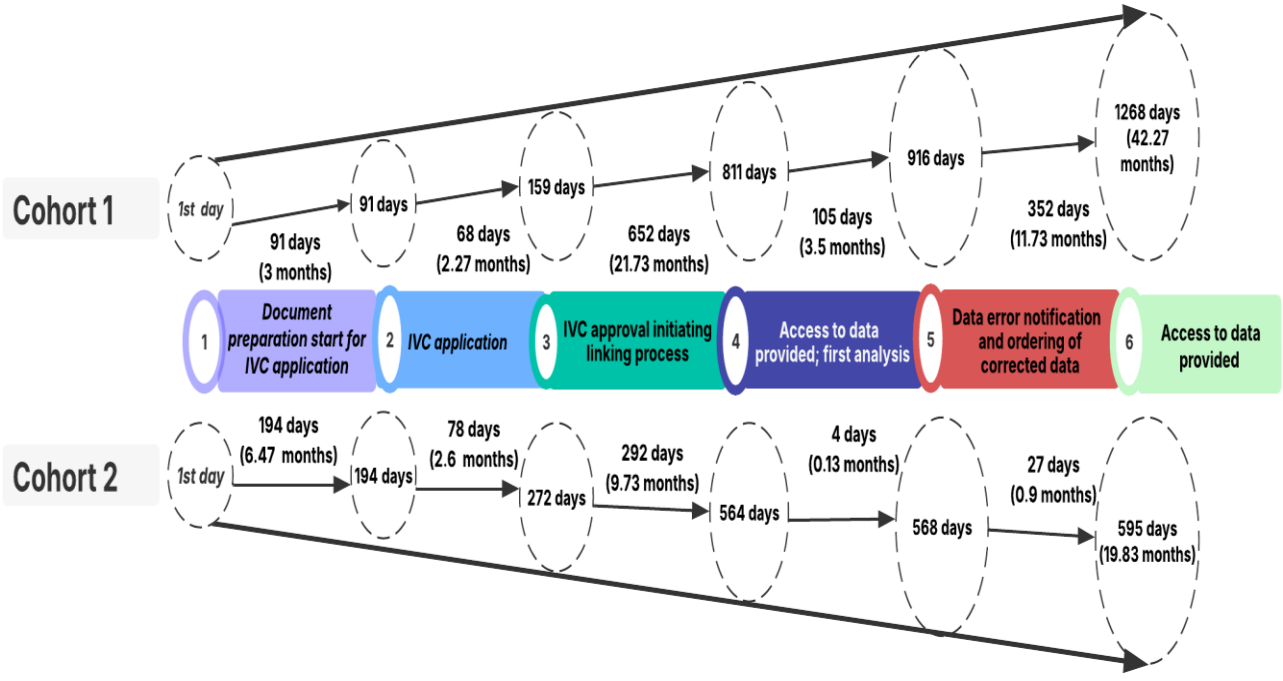


Figure 1: Timeline illustrating the key milestones and actual timing of the data access procedure, including the duration between each milestone and from the initial document preparation. The timeline is presented for two cohorts: Cohort 1 is shown above the milestones and Cohort 2 below.

3.3. Practical challenges faced in accessing and utilizing data

Practical challenges that contributed to the relatively long data access journey were related to various required activities from the various stakeholders involved (i.e. the research group, the data holders, the ISC) responsible for approving data provision and overseeing data privacy and security, the TTP responsible for data linkages and KCE for small cell risk analysis) as well as the interplay between these entities. The encountered challenges in data access and utilization could be summarized into five main and interacting themes (**See Table 4**).

1. Bureaucratic, Regulatory, and Procedural Hurdles

Approval processes required extensive documentation and multiple authorizations to comply with privacy regulations. Coordination among interdependent parties was complicated by inconsistent communication, staff turnover, and the COVID-19 pandemic, contributing to delays.

2. Organizational Structure and Capacity

Resource limitations at data holders, including personnel shortages and high data request volumes, were a major challenge, worsened by absenteeism and holidays. Variations in organizational structures and inconsistent communication hindered streamlined data access. Researchers' limited experience with data requests led to incomplete ISC applications, inconsistent documentation, and delays in identifying errors. Reliance on multiple data holders for mapping added further complexity.

3. Data quality and accuracy: Human errors

Data quality and accuracy can be compromised at multiple stages, from initial recording to data utilization, mainly due to human errors. Observed issues included implausible values, missed variables in data requests, and misinterpretation of ISC-approved documents, which complicated later linkage and sharing. Additional errors arose during the selection of eligible records for the transfer of data to TTP responsible for linkage.

4. Operational and technical problems

Challenges included unclear data access procedures, including identifying first contact points and required steps, and lack of centralized information on available data sources. Additional issues were inconsistent data mapping, reliance on multiple data holders for linkage, recurring delivery issues, changes in data structure, and unclear ISC amendment guidelines. As linkage was performed by the TTP, researchers received only the linked data, which, combined with the secondary nature of the datasets, required extensive exploration, validation, and quality checks.

5. Responsibility and coordination

The necessity of shared responsibility across stakeholders in the data-sharing life cycle, combined with a less accountable data-sharing scheme, leads to errors in data sharing, increased complexity, and reduced predictability in timelines and planning. Competing priorities meant some data holders did not view data sharing as core business, resulting in delayed or unclear communication and undermining the efforts of more responsive parties.

Table 4: Overview of problems in data access and utilization, and implications for research and researchers for both cohort 1 and cohort 2.

Themes	Challenges/problems	Implications
Bureaucracy/ procedures/ regulations	The requirement of multiple approvals from different bodies (e.g. consortium, internal approval by data holders, the Belgian ISC)	Adds complexity in the preparation of necessary document for the application to ISC and increased the waiting time of pre -ISC approval **Note:** The approvals are not inherently a problem or a challenge. It's simply a necessary step to check if a project complies with requirements. A consequence of this - potential waiting times from different parties - is the actual challenge for the researcher (not the need for approval as such).
	Excessive documentation requirements, along with exploration of collaborative partners by the data host (such as TTP for linkage and partners for small cell risk analysis in our case KCE). **Note:** The coordination of the SCRA has now been taken over by Health Data Agency (HDA) whereas the communication with the TTP continues for now to be IMA-AIM as a data host, until the HDA gets more involved.	
	Unexpected situations: *The COVID-19 pandemic during data requests.* *Staff changes requiring time and training*	
	Collaboration agreement need to be signed by high level managers, some of whom were not at all involved in the study (of the universities, the data holders)	
	Unclear and inconsistent communication between different parties makes it difficult to identify which data holders are able to collaborate in data sharing.	Prolongs decision-making which data holders should be considered in the data request and delays the preparation of necessary documents, leading to inefficiencies in the data access process. Due to time pressures from the PhD and project funding timelines, we had to exclude one data holder, resulting in approximately 3,500 participants being omitted from Cohort 2. Consequently, we were unable to utilize the full range of available data. Although we referred to our study as "big data," the reduction in both volume and variety of data further compromised its overall scope. This exclusion contributed to change in the eligibility criteria. For Cohort 2, we initially planned to include only nursing home residents at the end of life. However, after data management, we found that limiting the study population to end-of-life cases would reduce study power. Therefore, we expanded the criteria to include all nursing home residents, with a plan to perform a sensitivity analysis by excluding end-of-life cases to assess the impact on the findings.
	The mutual dependence among all parties involved in data linkage and sharing—researchers and data holders on one side, and partners responsible for TTP and SCRA on the other: e.g.; Waiting times for data flow (in the linkage procedure) between agencies, as well as waiting times in conducting the small cell risk analysis by partners (4 months from first agreement to completed analysis)	This slowed the data flow during the linkage process, increased waiting time, and contributed to the overall delay in data access. In our case, the turnaround time after ISC approval was approximately 25 months for Cohort 1 and about 10 months for Cohort 2 before the first data access occurred.
	Strict data protection limit level of detail of the variable needed for research (Low data granularity) Note: the ISC regarding data of deceased persons, there is no authorization needed. Data holders however still ask to provide sufficient motivation per requested variable. Submission to the ISC is no longer necessary, if no data of living persons are impacted / involved.	Limiting the ability to control possible residual confounding due to the loss of precision.

Structures and capacity	Limited resources: *Limited personnel in data agencies* *High increase in requests of data during the last decade* *Communication incontinuity; interrupted communication during holidays*	Backlog management, where requests are handled in turn, hinders the ability to deliver requested data on time Increased the waiting time and influence the activity of the data holders working in the holiday and the researcher. For example, in Cohort 1, after researchers notified the data holders about errors identified during data exploration following the first data access, one of the data holders acknowledged the error only four months later, citing reduced activity during the summer holiday as the reason.
	Communication approach varied depending on the organizational structure of the data holder	Navigate different communication processes and requirements by the data holders, contribute to delaying data access and hindering project progress. Note: Although the HDA has recently partly addressed these issues by centralizing communications through HDA, this has not been the case for our project.
	Lack of experience with data requests and data usage (first-time use of the data): *Incomplete document application to ISC approval (from the side of researcher)* *Inconsistent documentation across different sections of the data request form led to confusion.* For example, in Cohort 1, the eligibility criterion—requiring healthcare reimbursement data, hospitalization data, and reimbursed medication data dispensed at community and hospital pharmacies for the 720 days prior to death—was only specified in the section concerning the population dataset (i.e., the dataset listing all reimbursed individuals). However, this criterion was not clearly stated in the corresponding sections for the other datasets. *Delay in identifying errors (need much time for data exploration),*	Contribute to the overall delay: Preparing and completing the new document for reapplication to ISC Increased the risk of misinterpretation of the ISC approved document by the data holders and leads to receiving data not as expected (less data)
	The data holder dependence on the other data holder for data mapping to share data (this do not work for all data holders in theory all data holders depended on thier own mapping)	Procedural delays, extending waiting times and hindering timely data request.
Data quality and accuracy: Human errors	Errors in the selection of cohorts (eligible participants based on the eligibility criteria) as per ISC approval	The data flow needs to be rechecked to identify how and where the errors occurred, going through all stages of the linkage again. This process took almost one year from the first data access to the redelivery of corrected data for cohort 1. However, due to error correction, the redelivered data included an additional 153,390 records, compared to the initial delivery of 139,197 records, which is 52.4% of the final delivery (= 292, 587 records)
	Missing of relevant variables in the original data request (from the side of researcher)	Researchers face a trade-off between proceeding without relevant variables and investing additional time to request an amendment to the ISC approval.
	Misinterpretation of the ISC approved document: Discrepancies in the interpretation by researcher versus data holders	Limit the analysis to the delivered data, accepting a compromise in the number of records available, in order to manage the pressure imposed by the project timeline.
	Implausible data values (error in recording of data): poor data quality	Excluding implausible values contributes to reduced study power, especially when analyzing rarely prescribed medications. For example, in cohort 2, we identified 63 records where nursing home residents had a BelRAI LTCF assessment recorded after their date of death.

		This indicates incorrect data, either in the BelRAI dataset or the population dataset regarding the date of death (Note: In some cases, healthcare services may be billed after the recorded date of death. This should be checked and validated on a case-by-case basis, depending on the project; however, in our case, the variable of interest is recorded based on the date of service).
Operational and technical problems	Lack of explicit list of data sources and available data for research	Unclear starting point, requiring significant time to explore all possible data sources for linkage.
	Lack of clear and standardized mapping to share data	Difficulties in sharing data held by different data holders required researchers to wait for a clear mapping—an uncertain process in terms of time. Note: Provision of data for linkage by data holders depends on their own data mapping; however, when data sharing is new, some data holders have not yet created their own mappings and instead rely on mappings to be created by other data holders with similar data.
	Recurrent issues across cohorts, such as missing the same variables in data delivery	Waiting time for the delivery of missing variables contributed to the overall delay in data availability for the analysis
	Unclear guide for which issues required to request ISC amendment apart from the new request of the researchers after the ISC approval	Varied expectations between the researcher and data holders on the need of ISC amendment, and in order to avoid additional time for amendments, the decision was made to proceed despite missing records.
	Complex data linkage, especially when using the data as a pioneer for new research questions, requires new conceptualization and mapping of data delivery and linkage.	Requires significant time for the researcher and the data holder, as it involves the validation and operationalization of the data to align with the research aim, delaying the analysis.
	Linkage is external to the researcher; despite active involvement in discussions with data holders about data flows and linkage, the researcher ultimately only receives the linked data.	Difficult for the researcher to fully validate the correctness of the accessed linked data, requiring extensive communication with the data holder, which took a significant amount of time to clarify the data and begin the analysis.
	The data requires extensive validation due to its secondary use.	Operationalizing data to the research context requires an extensive knowledge of each datasets and how they recorded and also need to consult the experts in the data holders as the way of records may change across years that should be validated and complicate the analysis (sometimes need to drop the variable for the analysis).
	Changes in data structure or naming between deliveries	Impacts data management and analysis. For example, in the initial delivery, the date indicating healthcare received prior to death was represented as a positive value, but in the corrected version, it was changed to a negative value. Additionally, some variable names were modified, requiring extra time to adjust the coding and reprocess the data.
	High costs for data access and warehousing (e.g., for Cohort 2, €13,656). Note: These costs depend on the data holders and hosting arrangements; however, in our case, the issue relates to the proportion of these costs within the overall budget rather than comparison with other data hosts.	Need for securing additional budget, including reliance on internal departmental funding, to cover unexpected high data access and warehousing costs.

Responsibility and coordination	Necessity of shared responsibility across stakeholders combined with a less accountable data-sharing scheme. For example, in one of our cohorts, one data holder followed the ISC-approved variable list, while the other relied on an earlier version of the document. Since the selection of the data flow was interdependent, this discrepancy only became evident after we received the data, when records from one data holder were not complemented by corresponding data from the other. Upon investigation with the data holders, we identified that the issue stemmed from delivering data based on the initial document rather than the ISC-approved version. While researchers are responsible for sharing the ISC approved document, all parties should verify the ISC-approved list of variables before delivering the data and act proactively to prevent such errors.	This resulted in the entire linkage process needing to be repeated.
	Competing goals: some of the data holding parties do not see data sharing as their core business	Communication became unclear and less straightforward, leading to significant delays in responses to researchers' emails
	Delay in notifying the ISC deliberation for all data holders	The data holder delivered the data based on their contractual provisions rather than the ISC-approved list of variables, which resulted in the need for redelivery.
	Inconsistent implementation of ISC-approved variables	Required additional waiting time to receive the missing variables in the delivered dataset
	Poor coordination among the different parties involved in data sharing undermines the data linkage process (e.g., the unavailability of project managers on the data holders' side could be mitigated by providing alternative contact points, a practice that some data holders consistently apply but not all).	Contribute to the length turnround time

BelRAI: Belgian Resident Assessment Instrument; ISC: Information Privacy Commission; KCE: Belgian Health Care Knowledge Center; TTPs: Trusted Third Parties, HDA: Health Data Agency

3.4. Implications of the challenges on the study

The different encountered data access challenges translated into several important implications for the study **(Table 4)**. These challenges affected the project's timelines, study design, and the efficient use of public funds. The three main implications are summarized below.

Timeliness of the evidence

Periodic delays and extended waiting times in the data-sharing process impacted the planned 4-year project schedule. For Cohort 1, data covering 2013 to 2019 was requested early in the project but only received in mid-2023, about 3.5 years late, omitting at least three more recent years. Updating the request to include these years would have required ISC amendments and additional linkage time, which was not feasible within the funding period, leaving the analysis without the most recent data.

Limit the scope of the study and design adjustment

The study's scope was constrained by the non-exhaustive use of available sources for data linkage, which was caused by unclear data mapping and errors in both the initial data delivery and subsequent redelivery. In Cohort 2, unclear mapping caused the loss of about 3,500 records (8% of available data), reducing the study population and prompting adjustments such as broadening eligibility criteria from only residents at the end of life in nursing homes to all residents to preserve statistical power. In Cohort 1, likely misinterpretation of the ISC approved document, partly due to inconsistent documentation, resulted in insufficient data for 2013, narrowing the intended 2013 to 2019 period to 2014 to 2019 and excluding roughly 50,000 records (17%).

Inefficient use of public funds

The overall delay and slow progress of the project led to inefficient use of public funds. After the initial four-year project funded by the Research Foundation – Flanders (FWO) ended, additional funding was required to complete the project and support the researcher's ongoing scholarship. Moreover, data access and warehousing costs, though anticipated, represented a notable portion of the budget (about 10%, e.g., €13,656 for Cohort 2).

4. DISCUSSION

4.1. Summary of main findings

This study outlines practical challenges in accessing and using big data for secondary research based on two national data requests. Our findings indicate that the data access process was excessively prolonged in comparison with the project plan and the expectations of the research team, which anticipated access within one year, taking around 3.5 years for Cohort 1 and 20 months for Cohort 2. The delays in accessing and utilizing big data largely stem from the complexity built in the data access procedures, in the sense that various procedures are required (document review and signing, approval, data preparation, linking, oversight) from various parties involved (the research team, legal departments from the university, the ISC, the different data holders, the trusted third party for the linking), each with different priorities and context-dependent organizational challenges. The different challenges we encountered could be summarized and categorized into five interacting key themes: 1) bureaucracy, procedures and regulations with substantial human dependency; 2), limitations of personnel capacity; 3) data quality and accuracy involving human errors; 4) operational and technical problems; 5) issues related to responsibility and coordination in the data sharing life cycle. These encountered challenges have significantly impacted the timeliness of research and the researcher.

Strength and limitations

Our study is timely, coinciding with EHDS implementation and countries' adaptation of national health data systems, offering practical insights into current challenges. It offers practical insights into current data access challenges. However, several limitations apply. First, this case study draws on a small number of linked healthcare administrative data sources and two pharmacoepidemiologic data requests, which may not capture all possible challenges, although many are likely generalizable given the similarity of data access procedures across studies. Still, some encountered difficulties may relate to the idiosyncratic aspects of these specific cases. Second, the assessment is retrospective over four years, and the expected one-year timeline relied on researcher assumptions rather than formal agreements, as data holders could only provide approximate estimates. Third, because the study relies on firsthand experience, some subjectivity is possible; this was mitigated by seeking feedback from data holders and involving an external researcher experienced in data requests. Despite these limitations, the study offers useful perspectives on needed improvements. Article 60(2) of the EHDS requires data holders to provide data within three months, extendable once [13], highlighting the need to shorten current procedures.

4.2. Interpretation of the challenges: suggestions for mitigation strategies and ways forward

Our study illustrates that, while expectations and enthusiasm around big data for research are high and opportunities have been reported repeatedly [19], the big promise of big data to deliver quick,

cheap, and reliable insights needs to be confronted with the reality of slow, complex, and eventually costly, data accessing and processing. Our study sought to objectively identify challenges that can help to make expectations about big data more realistic to other researchers. At the same time we believe that our experiences can also help to formulate advice to other researchers, to governments and to data holders on how some of the pitfalls can be mitigated or overcome.

For researchers we formulate 7 recommendations:

1) Data Quality Awareness: Researchers must recognize that the sheer volume of data does not ensure quality. Rigorous data cleaning and validation are needed, particularly to detect errors from data linkage. Any identified errors should be promptly reported to the data holders for further investigation and corrective action.

2) Operationalize and Validate core concepts: Researchers should put effort in carefully operationalizing and validating key metrics (exposure, confounders, outcomes) to ensure suitability of the data for the research question.

3) Strategic Variable Selection and Consistent Documentation: Missing variables in the data request can trigger new approvals and delays. Strategic selection using Directed Acyclic Graphs (DAGs) and literature is essential, along with consistent documentation across forms to avoid misinterpretation.

4) Early Engagement and Communication: Researchers should maintain clear, continuous communication with all parties to understand data structures, quality issues, and evolving procedures. This requires flexibility, allowing sufficient time for changing processes, and engaging proactively with stakeholders, ideally before submitting a grant proposal, even when procedures seem familiar.

5) Anticipate Delays and Impacts on funding: Acknowledge the potential for significant delays in data access and the limitations of fixed-term funding. Plan research timelines realistically and advocate for funding mechanisms that account for unforeseen delays.

6) Collaborate and Share Knowledge with other Researchers: Engaging with other researchers to share experiences, best practices, and strategies for navigating data access challenges can improve efficiency.

7) Coordinate the Data Access Process: While data holders and hosts provide standardized services to support data access, researchers must act as the main actors responsible for coordinating the overall process. They must integrate input from all parties, manage timelines, and maintain proactive communication, as many critical tasks fall outside their direct control.

For data holders we have a series of recommendations:

1) Improve Data Quality Assurance Processes: Implement rigorous checks from initial recording to data transfer and linkage, with clear protocols for detecting and correcting errors. While some data holders have these measures, staff shortages often limit full implementation.

2) Enhance Data Mapping and Metadata Documentation: Establish standardized data mapping procedures and comprehensive metadata to clearly describe structures, variable definitions, and linkage processes, facilitating data sharing and understanding. While established data holders (e.g., IMA-AIM) maintain clear metadata, those managing new data sources often lack robust documentation, resulting in non–linkage-ready data and added complexity.

3) Streamline Data Access Procedures: Simplify internal data access processes to reduce bureaucratic delays, and establish clear communication channels with realistic timelines. Data holders should adopt consistent practices, such as early notifications of service reductions and alternative contacts, to maintain transparency and continuity. While some already do this, broader adoption would better manage expectations and minimize delays.

4) Proactive Communication and Transparency: Keep researchers informed throughout the data access process, providing updates on request status and potential delays. Be transparent about data limitations and quality issues to manage expectations and allow methodological adjustments.

5) Foster Collaboration and Shared Responsibility: Collaborate with healthcare providers, researchers, and regulators to improve data quality and enable efficient sharing. Clearly define roles for all stakeholders, as multi-holder data linkage creates complex dependencies. Close coordination helps address inconsistencies, access delays, and align shared responsibilities throughout the data lifecycle.

6) Invest in Technical Infrastructure and Expertise: Invest in infrastructure and personnel training to improve data management, linkage processes, and the secure, timely delivery of high-quality data to researchers.

Recommendations for Governments:

1) Establish Centralized Data Access Resources: Create centralized platforms providing researchers with information on healthcare data sources, access procedures, and contacts to reduce uncertainty and streamline access. In Belgium and internationally, health data is fragmented across organizations and levels of authority [15]. This fragmentation hinders efficient use and leaves researchers unsure whom to contact or which datasets are available [12]. The HDA should develop a comprehensive roadmap for the full data lifecycle, aligned with the EHDS framework, with authority to enforce it. A centralized metadata repository would enable efficient discovery, foster data solidarity, and improve linkage; currently, only 33% of Belgian health data is linked for research, statistics, and monitoring [20].

2) Promote Harmonized Data Access Procedures: Standardize access procedures, including applications and data-sharing agreements, to create a seamless system for researchers. The HDA, established on 14 March 2023 as Belgium's national health data access body under the EHDS framework [15], is well-positioned to lead this effort. As a federal initiative, it can streamline processes, reduce administrative burden, and build trust. Strengthening its capacity and mandate ensures timely, secure, and equitable access to health data, supporting data-driven innovation in healthcare and public health.

3) Invest in National Data Infrastructure: Strengthen Belgium's health data infrastructure to align with initiatives like the EHDS (launched 26 March 2025 [13]), providing a roadmap for solutions and governance. Belgium collects diverse health data for health and social services [15, 21], offering an opportunity to build a robust ecosystem. Despite being a leader in e-health and data infrastructure [21], many components remain fragmented and under-optimized [22]. Priorities include reinforcing infrastructure, mapping the healthcare data ecosystem, and addressing inefficiencies such as fragmented sources, delayed access, inconsistent data quality, and communication gaps. Overcoming these challenges is essential for seamless EU-wide data sharing and realizing the EHDS vision.

4) Support Capacity Building in Data Agencies: Invest in personnel and technical infrastructure to enable efficient data request management, linkage, and high-quality delivery. Multi-holder administrative data is complex and requires coordination among all parties. Targeted capacity building is needed to ensure sufficient resources and a well-coordinated data sharing ecosystem, minimizing delays and errors.

5) Allocate Sustainable Research Funding: Recognize the time and costs of big data research and provide flexible funding to accommodate unforeseen extensions and evolving access processes. While the HDA aims to streamline access, ongoing investment is still needed to support researchers and ensure long-term, efficient, high-quality data access.

5. CONCLUSIONS

This study documents firsthand experience accessing and using big data for research, highlighting challenges and delays impacting researchers and their projects. For projects with fixed funding terms (e.g., PhD), such delays create substantial pressure and often require extensions. Our findings emphasize the need for streamlined data access supported by stronger collaboration, clear roles and responsibilities, and transparent communication. Researchers should identify data sources and variables early, preferably before grant submission, and establish agreed timelines. While initiatives like the EHDS offer promising solutions, their success depends on strengthened national infrastructure and improved interoperability. Addressing these challenges is essential to fully realize big data's potential for research, policy, and healthcare innovation.

References

1. Morin L, Onwuteaka-Philipsen BD. The promise of big data for palliative and end-of-life care research. Sage Publications Sage UK: London, England; 2021. p. 1638-40.
2. Ristevski B, Chen M. Big data analytics in medicine and healthcare. J Integr Bioinform. 2018;15(3):20170030.
3. Panahiazar M, Taslimitehrani V, Jadhav A*, et al.* Empowering Personalized Medicine with Big Data and Semantic Web Technology: Promises, Challenges, and Use Cases. Proceedings : IEEE International Conference on Big Data IEEE International Conference on Big Data. 2014;2014:790-5.
4. Borges do Nascimento IJ, Marcolino MS, Abdulazeem HM*, et al.* Impact of big data analytics on people's health: Overview of systematic reviews and recommendations for future studies. J Med Internet Res. 2021;23(4):e27275.
5. Keskar V, Yadav J, Kumar AH. 5V's of Big Data Attributes and their Relevance and Importance across Domains. International Journal of Innovative Technology and Exploring Engineering (IJITEE) ISSN. 2020:2278-3075.
6. Huser V, Cimino JJ. Impending challenges for the use of big data. Elsevier; 2016. p. 890-4.
7. Schneeweiss S. Improving therapeutic effectiveness and safety through big healthcare data. Clin Pharmacol Ther. 2016;99(3):262-5.
8. Surbakti FPS, Wang W, Indulska M*, et al.* Factors influencing effective use of big data: A research framework. Information & Management. 2020;57(1):103146.
9. Berry RC, Johnston L. Big data and doctoral research: Opportunities, challenges, and cautions. Enhancing the Role of ICT in Doctoral Research Processes. 2019:67-83.
10. Stice-Lawrence L. Practical issues to consider when working with big data. Review of Accounting Studies. 2022;27(3):1117-24.
11. Lugg-Widger FV, Angel L, Cannings-John R*, et al.* Challenges in accessing routinely collected data from multiple providers in the UK for primary studies: Managing the morass. International Journal of Population Data Science. 2018;3.
12. Ho HKK, Görges M, Portales-Casamar E. Data Access and Usage Practices Across a Cohort of Researchers at a Large Tertiary Pediatric Hospital: Qualitative Survey Study. JMIR Med Inform. 2018;6(2):e32.
13. European Parliament and Council. Regulation (EU) 2025/327 of the European Parliament and of the Council of 11 February 2025 on the European Health Data Space and amending Directive 2011/24/EU and Regulation (EU) 2024/2847 (Text with EEA relevance). Official Journal of the European Union (OJ L) [Internet]. 5 March 2025; 2025/327:1–XX. ISSN 1977-0677. Available from: http://data.europa.eu/eli/reg/2025/327/oj. 2025.
14. Dalglish SL, Khalid H, McMahon SA. Document analysis in health policy research: the READ approach. Health Policy Plan. 2020;35(10):1424-31.
15. Health Data Agency. Belgian Health Data Agency 2025 [cited 2025 14/08/]. Available from: https://www.hda.belgium.be/en.
16. FOD BOSA. Informatieveiligheidscomité (IVC). Brussels: BOSA; [cited 2025 Jul 25]. Available from: https://bosa.belgium.be/nl/themas/digitale-overheid/samenwerking-en-kennisdeling/informatieveiligheids-comite-ivc 2025 [
17. KSZ-BCSS. IVC in het kort. [cited 2025 Jul 25]. Available from: https://www.ksz-bcss.fgov.be/nl/page/ivc-in-het-kort 2025 [
18. Atlan. What is data mapping? [cited 2025 Jul 25]. Available from: https://atlan.com/what-is-data-mapping 2024 [
19. Maetens A, De Schreye R, Faes K*, et al.* Using linked administrative and disease-specific databases to study end-of-life care on a population level. BMC Palliat Care. 2016;15:1-10.
20. Oderkirk J. Survey results: National health data infrastructure and governance. OECD Health Working Papers. 2021(127):0_1-138.
21. Invent C, Page M, Winkel R*, et al.* 2024 digital decade ehealth indicator study. 2024.
22. Health Data Talk Series group. HDA Academy : Secondary use of data leading to innovation in health (from an industry perspective). https://academy.hda.belgium.be/pluginfile.php/571/mod_resource/content/1/artikel%204%20-%20Value%20of%20secondary%20use%20of%20data%20for%20innovation.pdf. 2024.

PAR VI

GENERAL DISCUSSION

Chapter 9

General discussion

Nursing home (NH) residents approaching the end of life are characterised by a high medication burden, a key driver of PIMs, and an increased susceptibility to adverse drug effects, driven by multimorbidity, cognitive impairment, and age-related pharmacokinetic and pharmacodynamic changes.[1-3] In this context, the balance between the potential benefits and harms of medications becomes particularly critical, as many treatments offer limited or no meaningful benefit, making this population a priority group for deprescribing. [4-6]

The overall aim of this thesis is to strengthen the evidence on the real-world implementation of deprescribing in NH residents with limited life expectancy and on the effects of deprescribing medications on outcomes relevant to end-of-life care, addressing the evidence gaps identified in existing deprescribing tools and guidelines through the use of linked population-level health-care data.

To achieve this aim, the dissertation is structured around four specific aims: (1) establishing a comprehensive evidence base through the synthesis of existing deprescribing tools and guidelines; (2) investigating the real-world implementation of deprescribing by analysing trends in deprescribing of medications, the impact of existing guidelines on actual practice, identifying barriers and enablers to deprescribing, and the sustainability of deprescribing through the assessment of medication reinitiation in residents with limited life expectancy; (3) assessing the effects of deprescribing medications on end of life care–relevant outcomes by exploring associations between changes in the use of chronic and PIMs and corresponding changes in outcomes relevant to end-of-life care, and investigating the causal effect of PPI deprescribing on these outcomes; and (4) analysing challenges in accessing and using linked national healthcare administrative data for end-of-life research, using the data requested for this PhD project as a case study.

This chapter summarizes the main findings and discuss methodological considerations, interpretations, and implications for future research, clinical practice, and policy-making, followed by a general conclusion.

9. 1. Summary of the Main Results

9.1.1. Synthesis of medication appropriateness lists

As a preparatory phase for this PhD project, we conducted an umbrella review to provide a clear evidence base for subsequent work and identify gaps in the evidence (chapter 2). This umbrella review identified 15 systematic reviews, with substantial variation in the included tools and guidelines intended to support clinicians in assessing medication appropriateness and deprescribing. We identified a total of 95 tools (72 explicit tools, 12 mixed tools, and 11 implicit tools) and 9 deprescribing guidelines for commonly used medications (e.g. proton pump inhibitors,[7] and antipsychotics.[8]) Systematic (literature) review-based tool development was the most common approach, with 59 tools and guidelines developed using this method, of which 36 were developed solely based on existing tools and have not been updated to incorporate more recent publications. In total, 75 tools and guidelines were validated, most commonly using the (Modified) Delphi technique (n = 58/75; 77.3%). However, only 2 tools [9, 10] and 8 guidelines described the strength of evidence supporting their recommendations for classifying medication appropriateness and informing deprescribing decisions, with most relying on expert opinion. Among those that specified the strength of evidence, only about one quarter of the medications listed for older adults with normal life expectancy were supported by

high-quality evidence. For the 14 tools designed for older adults with limited life expectancy, the evidence base remained particularly limited, and none provided an explicit level of evidence.

Medications were systematically extracted from explicit and mixed tools and grouped by target population to support the development of comprehensive, thematic medication lists. Based on this synthesis, we developed a list of 484 PIMs for older adults with normal life expectancy, and a separate list of 202 medications (117 medication classes and 85 specific medications) for older adults with limited life expectancy. The latter was structured to allow classification of medications as appropriate, inappropriate, or without consensus, taking into account clinical context and remaining life expectancy. Source tools varied in focus, including populations such as advanced dementia,[11] palliative cancer,[12] frail older adults with limited life expectancy who were expected to die within one year (e.g., STOPPFrail), [13] and patients in the last 3 months of life.[14]

Many tools lacked clarity about target populations or provided conflicting recommendations, highlighting a fragmented and weak scientific foundation for deprescribing decisions. Notably, substantial inconsistencies in medication appropriateness classification were observed, particularly for older adults with limited life expectancy, where high-quality evidence remains very limited. These gaps and inconsistencies may hinder the implementation of deprescribing in clinical practice[15] and underscore the need to strengthen the evidence base.

9.1.2. Deprescribing trend and impact of deprescribing guidelines

We analysed nationwide linked administrative healthcare data from Belgium to evaluate real-world deprescribing practices of PIMs in NH residents with limited life expectancy, and to assess the impact of generic (STOPPFrail)[13] and drug-specific deprescribing guidelines (proton pump inhibitors,[7] and antipsychotics[8]) on these trends (chapter 3).

Overall, 29.7% of deceased residents had at least one STOPPFrail-listed PIM discontinued in the final four months of life, among those with prior use of at least one PIM (69%) between 6 and 12 months before death. However, we observed a small but statistically significant decreasing trend in deprescribing practices over time, with the proportion declining from 31.7% in the first quarter of 2014 to 27.7% in the last quarter of 2019 (average quarterly percent change: −0.47%). Joinpoint regression analysis identified no significant changes in trend over time, indicating a stable pattern without clear inflection points.

Furthermore, our interrupted time series analysis using ARIMA modelling did not provide evidence of an effect of the publication of international deprescribing guidelines on deprescribing trends for commonly used PIMs, including lipid-modifying agents, calcium supplements, PPIs, and antipsychotics.

These findings suggest that, despite the availability of international deprescribing guidelines, their publication alone did not influence deprescribing practices in this population. The persistently high prevalence of PIM use, together with a decreasing trend in discontinuation over time, albeit small, remains concerning and highlights important gaps in implementation. This underscores the need for more comprehensive strategies beyond guideline publication to effectively support deprescribing in clinical practice.

9.1.3. Barriers and enablers for deprescribing in NHs

Although admission to NHs offers opportunities for deprescribing, particularly through medication review at admission and over time,[16] these opportunities are often insufficiently realised, likely due to the complex organisation of care in NHs. [17-19] This complexity is even greater near the end of life, where the use of PIMs remains high[20] and resident involvement in decision making is often limited. [21, 22]

In Chapter 4, we identified the barriers and enablers for HCPs to deprescribe for NH residents approaching the end of life, operating across three levels. At the macro level, we identified healthcare system and policy factors as a theme, which included barriers such as the absence of context-specific deprescribing guidelines, the perception that existing tools are unclear, complex and too time-consuming to apply, and the lack of reimbursement or structural incentives for medication reviews. At the meso level (NH level), we identified two themes. The first, resource- and organisation-level factors, included limited staffing, time and budgets, poor documentation, restricted access to residents' medical files, and the perception that deprescribing is not a priority within NHs. The second theme, interprofessional collaboration and communication factors, reflected hierarchical relationships, limited recognition of expertise between professionals, fragmented communication between care settings, insufficient information about medications prescribed outside NHs, and reluctance of family physicians to deprescribe medications prescribed by their colleagues. At the micro level, we identified three themes. Professional role and competency factors included gaps in deprescribing knowledge and confidence and uncertainty about professional responsibilities, with nurses often perceiving deprescribing as outside their role. Triadic dynamics in deprescribing, referring to the interplay between residents, informal caregivers and HCPs, reflected resident resistance, family fears that deprescribing signals withdrawal of care, and the challenges of shared decision-making in the context of cognitive impairment. Finally, attitudes and perceptions toward deprescribing captured the emotional charge of deprescribing, fear of negative outcomes, and beliefs about medication use at the end of life, with facilitators often overshadowed by persistent barriers. These insights help explain why deprescribing is still not routine practice in NHs in the context of end-of-life, despite growing international attention. Overall, within these six themes, the identified barriers and enablers mapped to 13 Theoretical Domains Framework (TDF) domains, and for each domain, we identified corresponding Behavior Change Techniques (BCTs) as potential intervention components.

9.1.4. Initiation and reinitiation of previously deprescribed PIMs at the end of life

Complementing the deprescribing trend analysis from the previous chapter, in Chapter 5 we demonstrated that even when deprescribing occurs earlier in the disease trajectory, medications considered inappropriate by STOPPFrail are still frequently initiated or reinitiated in the final three months of life among residents who died from conditions potentially amenable to palliative care. Medication use near the end of life remained highly dynamic: among residents who had previously discontinued a medication (i.e., prescribed between 18 and 12 months before death but not prescribed between 12 and 3 months prior), 17% had that medication restarted, indicating that earlier deprescribing was not sustained for a significant number of residents. In addition, almost one in three residents (29.7%) initiated at least one PIM in the last three months of life, regardless of their prior use. These patterns varied considerably by medication type: initiation occurred in 25.53% of symptomatic medications compared with 6.71 % of preventive medications, while reinitiation occurred in 20.29 % of symptomatic medications compared with 11 % of preventive medications.

While some reinitiations and initiation likely reflected appropriate, symptom-driven needs consistent with palliative care context or the on-demand or intermittent use of previosly deprescribed medications, the frequent initiation and reinitiation of preventive medications, for which benefits are minimal this close to death, suggests ongoing challenges in maintaining goal-aligned prescribing. Residents with cancer, a hospital admission, and a high medication burden were most likely to experience initiation or reinitiation, indicating that acute care transitions and prognostic uncertainty may complicate and sometimes reverse earlier deprescribing decisions. Overall, these findings show that prescribing near the end of life is not a simple or linear decline but a fluctuating process in which medications are discontinued yet later restarted, and new PIMs are introduced.

9.1.5. Trajectories of chronic medication use and PIMs and their association with the evolution of health outcomes

In Chapter 6, we used a novel linkage between national medication reimbursement data and BelRAI LTCF assessments to create a prospective cohort study and provide a comprehensive picture of how medication use and resident health evolve longitudinally over one year within Belgian NHs. At baseline (first BelRAI LTCF assessment after NH admission), chronic medication use was almost universal, with 94.6% of residents taking at least one chronic medication, and the mean number of chronic medications increased from 5.87 to 6.10 during follow-up. Polypharmacy (≥ 5 chronic medications) remained both common and dynamic. The prevalence increased from 62.6% at baseline to 67.5% at follow-up, with 13% of residents transitioning into polypharmacy and 8% transitioning out.

Over the same one-year period within the NH, the proportion of residents using at least one PIM decreased from 72.7% to 56.0%. However, this overall reduction concealed divergent trends within specific medication classes, with PPI use increasing from 44.2% to 48.4% and antipsychotic use rising from 21.9% to 26.2%. Examining individual trajectories further highlighted the dynamic nature of PIM use: 48.3% of residents continued PIM use, 24.5% discontinued PIMs, 19.5% had no PIM use at either time point, and 7.8% initiated PIM use after baseline. We also assessed yearly trends in chronic medication and PIM use between 2016 and 2022. Over this period, the prevalence of chronic medication use remained consistently high, ranging from 92.6% to 94.1%. Similarly, PIM use remained high throughout the follow-up period, with prevalence estimates ranging from 69.9% to 74.5%, and no statistically significant change in the trend observed over time.

Regarding the evolution of health outcomes across domains, these remained largely unchanged over one year, with 70% to 88% of residents maintaining the same status across domains. When changes occurred, deterioration was more common than improvement, particularly in health instability, mood, cognition, activities of daily living (ADL), and pain. In contrast, no significant changes were observed in social engagement and falls. Changes in medication use were related to changes in health outcomes: transition into polypharmacy was associated with worsening ADL and cognition, and greater intensity of PIM from no use to discontinuation, new use, and continued use, was associated with declines in daily functioning, increases in aggression, and increases in comorbidity burden. Although exploratory and requiring further detailed evaluation, the findings point toward a divergence between evolving health trajectories and patterns of medication use among NH residents.

9.1.6. Effect of deprescribing proton pump inhibitors

Most of the existing evidence on long-term PPI use has relied on physiologic or disease process outcomes, [23-25] while quality-of-life-related outcomes, which are highly relevant for frail NH residents

with limited life expectancy, remain largely unexplored. [26] This leaves uncertainty about whether deprescribing PPIs, a commonly used and less deprescribed medication in NHs, [27] meaningfully improves these broader aspects of health. [26] To address this gap, in Chapter 7 we emulated a causal target trial that compared deprescribing with continued long term PPI use on six quality-of-life-related outcomes (extensive assistance for ADL, significant cognitive impairment, daily depressive symptoms, daily pain, falls, and self- reported health) as primary outcomes, as well as hospitalization and all-cause mortality as secondary outcomes. During the 12-month follow-up while residents were alive, the trajectory of all six primary outcomes remained similar in both treatment strategies, with no statistically or clinically meaningful differences.

For the secondary outcomes, however, we observed differences between the treatment strategies. The deprescribing group had 4.41 more survival days over the first 180 days; however, this difference reversed thereafter, and by 360 days they had 16.0 fewer survival days compared with the continuation group. We also found that deprescribing reduced hospitalization, with 19% fewer hospitalizations compared with continuation. These findings suggest that, while deprescribing PPIs does not meaningfully affect quality-of-life-related outcomes, the observed reductions in hospitalization, alongside time-dependent survival differences, point to a potential advantage from a cost perspective and highlight trade-offs when considering deprescribing as a deimplementation of low-value care in frail NH residents with limited life expectancy.

9.1.7. Structural challenges in data access

In the final study of this dissertation (chapter 8), we reflected on the experience of accessing and using big data in the quantitative components of the dissertation, which were based on two national-level data requests. Cohort 1 linked Belgian health insurance data with Statistics Belgium data (Chapters 3 and 5), while Cohort 2 linked health insurance data with BelRAI LTCF (Chapters 6 and 7); both of which were used in this case study. Although big data is often portrayed as readily available and efficient for research, our experience showed that accessing and using these data was a slow, complex, and resource-intensive process.

Using detailed document analysis, we mapped the full data access trajectory and identified challenges related to data access and use. Data access required substantially more time than anticipated, taking 3.5 years for Cohort 1 and 20 months for Cohort 2, far exceeding the initially expected one-year timeframe. We also identified five key themes of the data access and use challenges: (1) bureaucratic procedures and regulations with substantial human dependency involving extensive documentation and multiple authorizations; (2) limited personnel capacity, including resource limitations at data holders that contributed to backlogs in data request processing, limited experience with complex data requests, and fragmented communication across stakeholders; (3) data quality and accuracy issues, including human errors occurring across multiple stages, from data recording to data linkage, including implausible values, missing variables, and misinterpretation of approved documents requiring redelivery of data; (4) operational and technical problems, including unclear data access procedures, reliance on multiple interdependent data holders, unclear data mappings, and changes in data structures, which required extensive data exploration, validation, and quality checks, and (5) challenges in responsibility and coordination throughout the data-sharing lifecycle, where shared responsibility across stakeholders was required and, alongside limited accountability and competing institutional priorities, led to increased complexity and reduced predictability in the progress and timing of the project.

Within the project context, we translated these challenges into concrete implications, which compromised research timelines, restricted the intended scope of the studies, led to the inefficient use of public funds, and threatened the feasibility of completing time-bound projects. These findings highlight a clear gap between the promised efficiency of big data research and the realities of secondary data access in practice. By analysing these challenges, we also propose corresponding solutions that could promote a more streamlined data access process, such as strengthening data infrastructures, establishing transparent and jointly agreed upon timelines for data access, and enabling fast and transparent communication among all parties involved in the data-sharing lifecycle.

9.2. Methodological strengths and limitations

This dissertation uses multiple methodological approaches and data sources to assess medication utilization, the implementation of deprescribing, and the effect of deprescribing medications. A key strength of this approach is that it combines strengths of different methods, providing a more comprehensive understanding of deprescribing from different perspectives. However, it also introduces limitations, including heterogeneity in data quality and definitions, as well as the risk of temporal misalignment in data recording across datasets. Differing reporting delays and update cycles may lead to inaccurately timed exposure or outcome measurements. [28]

The specific strengths and limitationsof each study are presented in their respective empirical chapters. However, below I discuss the main strength and limitation from the over all dissertation perspectives.

9.2.1. Strengths

Population coverage and data linkage: Linking a selected range of administrative databases with individual clinical data provided detailed socio-demographic, clinical, medication, and healthcare utilisation data, allowing to study the real-world implementation and effects of deprescribing. The use of routinely collected data to study NH residents near the end of life, a periods that are often difficult to study using primary data collection, enabled the inclusion of a population that is typically hard to reach and underrepresented in clinical research due to its high vulnerability, including multiple chronic conditions, advanced frailty, dementia, and limited decision-making capacity. [29]

For the decedent cohort studies focusing on real-world deprescribing practices during the period preceding death (Chapters 3 and 5), the analyses were based on nationwide administrative healthcare data covering more than 99% of the insured population. This ensured near-complete population coverage, thereby minimising selection bias and enhancing the external validity and representativeness of the results. In other components of this PhD study, focusing on the effects of deprescribing on health outcomes relevant to NH residents (Chapters 6 and 7), a longitudinal cohort including both living and deceased residents was used. The study linked administrative data with regional clinical data from BelRAI LTCF assessments in the Flemish region, which was the early implementer of the BelRAI system. This linkage enabled the evaluation of the effects of deprescribing on quality-of-life–related outcomes and provided a unique opportunity to explore the feasibility and added value of integrating administrative and clinical data. At the same time, it allowed a more detailed characterisation of residents, helping to address the persistent lack of high-quality evidence on the effects of deprescribing in the end-of-life context.

The linkage with repeated BelRAI LTCF assessments enabled the longitudinal evaluation of outcomes that are particularly meaningful for NH residents, whose average survival is less than two years, [30] and for whom collecting such information for research purposes can be time-consuming and costly. The linkage also enabled the evaluation of prospective changes in medication use over longer NH stays. These outcomes go beyond traditional disease-centric endpoints and align more closely with goals of care in frail populations (e.g., ADL, cognition, mood, pain, falls, and health instability). [31, 32] Furthermore, BelRAI data are based on triangulated information from residents, informal caregivers, and HCPs, enhancing data completeness and representativeness. Collectively, these features allowed the dissertation to assess how medication use and deprescribing relate to quality-of-life–relevant outcomes, while also demonstrating the potential and constraints of using routine clinical assessment data for research.

Robust, and methodologically rigorous approach

A strength of the approach followed in this dissertation is that the empirical studies were grounded in a preparatory evidence synthesis. By systematically identifying gaps and inconsistencies in existing deprescribing tools and guidelines, the preparatory work ensured that the empirical analyses were anchored in (and could add to) the current state of evidence while informing the selection of medications and guidelines included in the study. Second, advanced statistical methods were applied to evaluate real-world deprescribing practices and trends. Interrupted time series analyses using ARIMA models were employed to assess the effects of specific deprescribing guidelines and address causal questions regarding their population-level impact, while joinpoint regression was used as a complementary approach to explore overall underlying trends and potential external influences, hence addressing the issue of history bias. The combination of these analytic strategies strengthened the robustness of the findings by allowing the convergence of evidence from different modelling perspectives (Chapter 3). Furthermore, through the application of advanced causal methods using target trial emulation to evaluate the effects of deprescribing on quality-of-life-related patient outcomes, this dissertation contirbuted to advancing the evidence base on deprescribing effects. The combination of the rigorous analyses of real-world data and innovative, robust causal inference methods contributed to findings on deprescribing effects with both good internal and external validity (chapter 7).

In exploring barriers and enablers of deprescribing, a theoretically informed qualitative analysis was conducted using the TDF. This theory-driven approach enhanced the validity and interpretation of the qualitative findings and allowed for the systematic linkage of identified domains to behaviour change techniques, providing a clear pathway toward the development of future deprescribing interventions (chapter 4). [33]

9.2.2.Limitations

Nevertheless, a number of limitations related to the use of routinely collected administrative medication and clinical assessment data, including potential issues regarding data completeness, accuracy, and quality, need to be acknowledged.

Limitations related to routinely collected administrative medication data: healthcare administrative and dispensing data are not primarily designed for research purposes. Although these data provide near-complete coverage of reimbursed medications, they do not fully capture non-reimbursed or over-the-counter medications (e.g; NSAIDs, vitamins, benzodiazepines). This may have led to under- or

overestimation of medication use, discontinuation, initiation, or reinitiation. However, given the high dependency of residents on assistance with ADLs, and the institutionalised nature of NHs, where medication use is largely managed through formal prescribing and dispensing channels, the impact of this limitation is likely reduced. Furthermore, dispensing data indicate that a medication was supplied, but they do not confirm whether the medication was actually taken. This may have influence the comparisons between residents who discontinued medication and those who continued treatment when evaluating health outcomes. However, because NH residents generally receive medication under the supervision or support of nurses and care assistants, the impact of non-adherence is likely to be limited. In addition, tools used to assess PIMs and deprescribing in the PhD study (e.g. STOPPFrail)[34] require clinical information (e.g. indications, symptoms, prognosis) that is often unavailable in administrative datasets. As a result, the analyses were restricted to medications for which the assessment of appropriateness depended less on detailed clinical information. Furthermore, only medications reimbursed in Belgium could be included. Consequently, of the 27 STOPPFrail criteria, only 15 medication-related criteria could be operationalised, primarily those based on chronic medication use. This represented a partial evaluation of the tool. [35] However, because deprescribing was assessed using chronic users of individual medications as the denominator, the impact of this limitation is liksidered to provide meaningful overall insights into deprescribing practices.

***Limitations in measuring deprescribing and medication appropriateness*:** In routinely collected healthcare data, deprescribing is not explicitly documented and remains largely indistinguishable from general medication discontinuation. This represents a fundamental limitation of dispensing databases. Deprescribing is a process driven by intentional clinical decision-making under professional supervision and aligned with patient goals and preferences, elements that are not observable in administrative data. Consequently, deprescribing can only be conceptualized as a subset of medication discontinuation within such data sources. Although the linkage of interRAI LTCF assessments with medication dispensing databases provides a comprehensive dataset, incorporating self-reported and interview-based information on residents such as mood, pain, and perceived health,[32] it does not allow for a direct link between specific medication discontinuation and individual treatment preferences or goals of care. This further reflects a broader challenge in assessing intentionality in large-scale pharmacoepidemiological research.

Furthermore, there is uncertainty regarding the deprescribing tools and guidelines used to evaluate deprescribing implementation in this thesis. As identified in the umbrella review (Chapter 2), most tools are primarily based on expert consensus, often lack a strong evidence base, and rarely provide a formal grading of the strength of their recommendations. Therefore, the implementation measures derived from these tools should be interpreted within the context of their limited evidence base. In particular, these measures assume that deprescribing medications identified by the tools as potentially inappropriate is clinically appropriate, an assumption that may not always hold at the individual patient level. The limited evidence underpinning these tools may also contribute to their limited uptake in clinical practice, which was identified as a barrier to deprescribing implementation.[15] Nevertheless, the overall conclusion of limited deprescribing implementation remains supported by findings across the thesis. For example, HCPs in Chapter 4 reported a lack of regular medication reviews and routine deprescribing practices, while Chapter 5 showed that preventive medications with limited expected benefit given residents' remaining life expectancy were frequently reinitiated after discontinuation. Overall, these findings suggest that, although the exact extent of

implementation may be influenced by limitations in the available tools, the conclusion that deprescribing is insufficiently implemented among NH residents with limited life expectancy is likely robust.

In this PhD study, deprescribing was inferred through longitudinal patterns in dispensing data. While this approach is increasingly accepted in observational research, there remains a risk of misclassification bias. To mitigate this bias, conservative methodological strategies were applied, including restrictive definitions of chronic use, requiring multiple dispensations before defining discontinuation, estimating prescription intervals, and implementing grace periods to distinguish true discontinuation from non-adherence (irregular refilling). [36, 37] Despite these measures, some degree of misclassification is unavoidable and represents a structural limitation. For example, gradual dose tapering may not be fully captured, although its typically short duration may limit its overall impact on study findings. [38] Across the respective chapters, we defined deprescribing pragmatically, with limitations explicitly acknowledged. Applying a strict definition of deprescribing would render real-world evidence of limited value, [37] as the necessary process-level information is rarely observable. At the same time, particularly in the context of end-of-life care, no feasible alternative methods can adequately capture deprescribing at scale, making findings based on real-world data essential despite their limitations. Therefore, despite these constraints, the application of rigorous methodology ensures that the findings of this dissertation remain valuable and contribute meaningfully to strengthening the evidence base on deprescribing near the end of life.

Finally, although linking administrative medication data with residents' clinical data from the BelRAI LTCF assessments substantially enriched the available information, several clinically relevant variables remain unavailable or incompletely captured, most notably the indication for prescribing. While the richness of the data allows clinical indications to be approximated using proxy measures,[39] these proxies may be imperfect and subject to misclassification. For example, in Chapter 7, the specific indication for long-term PPI use was not directly available; therefore, proxy indicators such as concomitant use of bleeding-risk–increasing medications and a history of gastrointestinal bleeding were used to approximate the clinical context. [40, 41] Nevertheless, despite these efforts, residual confounding by indication cannot be fully excluded. More broadly, this reflects a limitation in the use of observational population data: while it increases external validity and transferability, it may be somewhat more limited in terms of internal validity. RCTs are, in principle, better suited to provide internal validity, even if trial emulation methods attempt to follow similar principles.

***Limitations related to inconsistent implementation of BelRAI LTCF assessments*:** During the conduct of the studies included in this dissertation, the implementation of BelRAI LTCF assessment instrument in Belgium was still in a rollout phase and had not yet become mandatory, resulting in incomplete population coverage, inconsistent follow-up assessments, and missing data. However, this limitation reflects the real-world context of data adoption in routine care rather than a methodological flaw specific to this dissertation. [32] Moreover, the observed inconsistency is likely attributable to the early phase of implementation, as well as to repeated assessments triggered by deteriorating health status, rather than to systematic differences in resident characteristics. To partially mitigate the potential impact of these challenges, [42] Chapter 7 applied a target trial emulation framework to compare deprescribing with continued PPI use, using inverse probability of treatment weighting to create a pseudopopulation balanced on observed baseline characteristics. In addition, multiple imputation was used to address missing covariates and outcomes, and sensitivity analyses were conducted to assess

the robustness of the findings. While this analytical approach reduces bias related to measured variables, selection mechanisms driven by unobserved factors cannot be fully addressed.

BelRAI assessments are completed by different HCPs,[32] which may introduce inter-rater variability. Nevertheless, previous research has demonstrated almost perfect inter-rater agreement for BelRAI-based assessments, [43] and these instruments are validated and supported by structured training procedures. As a result, any remaining measurement variability is expected to be largely random rather than systematic. Furthermore, the BelRAI LTCF assessment has evolved over time, with three versions of the interRAI LTCF instrument and changes in certain items used to derive outcome scales. To minimize the potential impact of measurement bias, items corresponding to the study outcomes were recalculated using harmonized definations to ensure comparability across study periods.

9.3. Discussion of the main findings

Interpreting deprescribing findings: from individual medication appropriateness to population-level prescribing patterns

In routine clinical practice, medication appropriateness (i.e., whether medications are clinically indicated, beneficial, and aligned with the resident's goals and preferences)[44] is generally first evaluated at the individual resident level, considering factors such as the resident's clinical condition, prognosis, symptom burden, current medication use, goals of care, and preferences, which collectively determine prescribing decisions and subsequent prescribing patterns. These individual prescribing decisions can subsequently be aggregated to evaluate prescribing patterns and medication appropriateness at an aggregate level, such as the level of a prescriber, an institution, a health region or an entire country. It should be kept in mind, however, that many of the factors, including clinical reasoning underlying bedside prescribing decisions (including decisions to deprescribe, continue, initiate, or reinitiate medications) for NH residents with limited life expectancy, are not observable in routinely collected administrative data.

While this dissertation focused on medications identified as potentially inappropriate according to established medication appropriateness criteria (i.e., deprescribing tools and guidelines), medication appropriateness ultimately requires an individualized clinical assessment that incorporates factors unavailable in the study data. Consequently, it was not possible to fully determine whether individual decisions to deprescribe, continue, initiate, or reinitiate medications were clinically appropriate. Not every episode of deprescribing necessarily represents appropriate medication use, and not every continuation or reinitiation of a PIM necessarily represents inappropriate medication use. Within this framework, the evaluation of deprescribing implemetation in this thesis may be interpreted as an indicator of potential medication optimization at the population level, while recognising that the observed prescribing patterns may not fully reflect the clinical judgement underlying individual prescribing decisions.

9.3.1.Real world implementation of deprescribing

Deprescribing is widely recognized as a high-value care strategy, yet its real-world implementation remains limited.

Promoting and implementing high value care is a central goal of health system reform.[45] However, healthcare systems worldwide continue to struggle to deliver appropriate care to individuals with

complex needs. The widespread burden of excessive medication use among frail older adults and people with multimorbidity has been described as a persistent and systemic problem. Within this context, deprescribing has gained increasing attention as a high value care approach that addresses treatment overuse by reducing unnecessary medications and avoidable costs.[46] Health systems and payers increasingly recognise deprescribing as an essential strategy to limit low value pharmaceutical care and reduce medication related harm.[47] However, our findings demonstrate a rather small decline over the recent years in the rate of deprescribing of at least one PIM among NH residents with limited life expectancy, with no change in the underlying trend, even following the publication of international deprescribing guidelines. The persistently high prevalence of PIM use, along with the gradual decline in discontinuation rates, remains concerning and underscores important gaps in the actual implementation of deprescribing in routine practice.

Analysis of commonly used individual medications showed that discontinuation trends remained either stable over time (e.g., lipid modifying agents and antipsychotics) or decreased (e.g., PPIs and NSAIDs). This pattern is consistent with sustained or increasing overall medication use. Based on our prospective cohort study within NHs in Chapter 6, although the proportion of residents using at least one PIM decreased by 16.7% between baseline, usually shortly after admission to the NH, and one year later, the total number of chronic medications nevertheless increased. This indicates that other or alternative medications were introduced, for which we could not determine whether they were PIMs because the study was limited to a selected set of PIMs. Previous NH studies also reflect this pattern, showing a small decrease in PIMs in a post-hoc analysis of an interventional study[20] and an increase in chronic medication use in a prospective cohort study. [48] However, at the level of individual medications, changes varied by medication type. For commonly used drugs, chronic PPI use (44.2% to 48.4%) and antipsychotic use (21.9% to 26.2%) increased, while no significant change was observed for chronic lipid-modifying agents (23.89% to 23.24%). These patterns further indicate limited and inconsistent implementation of deprescribing. While they may suggest that some level of medication review and reconsideration occurs within NHs, the absence of substantial or consistent reductions in PIM use, alongside the increase in chronic medication use, indicates that such practices, if present, are not implemented in a systematic or sufficiently effective manner to meaningfully influence population-level deprescribing patterns over time.

Our qualitative study exploring barriers and enablers provides crucial contextual explanations for why deprescribing is not consistently enacted in real-world practice. The reported barriers, largely consistent with those identified in previous NH-based studies not specific to the end of life context,[49, 50] and in other healthcare settings, suggest that common factors beyond residents' life expectancy and setting-specific characteristics largely shape deprescribing behaviour. This may reflect that deprescribing is not yet embedded as a routine practice, resulting in similar barriers across different settings and populations. Key barriers include resource limitations such as time, staffing, finances, and lack of tailored guidelines, as well as poor documentation, communication, and coordination between care settings, which lead to discontinuity of care,[50] including when deprescribing is initiated in other settings during care transitions. A recent qualitative study in Australia exploring factors influencing successful deprescribing initiated in hospitals found that deprescribing is often started in hospital settings.[51] Our findings in chapter 3 similarly showed that residents with a recent hospital admission had higher rates of deprescribing compared to those without admission (43.5 % versus 20.5 %). However, the deprescribing process is not always continued after discharge, and recommendations are not consistently implemented. Key factors influencing continuity include acceptance of the

deprescribing decision, understanding of the plan, and a supportive post-discharge environment. Interestingly, in Chapter 5, residents with a recent hospital admission also had higher rates of reinitiation of previously discontinued medications (23.35% versus 10.15%). Although this may appear contradictory to the higher deprescribing rates observed in Chapter 3, hospitalization may create opportunities both to reassess and discontinue potentially unnecessary medications, and opportunities to initiate or reinitiate medications following acute clinical changes, symptom burden, or new diagnoses. NH residents admitted to hospital frequently have multiple comorbidities[52] and receive care from several specialists. In addition, the application of disease-specific clinical guidelines may encourage treatment decisions that focus on individual conditions or organ systems rather than on a comprehensive, holistic assessment of the resident. This may increase the likelihood of medication reinitiation from a specialty-specific perspective without fully considering the resident's overall medication burden and goals of care. This interpretation is supported by recent evidence showing that higher medication burden and a greater number of prescribers are associated with an increased risk of medication restart following deprescribing[53], highlighting the role of care complexity and fragmentation during care transitions in undermining the durability of deprescribing efforts. Our qualitative findings also highlight a lack of continuity of care with poor communication between care settings and care providers, limited access to residents' health information for deprescribing decisions, and poor documentation in NHs as important barriers, consistent with findings reported in the Netherlands.[22] These findings underscore the need to restructure the care environment by strengthening transmural care and interprofessional collaboration across settings to improve continuity and support deprescribing as part of routine clinical practice.

In the context of end-of-life care, HCPs report perceived gaps in knowledge and skills related to deprescribing, particularly in the presence of multimorbidity, consistent with findings from previous studies and highlighting important areas for improvement. [49, 50, 54, 55] While the interplay between HCPs, residents, and families through shared decision-making has been shown to facilitate deprescribing, as supported by systematic reviews and qualitative studies, [56, 57] cognitive impairment related to dementia, which is highly prevalent in this population, [58] is perceived as a major barrier because it limits residents' ability to actively participate in decision making. In addition, resistance from residents, driven by fear of change, concerns about symptom recurrence, or limited understanding of potential benefits, further complicates deprescribing.[57, 59] These findings highlight the need for tailored communication strategies that account for cognitive limitations and actively involve family members. Integrating deprescribing into advance care planning and initiating it earlier may support better decision-making. While deprescribing requires multidisciplinary collaboration in medication review, the roles of nurses and pharmacists remain limited, despite nurses providing essential clinical observations[60] and pharmacists contributing expertise in medication review. [57, 60] Expanding and formalising these roles is therefore essential to support deprescribing in routine practice, as supported by previous studies.[50, 61]

The publication of deprescribing guidelines was insufficient to influence real-world practice; we need 'better implementation'

An important contribution of this dissertation is that it provides evidence about the influence, or lack thereof, of deprescribing guidelines on actual practice at the level of the healthcare system. Increased attention to the identification of PIMs and to supporting clinicians in deprescribing decisions has led to the development of several expert-validated tools and guidelines. [62] Within this broader context

and applied to NH residents with limited life expectancy, Chapter 3 of this dissertation provides the first empirical evaluation of the impact of the generic deprescribing guideline (STOPPFrail)[34] and drug specific guidelines (antipsychotics[63] and PPI[64]) on deprescribing practices. Although the guidelines have demonstrated effectiveness in reducing PIMs when implemented through structured interventions in previous studies,[65-67] their mere publication was not reflected in a change in our observed trends in deprescribing in real-world clinical practice.

Some of the barriers and facilitators identified in the qualitative study (Chapter 4) help to explain this lack of effect. [68] While HCPs may be aware of existing deprescribing guidelines,[69] their use in practice is constrained by guideline complexity, the additional time required for their application without adequate reimbursement, the lack of context-specific guidance, and the absence of formal national endorsement. Broadly, this finding is reflected in the lack of widespread and consistent implementation of deprescribing, both globally and in Belgium. [70-72] Several additional factors may explain this limited impact in the real world. First, guidelines requiring medication reviews are often seen as complex and difficult to implement owing to a lack of time for proper review. Many HCPs struggle to apply them effectively. [73] Second, while the guidelines were published and made available they have largely remained standalone guidelines without adequate implementation strategies, including their integration into broader clinical practice guidelines.[74] While integration of deprescribing recommendations into clinical guidelines has been proposed to reduce inappropriate medication use and related harm, [75] and is increasingly observed (29%), many guidelines still lack clear, actionable instructions on how to deprescribe, limiting their practical applicability.[76]

Furthermore, the focus on single diseases in a large proportion of guidelines may limit their applicability to populations with multimorbidity, as these approaches fail to account for coexisting conditions and concurrent therapies. [77, 78] This limitation is particularly relevant in NH residents with limited life expectancy, where multimorbidity is common and necessitates a more holistic, patient-centered approach to medication management.[79, 80] Although the importance of developing guidelines for multimorbidity and polypharmacy is widely recognized, available guidance remains limited. A recent systematic review identified 21 guidelines addressing multimorbidity and polypharmacy in older adults [81], while another review identified 8 national clinical practice guidelines for medication management of patients with polypharmacy in primary care.[82] Most guidelines recommended medication review with patient involvement as a key strategy for managing polypharmacy; however, guidance on task division among healthcare professionals and implementation in clinical practice remained unclear.[82] Furthermore, many of the guidelines lack methodological rigor, completeness, feasibility for implementation, and adequate attention to patient-centered dimensions such as preferences, goal alignment, and longitudinal follow-up.[81] These findings highlight the need for further improvement and implementation of guidelines.

Overall, from an implementation science perspective, the lack of an observed effect of the guidelines is not surprising. Changing clinical practice requires more than the publication of guidelines, it demands a context-informed implementation strategy and sustained effort to influence clinical practice and the normalization of new behaviors, [71, 83] supported by implementation frameworks or theories. [84, 85] This interpretation is supported by international evidence. A Canadian study in long-term care homes similarly found no sustained reduction in PPI use 12 months after introducing the PPI guideline in the NHs, with prescribing initially declining but returning to baseline levels after six months.[86] Similarly, evidence from Swedish NHs further suggests that while deprescribing

interventions are feasible to implement, they are difficult to sustain in routine care,[87] underscoring the importance of interprofessional collaboration and explicit sustainability strategies. [88]

In Belgium, efforts to implement deprescribing have largely been driven by pilot-level, bottom-up initiatives, which, although effective at the local level, have not translated into sustained system-wide change, and whose impacts have neither been maintained nor scaled up beyond the original intervention settings. The Collaborative Approach to Optimise Medication Use for Older People in NHs (COME-ON) project,[89] implemented a multifaceted, interdisciplinary intervention in NHs including training, local consensus meetings, repeated case conferences between general practitioners (GPs), pharmacists, and nurses, and web based tools to support medication reviews, and demonstrated improvements in prescribing appropriateness; however, its effects were highly context dependent, with variability across NHs and limited sustainability beyond the study period. Similarly, the Optimisation of Medication through Multidisciplinary Evaluation in NHs (OptiMEDs),[90] pilot introduced an automated electronic assessment tool for recognition of inappropriate medications, supported multidisciplinary medication review combined with nurse led symptom monitoring, and demonstrated short-term reductions in overall medication use and PIMs; however, its small scale and limited follow-up restricted sustainability. A psychotropic reduction program, implemented as part of quality improvement initiatives,[91] was also informed by a small scale pre-post study conducted in Belgian NHs, which showed reductions in psychotropic drug use primarily when educational interventions were combined with broader professional support, with limited effects observed from education alone. Information sharing and guidance through the Belgian Centre for Pharmacotherapeutic Information (BCFI/CBIP),[92] as well as Deprescrire.be, a Belgian initiative from the UCLouvain DI-PRESCRIBE research group, which provides clinicians with reliable, up-to-date access to evidence-based deprescribing tools, guidelines, algorithms, training resources, and relevant publications to support safe deprescribing, [93] could improve access to evidence based deprescribing resources but has similarly lacked the structural integration necessary to ensure routine uptake across NHs and medication classes. More recent initiatives, including POOMAH (Process Optimization of the Medicines' pAthway in NHs),[94] have adopted a system-oriented approach by targeting the entire medicines pathway through varying levels of organisational support ranging from toolboxes and intervision to external coaching and integration of a coordinating pharmacist; however, POOMAH remains an evaluated intervention rather than an embedded policy mechanism, with its long-term impact dependent on future regulatory and financing decisions.

In addition, although not specific to NHs, government initiatives adopting a top-down approach, including reimbursement for benzodiazepine withdrawal in community dwelling adults, [95] and the introduction of prescribing quality indicators for PPIs by the National Council for Quality Promotion (NCQP), with yearly feedback to individual prescribers (GPs) from the National Institute for Health and Disability Insurance,[96] aimed to influence prescribing behaviour and could potentially be extended to the NH setting. However, evidence suggests that audit and feedback or information provision alone are insufficient as standalone strategies. [97] Despite these efforts, PIM use remains high, with persistently low deprescribing rates in NH residents.

Overall, while Belgian deprescribing initiatives have demonstrated proof of concept and short-term improvements, they have not yet resulted in sustainable system-wide change. This body of evidence indicates that bottom-up approaches, although locally effective, remain fragmented, narrowly focused, and vulnerable to contextual and organisational barriers in the absence of sustained top-

down policy support. Moreover, the scope and impact of existing initiatives remain limited and require expansion across a broader range of NHs and medication classes to achieve meaningful and lasting reductions in inappropriate medication use. Therefore, broader implementation of deprescribing will require coordinated policy action, mobilised through various mechanisms such as regulatory measures, funding strategies, allocation of resources, and guidelines and algorithms.[45] Similarly, previous international policy reviews have shown that deprescribing efforts, despite growing policy interest, remain focused on specific medication classes and are implemented inconsistently across countries. These initiatives typically target high-risk drugs such as sedative hypnotics and antipsychotics, rather than addressing overall medication burden or end of life treatment goals. As a result, their benefits may be reduced by unintended consequences, including substitution with alternative medications, fragmented implementation, and limited integration into routine clinical decision making.[97] Overall, interpreting our findings in light of the available literature indicates persistent challenges in implementing deprescribing, underscoring the need for clear and coordinated policy support, as the current initiatives do not fully account for the complexity of deprescribing.[45]

A need for nuances in deprescribing paradigms?

This dissertation suggests that there do not seem to be clear pathways for deprescribing in NHs, with deprescribing, if happening at all, not being sustained and sometimes followed by reinitiation. In Chapter 5, findings indicate that deprescribing is not always sustained in routine NH practice, with a significant number of medications deemed PIMs being reinitiated during the last three months of life. Nearly 17% of residents had at least one PIM reinitiated after it had previously been discontinued (20.3% of symptomatic medications and 11% of preventive medications), and 30% of residents initiated at least one PIM (25.5% of symptomatic medications and 6.7% of preventive medications). These patterns indicate that deprescribing decisions are frequently not maintained, with medications being restarted or newly introduced in addition to those that are continued. The meaningfully higher reinitiation and initiation rates of symptomatic relief medications (e.g., PPIs, antipsychotics, corticosteroids, and gastrointestinal antispasmodics) near the end of life suggest a greater tendency to use medications for palliative care purposes, [98] and a previous study also described higher initiation rates of symptomatic medications in NHs. [99]

This could suggest a need to nuance the classification of medications as potentially inappropriate as this is also illustrated by discrepancies between existing tools, [14, 34, 68, 100] which differ in whether these medications are considered inappropriate or appropriate at the end of life. Our study contributes empirically to this ongoing debate and highlights a need for a more nuanced approach that distinguishes inappropriate prescribing from justified palliative use, particularly given that medications may be appropriately reinitiated for new clinical indications and could otherwise be misinterpreted as unsuccessful deprescribing. However, a notable proportion of NH residents had preventive medications either reinitiated or newly initiated, which are unlikely to offer meaningful benefit and are expected to be sustainably deprescribed, highlighting an ongoing gap in balancing appropriate prescribing in the palliative care context. The literature reveals a lack of consensus regarding which medications are strictly preventive and therefore potentially futile at the end of life. [101] Future guidance should explicitly describe the purpose for which medications are considered inappropriate or appropriate, for example, PPIs used for preventive versus symptomatic indications. This could help prevent both overprescribing and underprescribing. For example, although PPIs are

commonly used and overprescribed in NHs, a significant number of residents experience underuse of PPIs (38.5%), illustrating the need for more balanced and individualized prescribing practices.[102]

The higher initiation and reinitiation rates of symptomatic medications compared with preventive medications, coupled with low deprescribing rates, suggest increased use of symptomatic medications as death approaches in NHs, consistent with previous research. [98, 103] Similarly, the high initiation and reinitiation rates of preventive medications, along with low deprescribing rates, suggest that residents continue to use clearly futile medications, necessitating re-prescribing decisions. [104] However, re-prescribing at the end of life requires a dual responsibility for prescribers (mainly GPs in Belgian NHs), which may contribute for inappropriate prescribing,[98, 105] namely estimating remaining life expectancy and evaluating treatment appropriateness. [106] To reduce PIMs, multidisciplinary medication review has been reported to be effective. [90, 107-109] However, our qualitative study showed a lack of time and reimbursement for multidisciplinary medication review as a barrier to deprescribing. In addition, the challenge of estimating remaining life expectancy may contribute to the late initiation of palliative care. Although the literature shows that palliative care is associated with increased deprescribing, [110, 111] and residents often have high palliative care needs, palliative care is, on average, initiated only 2 weeks prior to death, [112] representing a missed opportunity for deprescribing. Therefore, earlier identification and initiation of palliative care are crucial, [98] and these measures can inform medication re-prescribing in accordance with anticipated benefit and remaining life expectancy and be supported through interprofessional collaboration.[113]

9.3.2. Effects of deprescribing PIMS: reducing low-value care without compromising patient-centred outcomes

Despite reductions in PIM use over time, our longitudinal analyses showed that deterioration across physical, cognitive, and psychosocial domains remained more common than improvement. This pattern is consistent with international long-term care literature [114-116] and reflects the advanced frailty and limited life expectancy of Belgian NH residents, whose average length of stay is under two years.[30] In this context, improvement in global health outcomes cannot realistically be expected. Importantly, this does not invalidate deprescribing efforts; rather, it necessitates a reframing of their intended impact. Deprescribing in NH populations is unlikely to reverse decline but may help preserve valued aspects of daily life, prevent avoidable harms, or reduce treatment burden during the remaining disease trajectory. Evidence from the systematic review supports this interpretation, indicating that deprescribing in those with life-limiting conditions does not necessarily lead to improvement in patient experience, while showing limited evidence of harm and conferring benefits in terms of reduced medication burden and related costs.[117]

Interpretation of the observed PIM reductions also requires consideration of concurrent changes in overall medication burden and the limited scope of PIMs assessed in this study. PIM prevalence was already high at baseline, making a subsequent decrease plausible. At the same time, the number of chronic medications increased, indicating that new medications were prescribed during follow-up. Because our analyses classified PIM change based on the presence of at least one PIM and were restricted to a predefined and limited set of PIMs, reductions in PIM exposure may have been diluted by increases in overall chronic medication use, reinitiation of non selected PIMs, or the accumulation of multiple PIMs within individuals. While the burden of chronic medication increased, and decline in ADL and cognitive impairment was observed, a previous study also showed the assocation betwen baseline polypharmacy with 1-year decline in cognitive imparment.[118] Similarly, patterns of

intensification in PIM use, from no PIM use to deprescribing, to newly initiated or continued use throughout follow-up, were associated with deterioration in ADL, increased aggressive behaviour, and greater comorbidity burden, while most outcomes showed no significant change. Within this framework, our findings should be viewed as exploratory and hypothesis-generating, suggesting that changes in health are associated with changes in medication use. These findings support the need for future studies that examine individual medications and apply causal methods, and our exploratory work demonstrates the feasibility of such individual-level analyses using clinically meaningful outcomes in NH populations, an area currently underrepresented in the literature due to limitations in data linkage.

Building on these observations, Chapter 7 focuses on a commonly used medication class for which balancing benefits and risks is challenging [102] and whose appropriateness remains controversial across deprescribing tools, in order to more precisely evaluate the effects of deprescribing. Proton pump inhibitors remain among the most frequently prescribed and costly medications, with pantoprazole alone ranking sixth in outpatient pharmaceutical expenditure in Belgium in 2023, highlighting persistent overuse alongside potential underuse in selected high-risk patients. [119] In this context, our findings suggest that PPI deprescribing in NH residents does not meaningfully alter trajectories of quality-of-life-related outcomes, which in itself may be considered a favourable result. In a population characterised by frailty and progressive decline, the absence of deterioration following deprescribing supports its clinical acceptability when long-term indications are unclear. Importantly, deprescribing was associated with fewer hospitalisations, reinforcing its potential value at both the individual and system level. [120-122] These findings align with broader deprescribing research showing reduced medication burden without compromising patient-centred outcomes, and support the need for ongoing medication review efforts in NHs.

With respect to mortality, the finding contribute to an ongoing and unresolved debate. [120, 122, 123] The early survival advantage observed during the first six months after deprescribing is consistent with evidence suggesting potential benefit of deprescribing in residents approaching the end of life. [124] In contrast, the later attenuation or reversal of the survival benefit highlights the complexity of deprescribing decisions for residents with relatively longer life expectancy, for whom continued PPI therapy may confer a survival advantage. However, this result should be interpreted cautiously, as our study relied on proxy indications rather than verified clinical indications for long-term PPI use (e.g., severe esophagitis, Barrett's esophagus),[64] while only partially addressing appropriate use in residents receiving high bleeding-risk medications. [125] Future research incorporating confirmed clinical indications and richer sources of clinical data may better distinguish residents who benefit from deprescribing from those for whom continuation remains necessary. Overall, our findings support deprescribing PPIs as a safe and rational strategy when long-term use lacks a clear indication.

9.4. Implications and recommendations

Bringing together evidence from all studies included in this thesis, the integrated findings have important implications for future research, clinical practice, and policy. Despite the availability of international deprescribing guidelines, the findings consistently demonstrate low deprescribing rates and a high prevalence of PIMs at the population level. In addition, the reinitiation of PIMs for a significant number of residents near the end of life indicates a persistent gap between existing evidence and real-world practice. The results further identify diverse and interacting barriers to deprescribing operating at multiple levels, including individual HCPs, organizational factors within

NHs, and broader policy and health system contexts. Collectively, these insights provide a foundation for supporting decision-makers in adapting policies and deprescribing interventions, underscoring the need for targeted, multi-level strategies to address deprescribing challenges and to strengthen the implementation of deprescribing in routine practice.

Contextual health care organizational specificities need to be kept in mind in the recommendations based on our findings. In Belgium, GPs are independent (usually self-employed) and not embedded within specific NHs, a feature that shapes communication patterns and deprescribing dynamics. For example, previous study found that assigning dedicated GPs to NHs improved health outcomes and reduced healthcare spending by streamlining communication, reducing the number of physicians involved, and enabling regular multidisciplinary discussions and training around residents' treatment plans.[126] In contrast, consultations in Belgian NHs are often provided by multiple GPs, with average of 30 GPs per NH, [127] who are not consistently attached to a single facility. Combined with a fee-for-service system, in which reimbursement is primarily based on individual consultations rather than multidisciplinary collaboration, this organisation of care may contribute to fragmentation and create challenges for coordination in deprescribing.

Recent research has demonstrated substantial heterogeneity in the organisation of medical care across European NHs. Aasbrenn et al. proposed a typology comprising three broad models: (1) specialist-led systems with structured admission processes and dedicated nursing home physicians, (2) GP-led systems with strong admission gatekeeping, and (3) predominantly GP-led systems with less formalised admission procedures and limited specialist involvement, with Belgium classified within the latter model.[128] The authors emphasized that these models represent different organizational approaches rather than superior or inferior models of care. The typology provides a useful framework for considering the transferability of our findings across different healthcare systems. Importantly, despite these organizational differences, many challenges are shared across models, including multimorbidity, polypharmacy, PIM use, fragmented communication, and the complexity of end-of-life decision-making. Furthermore, physicians in many European NH systems typically visit facilities on scheduled days rather than being continuously present on-site, creating similar challenges for medication review and care coordination.

Consequently, I believe that the knowledge generated by this thesis is likely transferable to other European countries and beyond, particularly because the studies were informed by international deprescribing guidelines and address widely recognized concerns regarding low-value care and shared challenges facing healthcare systems. Many of the barriers identified are also relevant across countries, such as the limited consultation time of GPs (5 to 20 minutes), [129] which may restrict opportunities for medication review, as well as discontinuity of care and fragmented information sharing between healthcare settings. Nevertheless, the nature and extent of these challenges may vary according to local reimbursement mechanisms, staffing models, and the degree of integration between healthcare professionals.

Based on the findings, I will formulate recommendations for future research, for clinical practice and for policy.

9.4.1. Implications for future Research

1) Expanding and enriching the data sources used for deprescribing research

Although previous research in Belgium has identified and utilised multiple data sources to study end-of-life care at the population level,[130] these remain insufficient to capture the clinical complexity needed to support deprescribing decisions. In line with this, in our data linkage, although relevant patient outcomes from the BelRAI LTCF dataset were linked to medication data, clinically meaningful information remained limited. Key elements such as medication indications, symptom-driven use, patient preferences, goals of care, and prognostic considerations were frequently unavailable or only partially captured. This limits the ability to distinguish appropriate medication continuation from low-value prescribing that may be eligible for deprescribing and constrains adequate control of confounding when comparing the effects of deprescribing. In Belgium, as in many other countries, a substantial proportion of relevant clinical information is embedded in free-text documentation. Consequently, important information from GP and hospital records is often unavailable for research purposes because of the unstructured nature of routine clinical documentation, which complicates data linkage and sharing.

Future research should therefore prioritise the expansion and integration of available data sources through improved linkage and data integration. Linking administrative prescribing data with GP records, hospital data, and records of non-reimbursed medications dispensed through pharmacies, as well as information on non-pharmacological supports such as rehabilitation services, supportive care interventions, and lifestyle-related care, would substantially strengthen the evidence base. Such enriched data sources would allow a more comprehensive assessment of treatment decisions and better account for important clinical and contextual factors influencing deprescribing. In addition, artificial intelligence methods, including natural language processing, could be leveraged to transform unstructured free-text documentation and enhance the structured recording of routine clinical information in electronic health records, making these data more shareable, linkable, and analysable.[131] This could reduce the information loss that currently occurs when clinical reasoning, treatment indications, and care context are not adequately captured in structured datasets.

2) A need to providing causal evidence of deprescribing for various medications, applying causal inference methods such as trial emulation

In Chapter 7, we evaluated the effect of PPI deprescribing, demonstrating the feasibility of using target trial emulation with linked IMA medication data and interRAI long-term care facility assessments to assess the effects of deprescribing on outcomes relevant near the end-of-life. The availability of interRAI assessments, which are validated and implemented in more than 35 countries, and their linkage with healthcare reimbursement and dispensing data enables population-level causal analyses in NH settings and support the extension of this approach to other drug classes.

Future work could apply similar target trial emulation methods to additional medications frequently prescribed in NHs, including antipsychotics, antidepressants, sedatives and hypnotics, cardiovascular medications, and other preventive or symptomatic treatments. Our umbrella review (Chapter 3) provides compiled lists of medications derived from multiple medication appropriateness tools. These lists can serve as a foundational database to support medication selection for evidence generation and to formulate testable hypotheses aimed at validating consensus-based classifications using real-world data. Such hypotheses include comparisons of deprescribing versus continued use of PIMs, initiation versus omission of medications considered beneficial near the end of life, and evaluation of

medications for which appropriateness classifications differ across tools. Extending causal analyses to these medication classes would further strengthen the empirical evidence base supporting deprescribing decisions and improve alignment between prescribing practices and outcomes that are meaningful for residents with limited life expectancy.

3) ***More evidence and triangulation of evidence from real world data studies and intervention study***

Our findings indicate that the evidence base supporting deprescribing decisions in NH residents with limited life expectancy remains fragmented and largely reliant on expert consensus rather than high-quality empirical data. Existing tools show substantial inconsistencies in medication classification, while real-world studies have shown persistently high use of PIMs, low and unsustained deprescribing rates, and frequent medication initiation and reinitiation near the end of life, with limited impact following guideline publication. At the same time, our exploratory analysis (Chapter 6) showed that increasing medication burden over time was associated with either clinical decline or no improvement in health outcomes, while our causal emulation study (Chapter 7) demonstrated that deprescribing proton pump inhibitors was not associated with deterioration in quality-of-life related outcomes and was associated with fewer hospitalisations, with no clear effect on survival. Near the end of life, evidence of noninferior or improved outcomes can be regarded as clinically meaningful and supportive of deprescribing.

These findings suggest that progress in deprescribing will not be achieved through the continued proliferation of consensus-based tools and guidelines alone. Rather, higher-quality empirical evidence is needed to support implementation frameworks for appropriate medication management, encompassing both the deprescribing of unnecessary medications and the prescribing of treatments that remain aligned with residents' goals of care. In recent years, real-world evidence alone has increasingly been accepted by regulatory authorities, including for drug approval,[132] yet its efficient and methodologically robust use remains challenging. While observational real-world studies are essential for assessing long term prescribing patterns, sustainability, and outcomes under routine care conditions, they remain limited by incomplete clinical detail and residual confounding, and individual level RCTs are often ethically and practically challenging near the end of life. Until sufficiently robust and comprehensive data linkages that can stand on their own to inform decision making are achieved, triangulation of evidence can provides a pragmatic and credible evidentiary basis. This includes evidence from real-world data, which typically informs the effects of individual medication deprescribing, and from cluster randomized trials interventions conducted at the NH level, which evaluate comprehensive multidrug deprescribing.[133, 134] Such triangulation allows observational evidence to inform hypothesis generation,[135] while interventional studies provide complementary causal insight into changes in prescribing behaviour and care processes, and how these translate into clinically relevant outcomes. Integrating evidence across these approaches is therefore essential to reduce uncertainty, enhance generalisability, and support the translation and adoption of deprescribing into routine NH practice.

4) Research on implementation strategies for deprescribing guidelines is needed

Our findings demonstrate that the publication of deprescribing guidelines alone does not lead to their routine use in clinical practice, even when clinicians are aware of their availability. This underscores a clear need for future research that moves beyond guideline development to focus on how deprescribing guidelines are (or can better be) disseminated, adopted, implemented, and sustained

across different healthcare contexts—within and across countries, organisations, and institutions—to produce the desired changes. Such research should also explore how contextual factors influence their real-world use. Embedding mechanisms for monitoring guideline implementation will be essential to support the effective adoption and long-term integration of evidence-based deprescribing recommendations into routine clinical practice.

This research can best apply implementation science frameworks, such as the Consolidated Framework of Implementation Research (CFIR), the Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) framework[136, 137] or the Practical, Robust Implementation and Sustainability Model (PRISM),[138, 139] to systematically assess and address multilevel determinants of implementation. These frameworks can support the identification of key intervention components and mechanisms at organisational, professional, and health system levels, and inform the development of context-specific strategies to support sustained deprescribing practices in Belgium and beyond. In addition, they can help explain variations in implementation success across settings and identify adaptations required to integrate deprescribing recommendations into routine care.

5) *Studies developing and evaluating deprescribing interventions in NHs using implementation and/or behaviour-change frameworks*

Findings from this dissertation clearly demonstrate that deprescribing in NH residents with limited life expectancy remains persistently low, with a high proportion of residents continuing to receive PIMs as they approach the end of life and with low rates of deprescribing. These patterns persist despite the availability of consensus-based guidance and are underpinned by diverse barriers operating across micro-, meso-, and macro-level contexts. This complexity underscores the need for future research agendas to be aligned with implementation science, ensuring that evidence generation is explicitly linked to how deprescribing can be integrated into routine NH care rather than being evaluated solely under idealised conditions. The Consolidated Framework for Implementation Research (CFIR)[140] is well suited to capturing the complex, multilevel determinants influencing deprescribing across individual, organisational, and system contexts but is limited in its ability to explain behavioural mechanisms.[141] The Theoretical Domains Framework (TDF) adds this behavioural perspective by specifying individual-level barriers and enablers and informing the selection of targeted intervention components. The combined use of CFIR and TDF can therefore benefit studies by enabling deprescribing interventions to address both contextual complexity and behaviour change.[142] Our qualitative study identified key barriers and enablers to deprescribing, which were systematically mapped to theoretical domain frameworks, providing a foundation for the development of context-sensitive and implementable deprescribing interventions.

6) *Integrating economic evaluation into future deprescribing implementation research*

Although this dissertation did not include a formal economic evaluation of deprescribing interventions, findings from the qualitative component identified the lack of reimbursement for medication review and deprescribing activities as a key barrier to implementation, highlighting the need for economic evidence that is meaningful to payers and policy makers. Future research should therefore systematically embed robust economic evaluation within the implementation and evaluation of deprescribing interventions. Evidence from Australian NHs showed that a deprescribing intervention costing $239 per frail resident generated medication savings of up to $329 over 12 months, without reductions in quality-adjusted life-years.[143] Recent comprehensive systematic

reviews suggest that deprescribing interventions are often cost-effective or cost-saving; however, they also demonstrate that economic value is highly context-dependent across settings.[144] Such evaluations should extend beyond short-term medication cost reductions to consider longer-term consequences, including downstream healthcare utilisation, implementation and workforce costs, and potential unintended effects.[47] Incorporating comprehensive and setting-specific economic evaluations into future deprescribing studies is therefore essential to inform reimbursement decisions and support sustainable implementation, as focusing solely on medication cost savings provides an incomplete basis for assessing overall value.

7) Understanding the nuances of trade-offs in deprescribing

Deprescribing decisions at the end of life are preference-sensitive and involve complex trade-offs between potential benefits and harms, costs, treatment burden, and remaining life expectancy. While in Chapter 4 of the thesis we explored HCPs' barriers to deprescribing, it did not examine how such trade-offs are made by patients, family caregivers, or HCPs themselves, nor did it include patients or caregivers in the qualitative component, despite the relevance of their views. Notably, clinicians described fears of negative patient outcomes, anticipated patient and family resistance, emotional difficulty associated with deprescribing at the end of life, and uncertainty regarding prognosis—barriers that reflect underlying value-based judgements rather than purely clinical considerations. Discrete choice experiments, for instance, could address this gap by quantifying the relative importance of decision attributes and revealing how patients, caregivers, and clinicians prioritise outcomes and acceptable trade-offs.[145] Such evidence can support shared decision-making at the end of life by informing preference-aligned conversations and reducing reliance on clinician assumptions or anticipated resistance, particularly in contexts of prognostic uncertainty.[146]

8) Researchers as key coordinators in the data-sharing lifecycle

Researchers planning to work with linkages of routinely collected data should treat data access and linkage as a central, resource-intensive phase of the research process rather than as a brief preparatory step. This requires assessing data readiness and feasibility prior to grant submission, in close consultation with data holders, and carefully operationalising and validating core study concepts in dialogue with those responsible for the data. Researchers should also plan for sufficient time buffers to accommodate anticipated delays. Early, continuous, and proactive multi-channel communication with all stakeholders is essential, even when procedures appear familiar. In addition, researchers should anticipate funding and timeline constraints, actively share lessons learned with peers, and assume a proactive coordination role throughout the data-sharing process to integrate inputs, monitor progress, and address emerging issues in a timely manner.

9.4.2. Recommendations for clinical practice

1) Position deprescribing as a continuous and necessary component of care

In current practice, deprescribing is not routinely implemented in Belgian NHs. Findings from this dissertation further illustrate that deprescribing in NH residents with limited life expectancy is neither a linear nor a one-time event, but rather a fluctuating process shaped by different factors, such as care transitions (e.g., hospitalizations), and is often not sustained over time. Preventive medications continue to be initiated or restarted close to death, while symptomatic medications are frequently prescribed in ways that blur the boundary between appropriate palliative care and potentially inappropriate treatment. Once initiated, symptomatic medications also tend to be continued for

prolonged periods. Our qualitative findings further show that deprescribing is often not a priority in NH practice.

Overall, these patterns highlight the complexity and dynamic nature of medication use near the end of life and underscore the importance of medication review, particularly after acute events (e.g., hospitalisation), to ensure that medication use remains appropriate and to minimise the risk of prescribing cascades and unintended harm. These findings support the need to explicitly recognise deprescribing as a core component of high-quality care aimed at aligning medication use with residents' evolving clinical needs.

2) *Consider deprescribing as a strategy to reduce low-value care in appropriate clinical contexts*

Building on our findings (Chapter 7), deprescribing PPIs in NH residents did not worsen quality-of-life-related outcomes and reduced hospitalisations. These results suggest that PPI deprescribing can be safely undertaken in residents without a clear long-term indication, provided that continued monitoring is in place, while reducing costs for both the patient and healthcare system. Deprescribing may not lead to improved resident experiences, but it does reduce potential drug side effects, burdensome hospitalisations, and costs, thereby aligning care more closely with the needs and priorities of residents nearing the end of life. Overall, this highlights the potential of deprescribing as a strategy to reduce low-value care.

3) Perform recurrent multidisciplinary medication review

Medication prescribing in Belgian NHs is largely led by GPs, who face substantial time constraints that limit opportunities for comprehensive medication review in residents with complex needs. [129] This context highlights the need for a structured multidisciplinary medication review that extends beyond the sole role of the GP, as the lack of such collaborative review was identified as a key barrier to deprescribing. Nurses, who have close and continuous contact with residents and are well positioned to monitor residents' daily functioning, symptom changes, and evolving care needs, and pharmacists, who contribute pharmacotherapeutic expertise, have essential yet underutilised roles in identifying opportunities for deprescribing. Involving geriatricians where appropriate can further support nuanced decision-making in complex cases, particularly given their limited systematic involvement in Belgian NHs.

Such medication reviews should support the ongoing assessment of medication appropriateness by considering the balance between expected benefits, potential harms, treatment burden, prognosis, and evolving care goals. Through this process, opportunities for medication optimisation and deprescribing can be identified and addressed in a timely manner. Reviews should be undertaken proactively and regularly, as well as whenever changes occur in residents' clinical status, functional abilities, care needs, treatment goals, or during key transitions such as NH admission, transfer from other healthcare settings (e.g., hospitalisation), or clinical deterioration.

4) Engage residents and caregivers in deprescribing decisions

While patient preferences were often not captured in the data analysed in this dissertation, deprescribing decisions should actively involve residents and their caregivers through shared decision-making. Incorporating residents' preferences, values, and treatment goals alongside clinical considerations supports a patient-centred approach to deprescribing and may improve the appropriateness and acceptability of medication-related decisions. Meaningful involvement of

residents throughout the deprescribing process is vital and may improve long-term health outcomes.[147] Family members and caregivers can play an important role in this process by contributing insights into residents' wishes and priorities, particularly for those with cognitive impairment or limited decision-making capacity. Their active involvement in deprescribing discussions may also support resident autonomy by helping residents feel more involved and in control of decisions regarding their care.[148]

Clear communication and reassurance are essential, framing deprescribing as a flexible, reversible, and monitored process rather than a final decision, particularly given that fear of negative consequences was identified in this thesis as a key barrier to deprescribing at the end of life. To address this barrier and promote sustainable deprescribing practices, collaboration, input from different HCPs, residents, and caregivers, and effective communication are essential.[149] In this context, embedding deprescribing within existing care processes is crucial, [150] and it should be framing as a longitudinal, team-based activity that is revisited as goals of care evolve.

5) Explicitly include deprescribing in advance care planning

High-quality prescribing extends beyond medication initiation to include the careful and appropriate withdrawal of medicines. Effective deprescribing relies on clear, ongoing communication that supports shared decision-making throughout the medication lifecycle, including decisions to initiate, continue, taper, or discontinue medicines.[151] In our qualitative study, HCPs described the difficult to address medication discontinuation when patients are approaching the end of life, particularly in the presence of cognitive decline or when family members are reluctant to stop long-term medications. Including medication discontinuation preferences explicitly within advance care planning could support shared decision-making and facilitate decision-making when dilemmas arise later in the care trajectory.

9.4.3. Policy recommendations

Considering the consistently low deprescribing rates and the lack of any influence on clinical deprescribing practice after the publications of deprescribing guidelines and tools, a number of policy recommendations for better implementation are formulated based on our findings.

1) Incorporate deprescribing as a quality indicator (QI) for NHs

In Belgium, the appropriateness of care for older people is monitored through indicators based on the proportion of individuals using medications and defined daily doses (DDD), [152] i.e. "the assumed average maintenance dose per day for a drug used for its main indication in adults."[153] These indicators are used to monitor prescribing at regional and national levels. In NHs, they include the use of antidepressants and antipsychotics, while, more broadly, indicators for the general older population include measures such as anticholinergic burden and polypharmacy.[152] While these indicators provide valuable insight into potentially excessive or inappropriate prescribing, they primarily capture the proportion of older people receiving medications chronically, rather than the processes of medication review, dose reduction, or discontinuation.

As a result, current indicators mainly incentivise the restriction of prescribing initiation, but do not explicitly measure or encourage active deprescribing practices among residents already exposed to long-term or high-risk medications. Introducing deprescribing-oriented indicators that capture person-centred medication optimisation processes, such as the proportion of residents receiving regular structured medication reviews or the proportion of documented deprescribing decisions for

selected high-risk medications, would complement existing measures. Framing deprescribing as a distinct quality indicator would shift attention toward proactive medication optimisation and recognise deprescribing as an essential component of appropriate prescribing in older populations, rather than merely a secondary or implicit outcome.

Deprescribing indicators could be developed at several levels, including the prescriber, NH, care region, regional, and national levels. For NHs, aggregation of appropriately defined resident-level indicators could facilitate internal quality improvement, benchmarking, and the identification of variation in medication review practices. At the regional or national level, population-level indicators could support surveillance of medication-use patterns and identify areas where further policy attention may be warranted. However, poorly designed indicators could create unintended incentives to reduce medication use regardless of clinical appropriateness, penalise NHs caring for residents with greater medication needs, or encourage documentation without meaningful clinical review. These risks are particularly relevant because medication appropriateness cannot be fully captured by medication discontinuation rates alone. Consequently, any future NH-level indicator system is likely to benefit from combining process measures of person-centred medication review with carefully interpreted population-level medication-use measures, rather than relying solely on the number or proportion of medications discontinued.

This approach aligns with recent developments in Belgium, where the National Council for Quality Promotion (NCQP) introduced prescribing quality indicators for PPIs in general practice, based on thresholds of more than 25% of patients receiving at least one PPI prescription and an average treatment duration exceeding 90 defined daily doses (DDD) per patient.[96] GPs receive annual individual feedback from the National Institute for Health and Disability Insurance (NIHDI/RIZIV) on their prescribing behaviour. Extending this established indicator-based feedback model to a deprescribing perspective could support clinicians in identifying patients suitable for treatment review and deprescribing, while promoting safer care and reducing healthcare costs. When appropriately implemented, QIs can influence clinical practice by making deprescribing visible, identifying gaps, and prompting reflection and action. They are therefore not only measurement tools but also drivers of improved prescribing behaviour. However, feedback or information provision alone are insufficient as standalone strategies; [97] sustained improvement is more likely when feedback is combined with education and planning.[154]

The feasibility of operationalising deprescribing-related indicators depends substantially on the availability and standardisation of the underlying data. In Belgian NHs, medication-related information is currently registered inconsistently. Deprescribing decisions and the rationale for medication discontinuation are not recorded in a sufficiently standardised manner to allow the straightforward calculation of deprescribing indicators across nursing homes. Therefore, implementation would require a careful operationalisation process involving relevant stakeholders, including professional associations, mutualities, the National Council for Quality Promotion (NCQP), the Flemish Institute for Quality of Care (VIKZ), and relevant governmental authorities, to establish feasible, valid, and meaningful indicators. Given VIKZ's established role in developing and reporting quality indicators across Flemish healthcare and residential care settings,[155] it could play an important role in supporting the development, implementation, benchmarking, and transparency of deprescribing-related indicators at the regional level.

Potential indicators could include the proportion of eligible residents receiving a documented medication review, the proportion for whom medication optimisation was considered, and, where appropriate, the occurrence and type of deprescribing according to medication class. Clear eligibility criteria and denominators would be essential to ensure meaningful interpretation and comparison across NHs. Such indicators should not be used to promote deprescribing per se, but rather to evaluate and monitor the quality of medication optimisation processes and provide population-level information on prescribing and deprescribing practices. Although deprescribing is not currently recorded in a consistent and standardised manner, establishing routine registration and reporting at the NH level could make these indicators feasible in the future.

2) Enable multidisciplinary medication review and deprescribing

Effective deprescribing in NHs requires a multidisciplinary approach, yet current policy frameworks in Belgium insufficiently support such collaboration. Evidence from a pilot multidisciplinary medication review (OptiMEDs) in NHs demonstrated a reduction in PIMs and showed that implementation is feasible with an acceptable additional time investment for each HCP.[90] Despite this evidence, our qualitative study in Chapter 4, consistent with previous research, identified the lack of reimbursement for multidisciplinary medication review as a key determinant limiting deprescribing, [156] as these activities are currently not structurally funded.

In Belgium, research has also been conducted to enhance the uptake of BZDA deprescribing in NHs using insights from behaviour change theory and implementation science (Evrard, Perrine, doctoral thesis, 2024). [157] Although Evrard's thesis focuses on specific drugs in NHs and does not specifically address deprescribing for residents nearing the end of life, it provides clear policy-relevant recommendations for NHs more broadly, as most reported barriers are similar. These recommendations align closely with the findings of this dissertation and reinforce the importance of structured multidisciplinary medication review, which was also highlighted in our qualitative study in Chapter 4 as a central enabling mechanism for deprescribing. Role expansion plays an important part, with distinct and complementary contributions from each professional group. Nurses are closest to residents and are uniquely positioned to support medication optimisation. Beyond monitoring for adverse drug events and changes in clinical status, nurses can identify PIMs and potential deprescribing opportunities, communicate residents' preferences and goals of care, facilitate discussions with residents and families about medication use, and contribute valuable information during multidisciplinary medication reviews. [158] As coordinators of care, they can support communication between physicians, pharmacists, residents, and caregivers, helping to ensure that medication-related decisions reflect residents' evolving needs and priorities. [159, 160] However, findings from the qualitative study suggest that the contribution of nurses to deprescribing remains underutilised. Limited involvement in decision-making processes, unclear responsibilities, insufficient pharmacological training opportunities, and workforce shortages may reduce their ability to contribute effectively to medication optimisation.[152] High nursing turnover in Belgian NHs further challenges continuity of care and limits the accumulation of resident-specific knowledge that is often essential for identifying inappropriate medications and supporting deprescribing discussions. Moreover, specialist nurses are frequently lost to other healthcare sectors, while nurse assistants with less pharmacological expertise increasingly undertake medication-related responsibilities. Pharmacists contribute specialised expertise in medication review and deprescribing support, but their involvement in NHs is often limited primarily to logistical tasks (e.g., medication supply).

Coordinating physicians provide oversight at the organisational level but frequently lack formal authority over individual prescribing decisions made by GPs. Policy actions should therefore prioritise formal recognition and organisational support of these expanded roles within NHs. For nurses, this may include clearer responsibilities in medication optimisation processes, greater involvement in multidisciplinary medication reviews, and targeted education in pharmacotherapy and deprescribing. Clear role definitions and structured multidisciplinary medication review processes may reduce uncertainty, improve coordination, and support deprescribing, while respecting the therapeutic autonomy of individual prescribers. Such measures would help embed multidisciplinary collaboration into routine care rather than leaving it dependent on individual motivation.

A persistent barrier identified in Chapter 4 concerns the structural misalignment between the required time-intensive nature of medication reviews to deprescribing and existing reimbursement models. While multidisciplinary medication review has been shown to be feasible, the substantial time required for conducting reviews and engaging in shared decision-making with residents and families is not adequately recognised or compensated within current financing structures. This challenge is also evident in the Netherlands, where the Dutch Health Care Inspectorate mandates regular pharmacist physician medication reviews for all NH residents. Despite this regulatory requirement, full compliance remains difficult, largely due to the considerable time investment needed for each review, which has led to calls for greater automation of medication review processes to improve efficiency.[161] This lack of reimbursement constrains not only the implementation but also the formal documentation of deprescribing activities. Introducing a specific nomenclature code or reimbursement mechanism for structured multidisciplinary medication review and deprescribing should be addressed in future policy. Recent Belgian initiatives that reimburse benzodiazepine deprescribing in home care provide a useful precedent [95] and could be extended to NHs and to other medication classes commonly used inappropriately toward the end of life. Aligning reimbursement with multidisciplinary medication review would support a transition from isolated, voluntary efforts to a sustainable and supported standard of care.

3) Supporting healthcare professionals through education, training, and clinical decision support (beyond guidelines)

A key policy priority is addressing gaps in knowledge, expertise, and confidence among HCPs in deprescribing, particularly for NH residents nearing the end of life, where clinical decision making is complicated by multimorbidity, polypharmacy, and uncertainty in prognosis. In the short term, targeted on-the-job training and sufficient organisational resources are needed to support clinicians in balancing medication use according to individual care goals. While many deprescribing tools and guidelines exist, training should move beyond tool awareness toward building critical appraisal, evidence synthesis, and contextual application skills. As evidence on deprescribing continues to evolve, clinicians need to interpret and integrate emerging evidence rather than rely solely on static recommendations. Education should therefore equip clinicians to evaluate the strengths and limitations of available tools and to apply them judiciously.

On-the-job training is particularly important, as lack of confidence, role ambiguity, and emotional strain were prominent barriers identified in our qualitative findings. Deprescribing near the end of life involves uncertainty, multimorbidity, cognitive impairment, and sensitive conversations with residents and families. Educational efforts should therefore emphasise clinical reasoning under uncertainty, emotional dimensions of deprescribing (fear of causing harm), communication skills for

shared decision-making, and reframing deprescribing as part of proactive, goal-oriented care rather than withdrawal of treatment. Supporting clinicians in these areas may be as important as improving technical knowledge, and may be key to sustaining deprescribing practices in NH care. Deprescribing, as an integral component of good prescribing practice, should be structurally embedded in healthcare education. As part of this effort, international experts in deprescribing have proposed an interprofessional educational and curricular framework to support its integration.[162]

In addition, policy efforts should support the integration of context-based guidelines and decision-support tools into routine practice to help clinicians balance treatment appropriateness with patients' remaining life expectancy. Such tools may help identify residents for whom the preventive benefit of medications is unlikely to be realised and facilitate timely, goal oriented medication review. In Chapter 4, one of the key barriers to deprescribing in Belgium was the lack of context-specific guidelines endorsed by relevant health authorities. Therefore, developing and/or endorsing context-specific guidelines, along with targeted implementation strategies, could support HCPs in deprescribing practices. A relevant example is the Dutch Multidisciplinary Guideline on Deprescribing Medication in Older People and its accompanying practical module, published in 2020 [163], which were developed in response to HCPs' need for more explicit guidance on deprescribing medications in older adults with polypharmacy. Beyond providing evidence-based recommendations for specific medication classes, the guideline emphasises patient involvement, multidisciplinary collaboration, monitoring after deprescribing, and shared decision-making. Importantly, its implementation has been supported through HCP training modules, e-learning programmes, integration into related national clinical guidelines, and patient-facing information resources. The evaluation of this guideline has been explored in the pharmacist-led Less Medicines in Older people in the Netherlands (LeMON) study, which evaluated a deprescribing-focused medication review targeting cardiovascular and antidiabetic medications in older adults with polypharmacy and reported a reduction in inappropriate medication use after its implementation. However, the evaluation also emphasized the need for dedicated knowledge and training, access to relevant clinical information, close collaboration between community pharmacists and physicians, effective communication with patients, and multidisciplinary agreements to address medication prescribed by specialist providers. [164, 165] These experiences illustrate that guideline development alone is unlikely to be sufficient; guidelines need to be accompanied by active implementation strategies. Such strategies may include educational initiatives, multidisciplinary medication reviews, clinical decision support systems integrated into electronic health records, and automated screening tools that identify PIMs or deprescribing opportunities in NH residents. Furthermore, emerging tools developed after the completion of Chapter 2 of this thesis, such as the criteria proposed by Elsten et al. for patients with a life expectancy of six months or less (2024), [166] and the recently developed ReNeWAL (Re-Prescribing in Nursing Home Residents with Limited Life Expectancy) tool (2024), [104] may complement these efforts by supporting clinicians in identifying PIMs, guiding prescribing and deprescribing decisions, and facilitating medication reviews for NH residents with limited life expectancy.

4) Strengthen data infrastructure and streamline access to support practice and research

The findings of this thesis highlight broader structural challenges related to health data access and use, which hinder both deprescribing decision-making and related research. They therefore call for government action to streamline health data access and strengthen national data infrastructure to support deprescribing practice and research, with relevance to broader healthcare decision-making, research, and policy development. One of the major challenges identified in this dissertation is that

much of the clinically relevant information needed to study deprescribing, which is also relevant to other topics, such as medication indications, patient preferences, and other detailed clinical information, is recorded in unstructured free text or remains siloed within institutional systems. This limits its suitability for linkage with population level datasets and constrains its shareability and reuse for research purposes.[131]

Access procedures remain highly time-consuming, even when data are available for sharing. In our study, data access delays of up to 3.5 years were observed, clearly indicating that current processes are not fit for timely and responsive research. Previous Belgian experiences, including national COVID-19 data linkage efforts, have similarly reported data access trajectories spanning several years (approximately 3.5 years), alongside challenges comparable to those observed in our experience, despite the urgency of the public health context. [167] Importantly, prolonged timelines for data access are not unique to this study but reflect persistent and systemic challenges in the Belgian data linkage landscape. These converging findings suggest that delays arise not from isolated project-specific inefficiencies but from shared and common structural challenges that need to be addressed. [167, 168] This stands in contrast to the European Health Data Space (EHDS) framework, which requires access to health data in compliance with national legislation within a reasonable timeframe of no more than three months from receipt of the request, extendable by a maximum of three additional months in justified cases.[169] These findings underscore the urgent need to shorten the current lengthy turnaround times for data access by identifying and addressing existing structural problems in data access and utilisation. These limitations directly affected study scope, flexibility, and timelines, revealing a persistent gap between the promise of data-driven research and its practical implementation.

Streamlining governance structures, clarifying the roles and responsibilities of different stakeholders across the data sharing lifecycle, and ensuring timely access to structured, high quality data are essential steps toward generating robust, practice-relevant evidence. These recommendations align closely with the ambitions of the EHDS and are particularly relevant in the Belgian context, while offering transferable insights for other health systems seeking to support evidence-based deprescribing policy and practice through improved data infrastructure. Building on the detailed case study presented in Chapter 8, the findings of this dissertation contribute to ongoing government efforts to improve data sharing. As part of knowledge dissemination, these insights were also shared through an opinion publication with the Belgian Health Data Agency, [170] providing a structured analysis of barriers to data access and utilisation that can inform future policy reform.

General conclusion

This doctoral thesis aimed to strengthen the evidence base for deprescribing by investigating its real-world implementation in NH residents with limited life expectancy and its effects on end-of-life-relevant outcomes. This thesis demonstrates that deprescribing in NH residents with limited life expectancy remains insufficiently embedded in routine practice, as reflected by a persistently high prevalence of PIM use, low deprescribing rates, a decreasing - albeit small- trend in discontinuation over time, and frequent restarting of discontinued medications. Despite the publication of international deprescribing guidelines (STOPPFrail and drug-specific guidelines for PPIs and antipsychotics), these alone did not influence deprescribing trends. This remains concerning and highlights important gaps in the real-world implementation of deprescribing, which will require more comprehensive efforts and strategies. The identified multilevel barriers and enablers at individual, NH, and healthcare system levels help explain the limited implementation of deprescribing in practice and provide a basis for targeted interventions. This thesis also highlights the need to reduce overall medication burden, as current prescribing practices near the end of life do not appear to be well aligned with residents' evolving clinical needs. The observed increased medication burden, as well as the use of PIMs, was associated with either a decline in quality-of-life-related outcomes or no improvement, suggesting that an increase in medication burden may be futile and even contribute to a worsening of health outcomes. At the level of specific medications, PPI was found to be a medication that can safely be deprescribed without worsening quality-of-life-related outcomes while at the same time reducing the chance of hospital admissions. Clinicians should therefore consider deprescribing PPIs when no clear long-term indication is present, while ensuring appropriate monitoring. Further research and policy efforts are needed to support the implementation of deprescribing and to strengthen the evidence base on its effects across a broader range of medications at the end of life. In addition, improving data linkage and data sharing across care settings is essential to enable robust causal inference and support well-informed deprescribing decisions. These efforts should also aim to ensure more timely and efficient access to healthcare data, which is currently often slow and fragmented.

References

1. Visser AGR. Deprescribing in nursing home residents: when less is more? 2024.
2. Taxis K, Kochen S, Wouters H*, et al.* Cross-national comparison of medication use in Australian and Dutch nursing homes. Age Ageing. 2017;46(2):320-3.
3. Ngcobo NN. Influence of Ageing on the Pharmacodynamics and Pharmacokinetics of Chronically Administered Medicines in Geriatric Patients: A Review. Clin Pharmacokinet. 2025;64(3):335-67.
4. Hertogh CMPM, Ribbe MW. [Palliative care and the health care for the elderly]. Tijdschr Gerontol Geriatr. 2008;39(6):220-3.
5. Holmes HM, Hayley DC, Alexander GC, Sachs GA. Reconsidering medication appropriateness for patients late in life. Arch Intern Med. 2006;166(6):605-9.
6. Paque K, Vander Stichele R, Elseviers M*, et al.* Barriers and enablers to deprescribing in people with a life-limiting disease: a systematic review. Palliat Med. 2019;33(1):37-48.
7. Farrell B, Pottie K, Thompson W*, et al.* Deprescribing proton pump inhibitors: evidence-based clinical practice guideline. Can Fam Physician. 2017;63(5):354-64.
8. Bjerre LM, Farrell B, Hogel M*, et al.* Deprescribing antipsychotics for behavioural and psychological symptoms of dementia and insomnia: evidence-based clinical practice guideline. Can Fam Physician. 2018;64(1):17-27.
9. Panel AGSBCUE. American Geriatrics Society 2023 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults. J Am Geriatr Soc. 2023.
10. Kojima T, Mizukami K, Tomita N*, et al.* Screening Tool for Older Persons' Appropriate Prescriptions for Japanese: Report of the Japan Geriatrics Society Working Group on "Guidelines for medical treatment and its safety in the elderly". Geriatrics & gerontology international. 2016;16(9):983-1001.
11. Holmes HM, Sachs GA, Shega JW*, et al.* Integrating palliative medicine into the care of persons with advanced dementia: identifying appropriate medication use. J Am Geriatr Soc. 2008;56(7):1306-11.
12. Lindsay J, Dooley M, Martin J*, et al.* The development and evaluation of an oncological palliative care deprescribing guideline: the 'OncPal deprescribing guideline'. Support Care Cancer. 2015;23(1):71-8.
13. Curtin D, Gallagher P, O'Mahony D. Deprescribing in older people approaching end-of-life: development and validation of STOPPFrail version 2. Age Ageing. 2021;50(2):465-71.
14. Morin L, Laroche M-L, Vetrano DL, Fastbom J, Johnell K. Adequate, questionable, and inadequate drug prescribing for older adults at the end of life: a European expert consensus. Eur J Clin Pharmacol. 2018;74(10):1333-42.
15. Malek Makan A, Lee MC, van Hein H, van Marum R. Barriers and enablers of elderly care specialists towards deprescribing practices in the nursing homes: a focus group study. BMC Health Serv Res. 2025;25(1):1466.
16. Harriman K, Howard L, McCracken R. Deprescribing medication for frail elderly patients in nursing homes: a survey of Vancouver family physicians. BC Med J. 2014;56(9):436-41.
17. Kool E, Cordemans K, Lepeleire JD. De Coördinerende en Raadgevende Arts in Woonzorgcentra – naar een nieuwe functieomschrijving binnen sterk interprofessioneel teamwerk. Crataegus v, Medica D, Leuven K, editors2021. 1-51 p.
18. De Vlaamse r. Besluit van de Vlaamse Regering tot wijziging van verschillende besluiten, wat betreft de invoering van infrastructuursubsidies voor woonzorgcentra en centra voor kortverblijf. 2017.
19. Evrard P, Damiaens A, Patey AM, Grimshaw JM, Spinewine A. Barriers and enablers towards benzodiazepine-receptor agonists deprescribing in nursing homes: A qualitative study of stakeholder groups. Exploratory Research in Clinical and Social Pharmacy. 2023;9:100258.
20. Fournier A, Anrys P, Beuscart J-B*, et al.* Use and Deprescribing of Potentially Inappropriate Medications in Frail Nursing Home Residents. Drugs Aging. 2020;37(12):917-24.
21. Hickman E, Almaqhawi A, Gillies C, Khunti K, Seidu S. Beliefs, practices, perceptions and motivations of healthcare professionals on medication deprescribing during end-of-life care: A systematic review. Prim Care Diabetes. 2024;18(3):249-56.
22. Visser AGR, de-Bruijn J, Spaetgens B*, et al.* Unlocking Deprescribing Potential in Nursing Homes: Insights from a Focus Group Study with Healthcare Professionals. Drugs Aging. 2024;41(3):261-70.
23. Boghossian TA, Rashid FJ, Thompson W*, et al.* Deprescribing versus continuation of chronic proton pump inhibitor use in adults. Cochrane Database Syst Rev. 2017(3).
24. Chaudhry M, Elahi M, Bukhari SHA*, et al.* Long-Term Proton Pump Inhibitor Use and the Risk of Kidney Disease, Dementia, and Fractures: A Systematic Review. Cureus. 2025;17(8):e90627.
25. Shahid MS, Ahmed N, Kamal Z*, et al.* A Systematic Review of Long-Term Use of Proton Pump Inhibitors (PPIs) in Older Adults on Polypharmacy: Do PPIs Deplete Nutrients? Cureus. 2025;17(8):e90888.
26. Wilsdon TD, Hendrix I, Thynne TRJ, Mangoni AA. Effectiveness of Interventions to Deprescribe Inappropriate Proton Pump Inhibitors in Older Adults. Drugs Aging. 2017;34(4):265-87.
27. Anlay DZ, Paque K, Van den Eynden B, Dilles T, Cohen J. International Deprescribing Guidelines Did Not Impact Actual Practice in Deprescribing of Potentially Inappropriate Medications for Nursing Home Residents: An Interrupted Time Series Analysis. Drugs Aging. 2025.
28. Eisinger-Mathason TSK, Leshin J, Lahoti V*, et al.* Data linkage multiplies research insights across diverse healthcare sectors. Communications Medicine. 2025;5(1):58.

29. De Schreye R. Population-level evaluation of the appropriateness of end-of-life care in Belgium. 2020.
30. Collingridge Moore D, Payne S, Keegan T*, et al.* Length of stay in long-term care facilities: a comparison of residents in six European countries. Results of the PACE cross-sectional study. BMJ Open. 2020;10(3):e033881.
31. InterRAI. Worldwide. Available from: https://interrai.org/applications/status-and-outcome-scales/ [Accessed 09 Jan 2026]. [
32. de Almeida Mello J, Wellens NI, Hermans K*, et al.* The Implementation of Integrated Health Information Systems - Research Studies from 7 Countries Involving the InterRAI Assessment System. Int J Integr Care. 2023;23(1):8.
33. Byrne M. Increasing the impact of behavior change intervention research: Is there a role for stakeholder engagement? Health Psychol. 2019;38(4):290-6.
34. Lavan AH, Gallagher P, Parsons C, O'Mahony D. STOPPFrail (Screening Tool of Older Persons Prescriptions in Frail adults with limited life expectancy): consensus validation. Age Ageing. 2017;46(4):600-7.
35. Paque K, De Schreye R, Elseviers M*, et al.* Discontinuation of medications at the end of life: A population study in Belgium, based on linked administrative databases. Br J Clin Pharmacol. 2019;85(4):827-37.
36. Hayes KN, Niznik JD, Gnjidic D*, et al.* Evaluation of real-world evidence to assess health outcomes related to deprescribing medications in older adults: an International Society for Pharmacoepidemiology-endorsed systematic review of methodology. Am J Epidemiol. 2025;194(8):2431-9.
37. Wastesson JW, Kamgang KS, Lundby C, Pottegård A. Studying Deprescribing Using Routinely Collected Healthcare Data: Old Challenges and New Opportunities. Basic Clin Pharmacol Toxicol. 2025;137(5):e70131.
38. Turner JP, Thompson W, Reeve E, Bell JS. Deprescribing proton pump inhibitors. Aust J Gen Pract. 2022;51(11):845-8.
39. Füssenich K, Boshuizen HC, Nielen MMJ, Buskens E, Feenstra TL. Mapping chronic disease prevalence based on medication use and socio-demographic variables: an application of LASSO on administrative data sources in healthcare in the Netherlands. BMC Public Health. 2021;21(1):1039.
40. Andrawes M, Andrawes W, Das A, Siau K. Proton Pump Inhibitors (PPIs)-An Evidence-Based Review of Indications, Efficacy, Harms, and Deprescribing. Medicina (Kaunas). 2025;61(9).
41. Gwee KA, Goh V, Lima G, Setia S. Coprescribing proton-pump inhibitors with nonsteroidal anti-inflammatory drugs: risks versus benefits. J Pain Res. 2018;11:361-74.
42. Kundu R, Shi X, Morrison J, Barrett J, Mukherjee B. A framework for understanding selection bias in real-world healthcare data. Journal of the Royal Statistical Society Series A: Statistics in Society. 2024;187(3):606-35.
43. Van Doren S, De Coninck D, Hermans K, Declercq A. Interrater reliability of the BelRAI Social Supplement in Flanders, Belgium: Simultaneous rating of community-dwelling adults with care needs during COVID-19. Front Psychol. 2022;Volume 13 - 2022.
44. Niehoff KM, Mecca MC, Fried TR. Medication appropriateness criteria for older adults: a narrative review of criteria and supporting studies. Ther Adv Drug Saf. 2019;10:2042098618815431.
45. Macq J, López-Toribio M, Spinewine A. How can policies impact the relational process of deprescription? A realist review protocol with an initial theory. Frontiers in Public Health. 2025;Volume 13 - 2025.
46. Gnjidic D, Johansson M, Meng DM*, et al.* Achieving sustainable healthcare through deprescribing. Cochrane Database Syst Rev. 2022;10(10):Ed000159.
47. Hung A, Wang J, Moriarty F*, et al.* Value assessment of deprescribing interventions: Suggestions for improvement. J Am Geriatr Soc. 2023;71(6):2023-7.
48. Ivanova I, Wauters M, Stichele RV*, et al.* Medication use in a cohort of newly admitted nursing home residents (Ageing@NH) in relation to evolving physical and mental health. Arch Gerontol Geriatr. 2018;75:202-8.
49. Heinrich CH, Hurley E, McCarthy S, McHugh S, Donovan MD. Barriers and enablers to deprescribing in long-term care facilities: a 'best-fit' framework synthesis of the qualitative evidence. Age Ageing. 2022;51(1).
50. Heinrich CH, McHugh S, McCarthy S, Donovan MD. Barriers and enablers to deprescribing in long-term care: A qualitative investigation into the opinions of healthcare professionals in Ireland. PLoS One. 2022;17(12):e0274552.
51. Johnstone KJR, Hilmer SN, Lo SY*, et al.* Reasons Behind Continuity of In-Hospital Deprescribing Post Discharge: A Qualitative Study. J Am Med Dir Assoc.
52. Rodrigues LP, de Oliveira Rezende AT, Delpino FM*, et al.* Association between multimorbidity and hospitalization in older adults: systematic review and meta-analysis. Age Ageing. 2022;51(7):afac155.
53. Reese TJ, Simmons SF, Vasilevskis EE*, et al.* Restarting Medications After Deprescribing in Adults Discharged From Hospital to Skilled Nursing. JAMA Network Open. 2026;9(6):e2617264-e.
54. Okeowo DA, Zaidi STR, Fylan B, Alldred DP. Barriers and facilitators of implementing proactive deprescribing within primary care: a systematic review. Int J Pharm Pract. 2023;31(2):126-52.
55. van Poelgeest EP, Seppala LJ, Lee JM*, et al.* Deprescribing practices, habits and attitudes of geriatricians and geriatricians-in-training across Europe: a large web-based survey. Eur Geriatr Med. 2022;13(6):1455-66.
56. Lundby C, Graabaek T, Ryg J*, et al.* Health care professionals' attitudes towards deprescribing in older patients with limited life expectancy: A systematic review. Br J Clin Pharmacol. 2019;85(5):868-92.
57. Alwidyan T, McCorry NK, Parsons C. Healthcare professionals' perspectives of deprescribing in older patients at the end of life in hospice care: a qualitative study using the Theoretical Domains Framework. Int J Pharm Pract. 2023;31(3):305-13.

58. Miranda R, Smets T, Van Den Noortgate N, Deliens L, Van den Block L. Higher Prevalence of Dementia but No Change in Total Comfort While Dying among Nursing Home Residents with Dementia between 2010 and 2015: Results from Two Retrospective Epidemiological Studies. Int J Environ Res Public Health. 2021;18(4).
59. Robinson M, Mokrzecki S, Mallett AJ. Attitudes and barriers towards deprescribing in older patients experiencing polypharmacy: a narrative review. npj Aging. 2024;10(1):6.
60. van Poelgeest E, Seppala L, Bahat G*, et al.* Optimizing pharmacotherapy and deprescribing strategies in older adults living with multimorbidity and polypharmacy: EuGMS SIG on pharmacology position paper. Eur Geriatr Med. 2023.
61. Rowe S, Pittman N, Balsom C, Druken R, Kelly DV. Beliefs and attitudes of residents, family members and healthcare professionals regarding deprescribing in long-term care: a qualitative study. Int J Clin Pharm. 2022;44(6):1370-9.
62. Chua S, Todd A, Reeve E*, et al.* Deprescribing interventions in older adults: An overview of systematic reviews. PLoS One. 2024;19(6):e0305215.
63. Bjerre LM, Farrell B, Hogel M*, et al.* Deprescribing antipsychotics for behavioural and psychological symptoms of dementia and insomnia: Evidence-based clinical practice guideline. Can Fam Physician. 2018;64(1):17-27.
64. Farrell B, Pottie K, Thompson W*, et al.* Deprescribing proton pump inhibitors. Can Fam Physician. 2017;63(5):354.
65. Hurley E, Dalton K, Byrne S, Foley T, Walsh E. Pharmacist-Led Deprescribing Using STOPPFrail for Frail Older Adults in Nursing Homes. J Am Med Dir Assoc. 2024;25(9):105122.
66. Curtin D, Jennings E, Daunt R*, et al.* Deprescribing in older people approaching end of life: a randomized controlled trial using STOPPFrail criteria. J Am Geriatr Soc. 2020;68(4):762-9.
67. Fournier J-P, Gaultier A, Riche V-P*, et al.* Deprescribing Intervention and Reduction of Proton Pump Inhibitor Use in Primary Care: A Cluster Randomized Clinical Trial. JAMA Internal Medicine. 2026.
68. Anlay DZ, Peremans L, Cohen J, Dilles T, Paque K. Deprescribing for nursing home residents with limited life expectancy: A qualitative study to identify barriers and enablers for healthcare professionals. Geriatric Nursing. 2025;62:1-11.
69. Anlay DZ, Peremans L, Cohen J, Dilles T, Paque K. Deprescribing for nursing home residents with limited life expectancy: A qualitative study to identify barriers and enablers for healthcare professionals. Geriatr Nurs. 2025;62(Pt B):1-11.
70. Okeowo DA, Zaidi STR, Fylan B, Alldred DP. Barriers and facilitators of implementing proactive deprescribing within primary care: a systematic review. Int J Pharm Pract. 2023;31(2):126-52.
71. Sawan M, Reeve E, Turner J*, et al.* A systems approach to identifying the challenges of implementing deprescribing in older adults across different health-care settings and countries: a narrative review. Expert Rev Clin Pharmacol. 2020;13(3):233-45.
72. Paque K. Deprescribing of medications at the end of life: Data of older adults living at home or in a nursing home, and advanced cancer patients receiving palliative care. 2019.
73. Visser AGR, de-Bruijn JBGP, Spaetgens B*, et al.* Unlocking Deprescribing Potential in Nursing Homes: Insights from a Focus Group Study with Healthcare Professionals. Drugs Aging. 2024;41(3):261-70.
74. Langford AV, Warriach I, McEvoy AM*, et al.* What do clinical practice guidelines say about deprescribing? A scoping review. BMJ Qual Saf. 2024.
75. Moriarty F, Pottie K, Dolovich L*, et al.* Deprescribing recommendations: An essential consideration for clinical guideline developers. Research in Social and Administrative Pharmacy. 2019;15(6):806-10.
76. Langford AV, Warriach I, McEvoy AM*, et al.* What do clinical practice guidelines say about deprescribing? A scoping review. BMJ Qual Saf. 2024;34(1):28-39.
77. Farmer C, Fenu E, O'Flynn N, Guthrie B. Clinical assessment and management of multimorbidity: summary of NICE guidance. BMJ. 2016;354:i4843.
78. Boyd CM, Darer J, Boult C*, et al.* Clinical Practice Guidelines and Quality of Care for Older Patients With Multiple Comorbid DiseasesImplications for Pay for Performance. JAMA. 2005;294(6):716-24.
79. Honinx E, van Dop N, Smets T*, et al.* Dying in long-term care facilities in Europe: the PACE epidemiological study of deceased residents in six countries. BMC Public Health. 2019;19(1):1199.
80. Morin L, Aubry R, Frova L*, et al.* Estimating the need for palliative care at the population level: a cross-national study in 12 countries. Palliat Med. 2017;31(6):526-36.
81. Yang J, Li H, Chen Y*, et al.* Quality and recommendations of guidelines for multimorbidity and polypharmacy in older adults: A systematic review. Ageing Research Reviews. 2026;117:103060.
82. Engels L, van den Akker M, Denig P*, et al.* Medication Management in Patients With Polypharmacy in Primary Care: A Scoping Review of Clinical Practice Guidelines. J Evid Based Med. 2025;18(1):e70015.
83. Thompson W, Reeve E. Deprescribing: Moving beyond barriers and facilitators. Research in Social and Administrative Pharmacy. 2022;18(3):2547-9.
84. Murray E, Treweek S, Pope C*, et al.* Normalisation process theory: a framework for developing, evaluating and implementing complex interventions. BMC Med. 2010;8(1):63.
85. Hansen CR, O'Mahony D, Kearney PM*, et al.* Identification of behaviour change techniques in deprescribing interventions: a systematic review and meta-analysis. Br J Clin Pharmacol. 2018;84(12):2716-28.
86. Thompson W, Hogel M, Li Y*, et al.* Effect of a Proton Pump Inhibitor Deprescribing Guideline on Drug Usage and Costs in Long-Term Care. J Am Med Dir Assoc. 2016;17(7):673.e1-4.
87. Mena S, Moullin JC, Schneider M, Niquille A. Implementation of interprofessional quality circles on deprescribing in Swiss nursing homes: an observational study. BMC Geriatr. 2023;23(1):620.

88. Mena S, Dubois J, Macé F*, et al.* Evaluating the implementation of a deprescribing intervention in Swiss nursing homes: An observational study using qualitative and quantitative methods. Exploratory Research in Clinical and Social Pharmacy. 2026;22:100713.
89. Anrys P, Strauven G, Boland B*, et al.* Collaborative approach to Optimise MEdication use for Older people in Nursing homes (COME-ON): study protocol of a cluster controlled trial. Implementation Science. 2016;11(1):35.
90. Wauters M, Elseviers M, Vander Stichele R*, et al.* Efficacy, feasibility and acceptability of the OptiMEDs tool for multidisciplinary medication review in nursing homes. Arch Gerontol Geriatr. 2021;95:104391.
91. Azermai M, Wauters M, De Meester D*, et al.* A quality improvement initiative on the use of psychotropic drugs in nursing homes in Flanders. Acta Clin Belg. 2017;72(3):163-71.
92. Belgisch Centrum voor Farmacotherapeutische Informatie (BCFI). Goed en veilig gebruik van geneesmiddelen: deprescribing; [cited 2025 Jul 14]. Available from: https://www.bcfi.be/nl/chapters/1?frag=9991233&matches=deprescribing [
93. Deprescrire. Deprescribing resources. [cited 2026 Apr 19]. Available from: https://www.deprescrire.be/ [
94. Damiaens A, Frisson A, Foulon V. Process Optimization Of the Medicines' pAthway in nursing Homes. https://www.isrctn.com/ISRCTN17231220 2023 [
95. (FAMHP); FAfMaHP. Flash Vig-news: the benzodiazepine withdrawal programme now has a permanent place in pharmaceutical care. 09 Jul 2025. Available from: https://www.famhp.be/en/news/flash_vig_news_the_benzodiazepine_withdrawal_programme_now_has_a_permanent_place_in. Accessed 29 Oct 2025. [
96. (RIZIV) Rvz-ei. Nieuwe indicatoren: doelmatig voorschrijven van protonpompinhibitoren bij overtollig maagzuur [Internet]. 16 Dec 2024. Available from: https://www.riziv.fgov.be/nl/pers/nieuwe-indicatoren-doelmatig-voorschrijven-van-protonpompinhibitoren-bij-overtollig-maagzuur. Accessed 2025 Nov 18. [
97. James Shaw ALMJPTDMGJLSZBDG, Cara T. Policies for Deprescribing: An International Scan of Intended and Unintended Outcomes of Limiting Sedative-Hypnotic Use in Community-Dwelling Older Adults. Healthcare Policy. 2019;14(4):39-51.
98. Jansen K, Schaufel MA, Ruths S. Drug treatment at the end of life: an epidemiologic study in nursing homes. Scand J Prim Health Care. 2014;32(4):187-92.
99. Paque K, Elseviers M, Vander Stichele R*, et al.* Balancing medication use in nursing home residents with life-limiting disease. Eur J Clin Pharmacol. 2019;75:969-77.
100. World Health Organization. Web Annex A. World Health Organization Model List of Essential Medicines – 23rd List, 2023. Geneva: World Health Organization; 2023. Contract No.: WHO/MHP/HPS/EML/2023.02.
101. Todd A, Husband A, Andrew I*, et al.* Inappropriate prescribing of preventative medication in patients with life-limiting illness: a systematic review. BMJ supportive & palliative care. 2017;7(2):113-21.
102. Wabe N, Urwin R, Meulenbroeks I*, et al.* Over- and Underuse of Proton Pump Inhibitors in Nursing Homes: A Multisite Longitudinal Cohort Study. J Am Med Dir Assoc. 2025;26(2):105393.
103. Van der Meer HG, Taxis K, Pont LG. Changes in prescribing symptomatic and preventive medications in the last year of life in older nursing home residents. Front Pharmacol. 2018;8:990.
104. Dijk MMT, A.M. Pouw CK, Hertogh CMPM*, et al.* Medication Appropriateness for Older Nursing Home Patients With a Limited Life Expectancy: From STOPP/START Version 2 to the ReNeWAL Criteria. J Am Med Dir Assoc. 2024:105143.
105. Morin L, Wastesson JW, Laroche M-L, Fastbom J, Johnell K. How many older adults receive drugs of questionable clinical benefit near the end of life? A cohort study. Palliat Med. 2019;33(8):1080-90.
106. Malek Makan A, van Hout H, Onder G*, et al.* Prevalence of potentially inappropriate medications according to STOPP-Frail criteria in nursing home residents, the SHELTER study. BMC Geriatr. 2024;24(1):882.
107. Wouters H, Scheper J, Koning H*, et al.* Discontinuing Inappropriate Medication Use in Nursing Home Residents: A Cluster Randomized Controlled Trial. Ann Intern Med. 2017;167(9):609-17.
108. Lenander C, Bondesson Å, Viberg N, Beckman A, Midlöv P. Effects of medication reviews on use of potentially inappropriate medications in elderly patients; a cross-sectional study in Swedish primary care. BMC Health Serv Res. 2018;18(1):616.
109. Anderssen-Nordahl E, Fernández-Liz E, Sabaté Gallego M*, et al.* The impact of a multidisciplinary team intervention on medication prescription in nursing homes in Catalonia. Front Pharmacol. 2024;15:1445141.
110. Marin H, Mayo P, Dersch-Mills D*, et al.* The effect of palliative care consults on deprescribing in palliative cancer patients. J Clin Oncol. 2018;36(34_suppl):92-.
111. Suhrie EM, Hanlon JT, Jaffe EJ*, et al.* Impact of a geriatric nursing home palliative care service on unnecessary medication prescribing. Am J Geriatr Pharmacother. 2009;7(1):20-5.
112. Ten Koppel M, Onwuteaka-Philipsen BD, Van den Block L*, et al.* Palliative care provision in long-term care facilities differs across Europe: Results of a cross-sectional study in six European countries (PACE). Palliat Med. 2019;33(9):1176-88.
113. Allen E, Stanek J, Lundorf J. Early Palliative Care Initiation: Role of the Primary Care Clinician. The Journal for Nurse Practitioners. 2022;18(5):493-5.
114. Mulla RT, Hirdes JP, McAiney C, Heckman G. Factors Associated with Mood Transitions among Older Canadian Long-Term Care Residents: A Multistate Transition Model. J Am Med Dir Assoc. 2025;26(7):105612.
115. Morris JN, Howard EP, Schachter E*, et al.* Cognitive Change Among Nursing Home Residents: CogRisk-NH Scale Development to Predict Decline. J Am Med Dir Assoc. 2023;24(9):1405-11.

116. Egbujie BA, Turcotte LA, Mulla RT, Heckman GA, Hirdes JP. Patterns of Transient and Terminal Transitions in Activities of Daily Living Performance Levels among Long-Term Care Residents: A Multistate Markov's Model Analysis of Population-Based Longitudinal Data in Canada. J Am Med Dir Assoc. 2025;26(6):105565.
117. Shrestha R, Shaw E, Mullen L*, et al.* Outcomes of deprescribing for people with life-limiting conditions: A systematic review. Palliat Med. 2026;0(0):02692163261416281.
118. Vetrano DL, Villani ER, Grande G*, et al.* Association of Polypharmacy With 1-Year Trajectories of Cognitive and Physical Function in Nursing Home Residents: Results From a Multicenter European Study. J Am Med Dir Assoc. 2018;19(8):710-3.
119. NIHDI. Infospot – The TOP 25 active ingredients in outpatient healthcare expenditure in 2023. Brussels: RIZIV; 26 Nov 2024. Available from: https://www.riziv.fgov.be/SiteCollectionDocuments/infospot_top25_medicaments_2023_eng.pdf. Accessed 2025 Nov 18
120. Roberts G, Pegoli M, Grzeskowiak L*, et al.* Hospital admission as a deprescribing triage point for patients discharged to Residential Aged Care Facilities. Age Ageing. 2021;50(5):1600-6.
121. Elli C, Novella A, Pasina L, Investigators R. Proton pump inhibitors and 1-year risk of adverse outcomes after discharge from internal medicine wards: an observational study in the REPOSI cohort. Intern Emerg Med. 2025;20(4):1119-26.
122. Palmowski L, von Busch A, Unterberg M*, et al.* Timely Cessation of Proton Pump Inhibitors in Critically Ill Patients Impacts Morbidity and Mortality: A Propensity Score-Matched Cohort Study. Crit Care Med. 2024;52(2):190-9.
123. Aubert CE, Blum MR, Gastens V*, et al.* Prescribing, deprescribing and potential adverse effects of proton pump inhibitors in older patients with multimorbidity: an observational study. CMAJ Open. 2023;11(1):E170-e8.
124. Veronese N, Gallo U, Boccardi V*, et al.* Efficacy of deprescribing on health outcomes: An umbrella review of systematic reviews with meta-analysis of randomized controlled trials. Ageing Research Reviews. 2024;95:102237.
125. O'Donnell LK, Ibrahim K. Polypharmacy and deprescribing: challenging the old and embracing the new. BMC Geriatr. 2022;22(1):734.
126. Weatherall CD, Hansen AT, Nicholson S. The effect of assigning dedicated general practitioners to nursing homes. Health Serv Res. 2019;54(3):547-54.
127. Van Leeuwen E, Anthierens S, van Driel ML*, et al.* General practitioners' perspectives on discontinuation of long-term antidepressants in nursing homes. Eur J Gen Pract. 2022;28(1):23-31.
128. Aasbrenn M, Jónsdóttir AB, Lundgren E*, et al.* Towards a typology of medical care in European long-term care homes. Eur Geriatr Med. 2026.
129. Irving G, Neves AL, Dambha-Miller H*, et al.* International variations in primary care physician consultation time: a systematic review of 67 countries. BMJ Open. 2017;7(10):e017902.
130. Maetens A, De Schreye R, Faes K*, et al.* Using linked administrative and disease-specific databases to study end-of-life care on a population level. BMC Palliat Care. 2016;15:1-10.
131. Mark JF Helbert RM, Filip Veldeman, Inneke De Laet, Ilse Dossche, and Sofie De Broe,. An urgent call for action: tackling challenges with Primary Health Data as prerequisite for EHDS implementation. Health Data Agency. Available from: https://www.hda.belgium.be/en/news. Accessed 2026 Apr 27. 2025.
132. U.S. Food and Drug Administration. FDA use of real-world evidence in regulatory decision-making. [cited 2026 May 1]; Available from: https://www.fda.gov/science-research/real-world-evidence/fda-use-real-world-evidence-regulatory-decision-making [
133. Das S, Shendage V, Maiti T*, et al.* Deprescribing preventive medications in older adults with advanced frailty, dementia, or limited life expectancy: a systematic review and meta-analysis. BMC Geriatr. 2026.
134. Bonnet F, Bénard A, Poulizac P*, et al.* Discontinuing statins or not in the elderly? Study protocol for a randomized controlled trial. Trials. 2020;21(1):342.
135. Moriarty F, Thompson W, Boland F. Methods for evaluating the benefit and harms of deprescribing in observational research using routinely collected data. Res Social Adm Pharm. 2022;18(2):2269-75.
136. Holtrop JS, Estabrooks PA, Gaglio B*, et al.* Understanding and applying the RE-AIM framework: Clarifications and resources. Journal of Clinical and Translational Science. 2021;5(1):e126.
137. Glasgow RE, Vogt TM, Boles SM. Evaluating the public health impact of health promotion interventions: the RE-AIM framework. Am J Public Health. 1999;89(9):1322-7.
138. McCreight MS, Rabin BA, Glasgow RE*, et al.* Using the Practical, Robust Implementation and Sustainability Model (PRISM) to qualitatively assess multilevel contextual factors to help plan, implement, evaluate, and disseminate health services programs. Transl Behav Med. 2019;9(6):1002-11.
139. Feldstein AC, Glasgow RE. A Practical, Robust Implementation and Sustainability Model (PRISM) for Integrating Research Findings into Practice. The Joint Commission Journal on Quality and Patient Safety. 2008;34(4):228-43.
140. Damschroder LJ, Reardon CM, Widerquist MAO, Lowery J. The updated Consolidated Framework for Implementation Research based on user feedback. Implementation Science. 2022;17(1):75.
141. Damschroder LJ, Reardon CM, Opra Widerquist MA, Lowery J. Conceptualizing outcomes for use with the Consolidated Framework for Implementation Research (CFIR): the CFIR Outcomes Addendum. Implementation Science. 2022;17(1):7.
142. O'Donovan B, Kirke C, Pate M*, et al.* Mapping the Theoretical Domain Framework to the Consolidated Framework for Implementation Research: do multiple frameworks add value? Implementation Science Communications. 2023;4(1):100.

143. Okafor CE, Keramat SA, Comans T*, et al.* Cost-Consequence Analysis of Deprescribing to Optimize Health Outcomes for Frail Older People: A Within-Trial Analysis. J Am Med Dir Assoc. 2024;25(3):539-44.e2.
144. Zhang Y, Chen Z, Chen X, Tian F. Economic Evaluation of Deprescribing in Older Adults: A Systematic Review. Value Health. 2026;29(3):521-9.
145. Xia Q, Kularatna M, Virdun C*, et al.* Preferences for Palliative and End-of-Life Care: A Systematic Review of Discrete Choice Experiments. Value Health. 2023;26(12):1795-809.
146. Raghunandan R, Howard K, Ilomaki J*, et al.* Preferences for deprescribing antihypertensive medications amongst clinicians, carers and people living with dementia: a discrete choice experiment. Age Ageing. 2023;52(8).
147. Reeve E, Shakib S, Hendrix I, Roberts MS, Wiese MD. Review of deprescribing processes and development of an evidence-based, patient-centred deprescribing process. Br J Clin Pharmacol. 2014;78(4):738-47.
148. Thorpe C, Niznik J, Li A. Deprescribing research in nursing home residents using routinely collected healthcare data: a conceptual framework. BMC Geriatr. 2023;23(1):469.
149. Momand B, Sun W, Abbass-Dick J, Dubrowski A, Papaconstantinou E. Communication and Medication-Related Deprescribing for Healthcare Professionals: A Rapid Review of the Literature. Worldviews Evid Based Nurs. 2026;23(2):e70138.
150. Radcliffe E, Servin R, Cox N*, et al.* What makes a multidisciplinary medication review and deprescribing intervention for older people work well in primary care? A realist review and synthesis. BMC Geriatr. 2023;23(1):591.
151. Weir KR, Tien A, Vordenberg SE. Communication and health literacy across the medication lifecycle: Implications for deprescribing and polypharmacy. Health Literacy and Communication Open. 2026;4(1):2651614.
152. S Gerkens, M Lefèvre, N Bouckaert, M Levy, C Maertens de Noordhout, C Obyn, C Devos, A Scohy, A Vlayen, H Yaras, C Janssens, P Meeus. Performance of the Belgian health system: Report 2024. Health Services Research (HSR) Brussels: Belgian Health Care Knowledge Centre (KCE). 2025. KCE Reports 376C. D/2025/10.273/44. https://www.kce.fgov.be/sites/default/files/2024-01/KCE376C_HSPA2024__Report.pdf.
153. World Health Organization. Defined daily dose (DDD). Geneva: WHO; [cited 2026 May 17]. Available from: https://www.who.int/tools/atc-ddd-toolkit/about-ddd [
154. Piekarska K, Bednarski P, Politynska B*, et al.* The Impact of Implementing Indicators of Quality of Oncological Care on Improving Patient Outcomes: A Cross-Sectional Review of Experiences from Countries Using Indicators in the Quality Assessment Process. Cancers (Basel). 2025;17(8):1362.
155. Vlaams Instituut voor Kwaliteit van Zorg (VIKZ). Over het VIKZ. Available from: https://www.zorgkwaliteit.be/over-het-vikz [cited 2026 Aug 12] [
156. Foley RA, Hurard LL, Cateau D*, et al.* Physicians', Nurses' and Pharmacists' Perceptions of Determinants to Deprescribing in Nursing Homes Considering Three Levels of Action: A Qualitative Study. Pharmacy (Basel). 2020;8(1).
157. Evrard P. Enhancing the uptake of benzodiazepine deprescribing in nursing homes: insights from behaviour-change theories and implementation science: UCL-Université Catholique de Louvain; 2024.
158. Barbuiani G, Terzoni S, Caruso R*, et al.* Nurses' role in deprescribing for older adults: A scoping review. Int J Nurs Stud. 2026;174:105274.
159. Wright DJ, Scott S, Buck J, Bhattacharya D. Role of nurses in supporting proactive deprescribing. Nurs Stand. 2019;34(3):44-50.
160. Hart L, Berrou I. 463 Understanding the role of nurses in deprescribing medicines for older people: A systematic review. Int J Pharm Pract. 2023;31(Supplement_1):i18-i9.
161. de Wit HAJM, Winkens B, Mestres Gonzalvo C*, et al.* Clinical practice of medication reviews in institutional care settings for older people in the Netherlands: an explorative survey. European Journal of Hospital Pharmacy. 2015;22(4):212-8.
162. Farrell B, Raman-Wilms L, Sadowski CA*, et al.* A Proposed Curricular Framework for an Interprofessional Approach to Deprescribing. Medical Science Educator. 2023;33(2):551-67.
163. Federatie Medisch Specialisten. Minderen en stoppen van medicatie. Richtlijnendatabase; 2020 Nov 30 [cited 2026 Jul 13]. Available from: https://richtlijnendatabase.nl/richtlijn/polyfarmacie_bij_ouderen/minderen_en_stoppen_van_medicatie.html
164. Abou J, Elders PJM, Huijts D, van Marum R, Hugtenburg J. Pharmacist-led deprescribing of cardiovascular and diabetes medication within a clinical medication review: the LeMON study (Less Medicines in Older Patients in the Netherlands), a cluster randomized controlled trial. Int J Clin Pharm. 2025;47(3):717-25.
165. Abou J, Elders PJM, van Marum R, Hugtenburg J. Evaluation of a Pharmacist-Led Intervention Focused on the Deprescribing of Cardiovascular and Antidiabetic Medication in Older Patients With Polypharmacy: Patients' and Pharmacists' Experiences. Basic Clin Pharmacol Toxicol. 2026;138(6):e70241.
166. Elsten EE, Pot IE, Geijteman EC*, et al.* Recommendations for Deprescribing of Medication in the Last Phase of Life: An International Delphi Study. J Pain Symptom Manage. 2024;68(5):443-55. e2.
167. Borre LVd, Cavillot L, Pauw RD, Devleesschauwer B. Unraveling Social Health Inequalities during COVID-19 in Belgium: The Vital Role of Data Linkages. The European Journal of Public Health. 2024;34.
168. Berete F, Demarest S, Charafeddine R*, et al.* Linking health survey data with health insurance data: methodology, challenges, opportunities and recommendations for public health research. An experience from the HISlink project in Belgium. Arch Public Health. 2023;81(1):198.

169. European Parliament and Council. Regulation (EU) 2025/327 of the European Parliament and of the Council of 11 February 2025 on the European Health Data Space and amending Directive 2011/24/EU and Regulation (EU) 2024/2847 (Text with EEA relevance). Official Journal of the European Union (OJ L) [Internet]. 5 March 2025; 2025/327:1–XX. ISSN 1977-0677. Available from: http://data.europa.eu/eli/reg/2025/327/oj. 2025.
170. Health Data Agency. Data linkages in Belgian (administrative) real-world data: the missing link. Health Data Talk Series; Available from: https://academy.hda.belgium.be/pluginfile.php/1001/mod_resource/content/1/artikel%208_BMT-HDTS%20-%20Data%20linkages%20in%20Belgian.pdf.

SUPPLEMENTARY MATERIALS

Chapter 2 supplementary materials

Supplementary file 2.1: Search strategy for each database

Medline and PubMed-not-Medline via Ovid

- Date searched: 7th July 2022
- No filters were used.

Concept 1: (tools/guidelines/criteria for the appraisal of the) appropriateness of medications

exp Potentially Inappropriate Medication List/ OR exp Inappropriate Prescribing/ OR exp Deprescriptions/ OR (Inappropriate Medication OR PIM OR PIMs OR medication appropriateness OR appropriate medication* OR Inappropriate Prescri* OR Deprescri* OR de prescri*).ti,ab,kf. OR ((benefi* OR indicat* OR questionable) adj3 (medication* OR drug*)).ti,ab,kf.

Concept 2: study design: systematic review

Systematic review.pt. OR meta analysis.pt. OR (systematic review* OR systematic literature review* OR meta analys* OR metaanalys* OR Cochrane review*).ab,ti,kf. OR Cochrane Database Syst Rev.ja.

Concept 3: Guidelines
Guideline.pt. OR exp Guidelines as Topic/ OR guideline*.ti,ab,kf.

Search combination: 1 AND (2 OR 3)

Embase (via Embase.com)

- Date searched: 7th July 2022
- No filters were used.

Concept 1: (tools/guidelines/criteria for the appraisal of the) appropriateness of medications

'inappropriate prescribing'/exp OR 'inappropriate medication*':ti,ab,kw OR 'inappropriate prescri*':ti,ab,kw OR 'PIM':ti,ab,kw OR 'PIMs':ti,ab,kw OR 'deprescription'/exp OR 'deprescri*':ti,ab,kw OR 'de prescri*':ti,ab,kw OR 'deprescribing'/exp OR 'medication appropriateness':ti,ab,kw OR 'appropriate medication*':ti,ab,kw OR ((indicat* OR questionable OR benefi*) NEAR/3 (medication* OR drug*)):ti,ab,kw
NOT 'conference abstract':ti

Concept 2: study design: systematic review
'systematic review'/exp OR 'systematic review':ti,ab,kw OR 'systematic literature review*':ti,ab,kw OR 'meta analys*':ti,ab,kw OR 'meta analysis'/exp OR 'metaanalys*':ti,ab,kw OR 'Cochrane review*':ti,ab,kw

Concept 3: Guidelines
'guideline'/exp OR 'practice guideline'/de OR 'precribing guideline'/exp OR guideline*:ti,ab,kw

Search combination: 1 AND (2 OR 3)

Web of Science (All databases: specifically: WoS Core Collection, Biosis Citation Index, Chinese Science Citation Database, Current Contents Connect, Data Citation Index, Derwent Innovations

Index, KCI-Korean Journal Database, Medline, Russian Science Citation Index and SciELO Citation Index)

- Date searched: 7th July 2022
- No filters were used.

Concept 1: (tools/guidelines/criteria for the appraisal of the) appropriateness of medications

TS=("inappropriate medication*" OR "inappropriate prescri*" OR "PIM" OR "PIMs" OR "deprescri*" OR "de prescri*" OR "medication appropriateness" OR "appropriate medication*" OR ((indicat* OR questionable OR benefi*) NEAR/3 (medication* OR drug*)))

Concept 2: study design: systematic review
TS=("systematic review" OR "systematic literature review*" OR "meta analys*" OR "metaanalys*" OR "Cochrane review*")

Concept 3: Guidelines
TS=(guideline*)

Search combination: 1 AND (2 OR 3)

Cochrane database for Systematic review (CDSR, via Cochrane library)

- Date searched: 7th July 2022
- No filters were used.

Concept 1: (tools/guidelines/criteria for the appraisal of the) appropriateness of medications

#1: ([mh "Potentially Inappropriate Medication List"] OR [mh "Inappropriate Prescribing"] OR [mh "Deprescriptions"])
#2: ((Inappropriate NEXT Medication*) OR PIM OR PIMs OR "medication appropriateness" OR (appropriate NEXT medication*) OR (Inappropriate NEXT Prescri*) OR Deprescri* OR (de NEXT prescri*)):ti,ab,kw
#3: ((benefi* OR indicat* OR questionable) NEAR/3 (medication* OR drug*)):ti,ab,kw
#4: #1 OR #2 OR #3

CINAHL (via EBSCO)

- Date searched: 7th July 2022
- No filters were used.

Concept 1: (tools/guidelines/criteria for the appraisal of the) appropriateness of medications

(MH "Inappropriate Prescribing") OR TI("inappropriate medication*" OR "inappropriate prescri*" OR "PIM" OR "PIMs" OR "deprescri*" OR "de prescri*" OR "medication appropriateness" OR "appropriate medication*" OR ((indicat* OR questionable OR benefi*) N3 (medication* OR drug*))) OR AB("inappropriate medication*" OR "inappropriate prescri*" OR "PIM" OR "PIMs" OR "deprescri*" OR "de prescri*" OR "medication appropriateness" OR "appropriate medication*" OR ((indicat* OR questionable OR benefi*) N3 (medication* OR drug*)))
Concept 2: study design: systematic review
(MH "Systematic Review") OR (MH "Cochrane Library") OR (MH "Meta Analysis")

OR TI(“systematic review” OR “systematic literature review*” OR “meta analys*” OR “metaanalys*” OR “Cochrane review*”) OR AB(“systematic review” OR “systematic literature review*” OR “meta analys*” OR “metaanalys*” OR “Cochrane review*”)

Concept 3: Guidelines
(MH "Practice Guidelines") OR PT ("practice guidelines")
OR TI ("guideline*") OR
AB ("guideline*")

Search combination: 1 AND (2 OR 3)

Guideline database

Guidelines international network (G-I-N)- https://guidelines.ebmportal.com/
Date searched: 7th July 2022
No filters were used.

The following terms searched separately:
1. Deprescribing
2. Inappropriate medication
3. Inappropriate medications
4. Inappropriate prescribing

Scottish Intercollegiate Guidelines Network (SIGN)- https://www.sign.ac.uk/our-guidelines/
Date searched: 7th July 2022
No filters were used.

The following terms searched separately:
1. Deprescribing
2. Inappropriate medication
3. Inappropriate medications
4. Inappropriate prescribing

Guideline centeral- https://www.guidelinecentral.com/guidelines/
Date searched: 7th July 2022
No filters were used.

The following terms searched separately:
1. Deprescribing
2. Inappropriate medication
3. Inappropriate medications
4. Inappropriate prescribing

Trip Database- https://www.tripdatabase.com/Home
Date searched: 7th July 2022
No filters were used.

The following terms were used with “OR” Boolean combination:

“Deprescribing” OR “Inappropriate medication” OR “Inappropriate medications” OR “Inappropriate prescribing”

Richtlijnendatabase (Guideline database dutch) - https://richtlijnendatabase.nl/

Date searched 7th July 2022
No filters were used.

The following terms searched separately:

1. Deprescribing
2. Inappropriate medication
3. Inappropriate medications
4. Inappropriate prescribing

Supplementary file 2.2–2.5: contain very large datasets, including extensive medication lists across multiple Excel sheets, which are difficult to include within the thesis. Please scan the QR code or follow the provided links to access these files.
(https://zenodo.org/records/14809497 or https://bpspubs.onlinelibrary.wiley.com/doi/10.1111/bcp.15906)

Chapter 3 supplementary materials

Supplementary file 3.1A: Data managing agencies, associated datasets, and linked variables

Data managing agency	**Data Sets**	**Key variables included in our analysis /codes used to define our outcome or predictors**
1.IMA-AIM: InterMutualistisch Agentschap	11. Socio-demographic database: All individuals with healthcare insurance.	• Age • Sex • Care region • Year and months of death
	12. National healthcare claims data: All reimbursed healthcare use data from 7 healthcare insurers.	• ATC_PROD_L (medications dispensed at hospital pharmacy) • SS00020 (health care service utilization , nomencluture code): forexample identify emergency admission to the hospital • SS00015: Start date of provision (E;g medication dispension date, admission to emergency) • INSTITUTION_SITE_CAT: Types of nursing home
	13. Katz-scale database: Evaluations of independence in activities of daily living for patients in outpatient nursing care or staying in nursing homes.	• KZ0040 (Forfait): category based on physcical and psychic dependency
	14. Pharmanet database: All reimbursed medication data dispensed in community pharmacies.	• ATC_PROD_L (medications dispensed at community pharmacy) • Combined with medications dispensed at hospital pharmacy used to define number of medications, and the outcome trend for each of the selected medications
	15. Hospitalization database: All hospital admissions.	• Hospital of admission: Whether or not hospitalized • Service of admission/discharge: help to define ICU admission
2. Statistics of Belgium	1. Death certificate database: Causes and place of death.	• Age at the time of death • Underlying cause of death • Contributory/indirect cause of death • Place of death
	2. Demographic and Census database	• Highest attained education level
	3. Fiscal database: including net taxable income.	• Net taxable income and related years

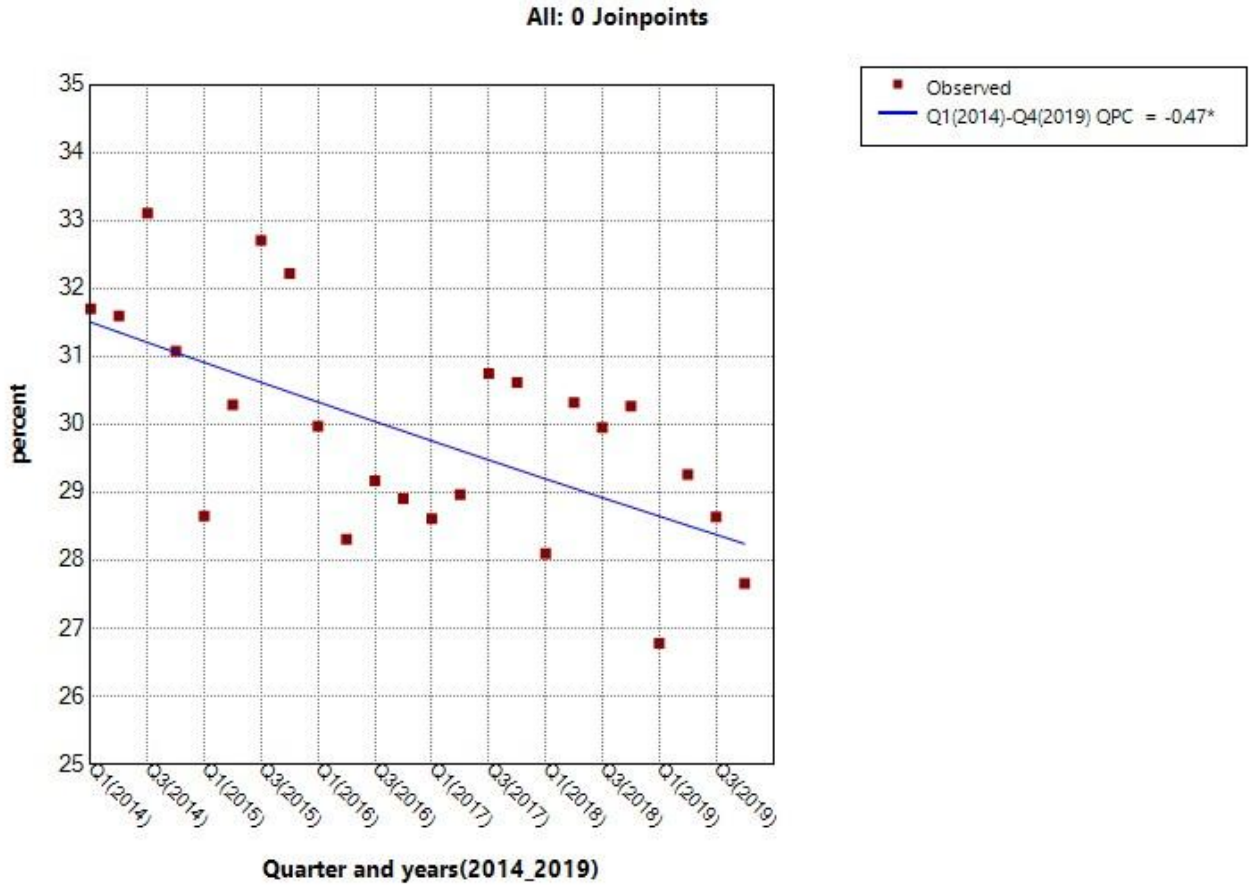
Supplementary file 3.1B: Variable descriptions, nomenclature, and algorithms.

Variable	Dataset	Source of variable	Codes in SAS (nomenclature and algorithms)
Nursing home: RVT	IMA_health claim data	institution_site_cat	750, 751, 752, 753
Nursing home:ROB	IMA_health claim data	institution_site_cat	730, 731, 732, 734, 735, 737, 739, 740, 741, 743, 744, 745, 749, 760, 761, 762, 764, 765
Nursing home: RVT	IMA_Pharmanet	INSTITUTION_CAT	750, 751, 752, 753
Nursing home:ROB	IMA_Pharmanet	INSTITUTION_CAT	730, 731, 732, 735, 737, 739, 740, 741, 743, 744, 745, 749, 760, 761, 762, 765
Sudden/accidental death	Statistics of Belgium	Underlying cause of death by ICD-10	Select the ICD-10 code starting with 'S%', 'T%', 'V%', 'W%', 'X%', 'Y%'
Trajectory of illness (amenable to pallative cares)	Statistics of Belgium	Underlying cause of death (CD_UCOD), Associated cause of death (CD_COD_ASS), Immediate causes of death (CD_COD_IMDT) and Intermediate cause of death (CD_COD_INT)	Neoplasms and hematological malignancies: C00-C26, C30-C34, C37-C41, C43-C58, C60-C85, C88, C90-C97, D00-D09, D32, D33, D37-D48
			Organ failure (trajectory of long-term limitations with intermittent acute episodes): E10-E14, G59.0, G63.2, H36.0, M14.2, N08.3, E70-E72, E75-E77, E84-E85 A520-A523, A527, A810, A812, B15-B19, B20-B24 D60, D61, D69, D70, D752, D758, D86 I231-I233, I238, I25, I50, I60-I64, I67, I688, I69, G46, I65, I66, I680-I682, I27, I42, I43, I51, I520, I70, I73, I74, I792, I970, I971, I978, I980, I981, I988 J40-J44, J47, J60-J62, J66, J701, J80, J841, J951-J953, J96, J980-J984, R060, R062-R065, R068 K70-K77, K44, K50, K51, K55, K56, K85, K86, K871, K90, L305, L40-L42, L44, L93, L945 M360, M361, M05, M06, M13, M15, M21, M30-M35, M40-M43, M45-M51, M53, M54, M638, M80, M81, M820, M821, M843, M844, M86-M88, M907,M961 N02-N05, N11, N12, N136, N160, N18, N19, N25, N312, N318, N319, N82, Q01-Q06, Q078, Q079, Q20-Q28, Q31, Q33, Q40- Q45, Q60-Q68, Q714, Q75-Q79, Q850, Q86-87, Q89-Q93, Q95-Q97, Q99
			Prolonged dwindling (trajectory of progressive loss of physical and cognitive capacities): G30-G32, F00, F01, F02, F03, F05, F06, R54, G20-G23, G35-G37, G10, G12, G70-G73, G03-G05, G07, G478, G518, G551, G608, G80-G83, G90-G99
Dementia case	Statistics of Belgium	Underlying cause of death (CD_UCOD), Associated cause of death (CD_COD_ASS), Immediate causes of death (CD_COD_IMDT) and Intermediate cause of death (CD_COD_INT)	Select the ICD-10 code starting with 'F00%', 'F01%', 'F02%', 'F03%', 'G30%'
Cancer case	Statistics of Belgium	Underlying cause of death (CD_UCOD), Associated cause of death (CD_COD_ASS), Immediate causes of death (CD_COD_IMDT) and Intermediate cause of death (CD_COD_INT)	Select the ICD-10 code starting with 'C%', 'D0%', 'D1%', 'D2%', 'D3%', 'D4%'

Hospitalization	IMA-hospitalization	stay_cat	'ADM', 'JF', 'SP'
ICU admission	IMA-hospitalization	serv_adm serv_dis	serv_adm=490 or serv_dis=490
Emergency admission	IMA_health claim data	**nomenclature codes (SS00020)**	588151,590122, 590144, 590166,590181, 590225,590310, 590435, 590446, 590472, 590516,590531,590553, 590575, 590590,590612, 590634, 590656, 590671, 590693,590715, 590730, 590752,590774, 590796, 590811,590833,590855, 590870, 590892, 590914,590951, 590973,590995
Number of chronic medication	IMA_health claim data IMA_pharmanet	ATC_PROD_L SS00015_i	Number of medications prescribed at least 2 times between 4-12 months prior to death

Supplementary file 3.2A: Joinpoint figure and results for deprescribing of at least one PIMs
Average Quarterly percentage change (joinpoint analysis)

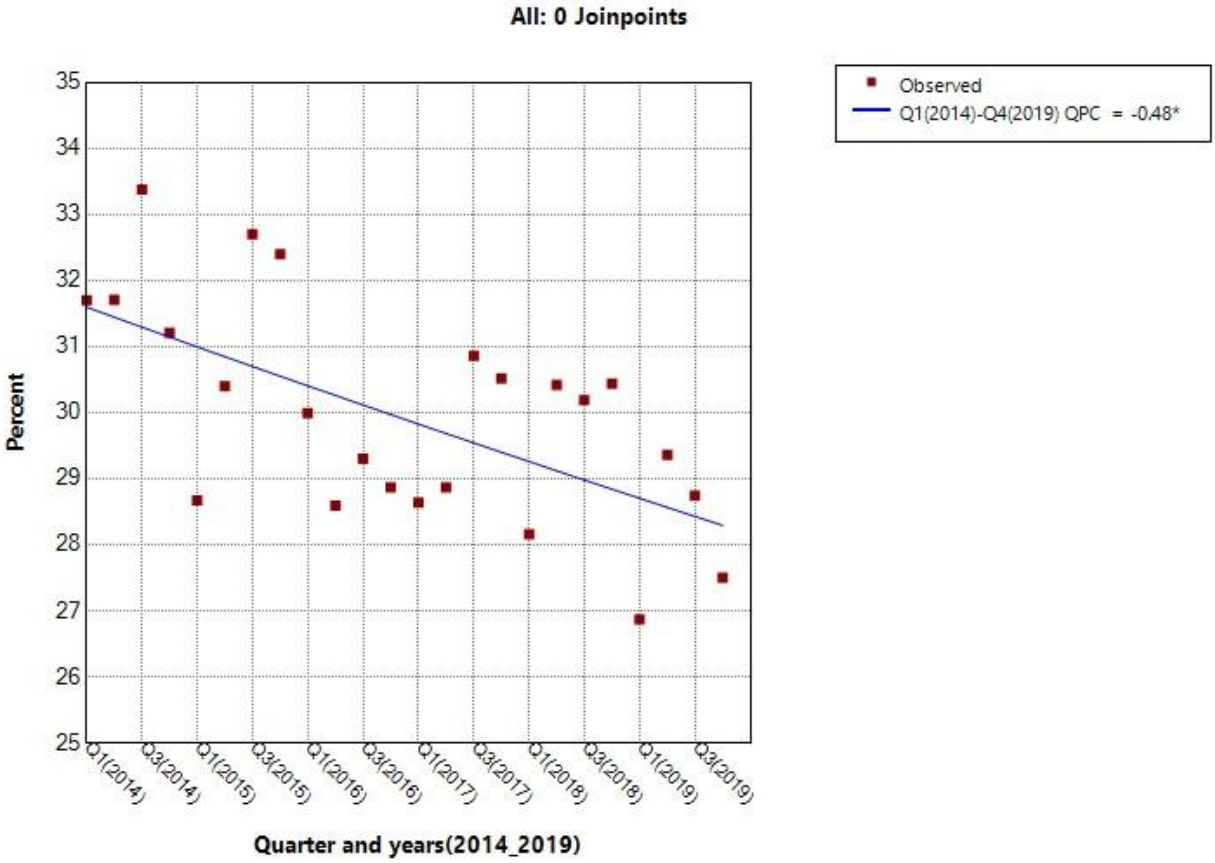
From the first quarter of 2014 to the fourth quarter of 2019, the prevalence of deprescribing at least one potentially inappropriate medication decreased from 31.7% to 27.66%. The analysis showed 0 joinpoints, indicating a consistent linear trend with no interruptions or statistically significant points in time where the rate of change in deprescribing prevalence shifted. The average quarterly percentage change (AQPC) was -0.47% (CI: -0.85% to -0.10%), with a statistically significant p-value of 0.01.



* Indicates that the Quarterly Percent Change (QPC) is significantly different from zero at the alpha = 0.05 level.
-- Test Statistic and P-Value not available for the Empirical Quantile method.
Final Selected Model: 0 Joinpoints.

Supplementary File 3.2B: Sensitivity analysis of at least one PIM deprescribing (average quarterly percentage change; joinpoint analysis)

From the first quarter of 2014 to the fourth quarter of 2019, the prevalence of deprescribing at least one potentially inappropriate medication decreased from 31.7% to 27.5%. The analysis showed 0 joinpoints, indicating a consistent linear trend with no interruptions or statistically significant points in time where the rate of change in deprescribing prevalence shifted. The average quarterly percentage change (AQPC) was -0.48% (CI: -0.88% to -0.09%), with a statistically significant p-value of 0.001. The result was almost the same as the analysis when sudden death was not excluded. As a result, we included residents who died suddenly in the analysis.



* Indicates that the Quarterly Percent Change (QPC) is significantly different from zero at the alpha = 0.05 level.
-- Test Statistic and P-Value not available for the Empirical Quantile method.
Final Selected Model: 0 Joinpoints.

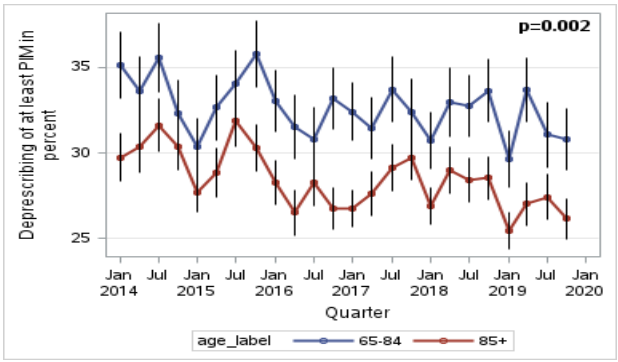
Supplementary file 3.3A: Prevalence of deprescribing of at least one PIMs by quarters of the year and AQPC, Belgium, 2014–2019 stratified by demographic and clinical variables

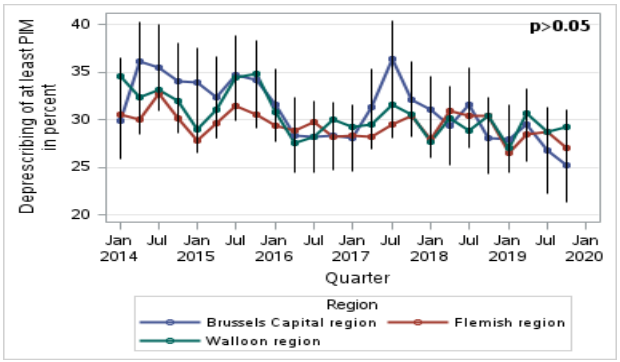
Demographic and clinical variables	Quarter 1 (2014) N=6435	Quarter 4 (2019) N=7604	Number of joinpoints	AQPC (%)	95% CI	P-value for trend for each strata	Comparison across strata p-value #
Overall	2040 (31.7%)	2103 (27.66%)	0	-0.47	-0.85 to -0.10	0.001*	
Sex							
Female	1327 (30.95%)	1324 (27.03%)	0	-0.59	-0.96 to -0.23	0.001*	0.17
Male	713 (33.21%)	779 (28.79%)	0	-0.27	-0.71 to +0.16	0.21	
Age							
65-84	820 (35.15%)	756 (30.82%)	0	-0.31	-0.65 to +0.03	0.07	0.002*
85+	1220 (29.74%)	1347 (26.15%)	0	-0.53	-0.97 to -0.09	0.02*	
Educational status							
No formal education	182(33.03%)	146 (25.43%)	0	-1.15	-1.62 to-0.70	< 0.001	<0.05* No formal Vs primary: 0.02 No formal Vs secondary: 0.01 No formal Vs Higher: 0.02
Primary education	778 (30.69%)	775 (28.48%)	0	-0.50	-0.81 to -0.19	0.001*	
Secondary education	705 (33.81%)	759 (27.4%)	0	-0.42	-0.78 to -0.06	0.02*	
Higher education	138 (34.94%)	191 (28.59%)	0	-0.32	-0.86 to 0.27	0.2	
Illness trajectory							
Amenable to pallative care	1704 (32.13%)	1489 (27.98 %)	0	-0.41	-0.75 to -0.09	0.004*	< 0.001*
Not amenable to pallative care	336 (29.68%)	614 (26.91%)	0	-0.48	-0.97 to 0.09	0.13	
Region							
Brussels Capital	152 (29.92%)	122 (25.21%)	0	-0.89	-1.38 to -0.39	0.001*	>0.05
Walloon	721 (34.53%)	707 (29.26%)	0	-0.33	-0.61 to -0.05	0.02*	
Flemish	1107 (30.59%)	1272 (27.07%)	0	-0.61	-0.97 to -0.25	0.001*	
Chronic medication							
<5	123 (19.62%)	118(18.55%)	0	-0.76	-1.44 to -0.15	0.019*	<0.05* 5-9 versus 10+: 0.004
5-9	827 (26.58%)	618(19.06%)	0	-1.17	-1.63 to -0.75	< 0.001*	
10^{+}	1090 (40.42%)	1367(36.70%)	0	-0.42	-0.67 to -0.14	0.002*	
Hospitalization							
Yes	1172 (22.66 %)	1284 (17.97 %)	0	-0.96	-1.48 to -0.46	<0.001*	0.003
No	868 (45.01%)	819 (42.14%)	0	-0.09	-0.36 to +0.18	0.48	

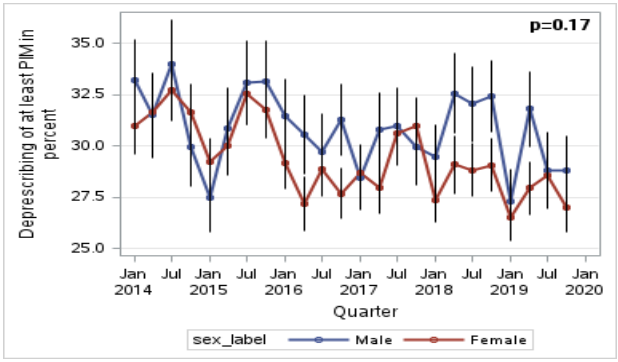
* The quarter percent change is significantly different from zero at alpha=0.05 level

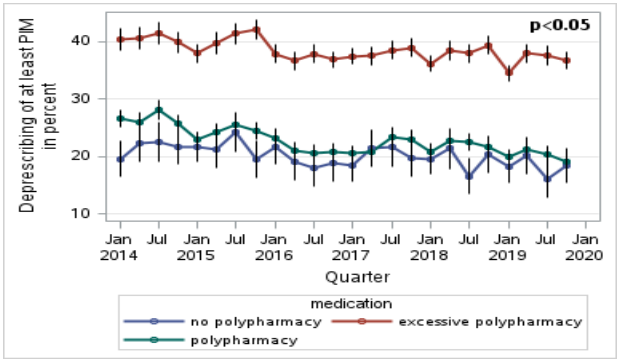
For variables with more than two categories, statistical tests were conducted pairwise because the AQPC value was a single estimated value rather than one at the quarter level. Using multiple observations for testing was challenging, as the AQPC represented a change estimated from all quarters combined. Pairwise comparisons were performed to determine if there was an overall difference among the groups. When a significant difference was found between any pair, it indicated that there was at least one pair of groups with a difference in AQPC. This suggested that an overall difference likely existed among the groups (<0.05 was reported as a significant difference, while >0.05 indicated no significant pair). The number of pairwise comparisons is given by N (N−1)/2, where N is the number of groups. Only the significant pair was reported.

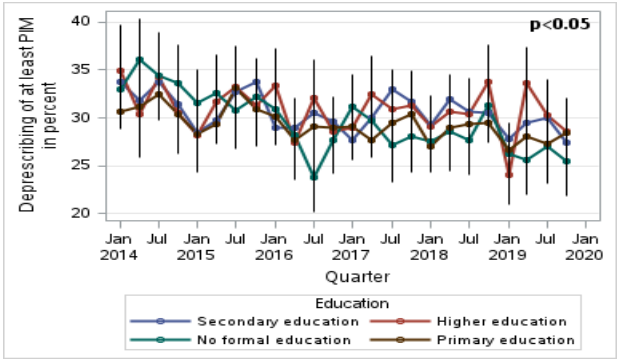
Supplementary file 3.3B: Quarterly deprescribing trend comparison across different categories of sociodemographic and clinical variables using quarter percent change (QPC)

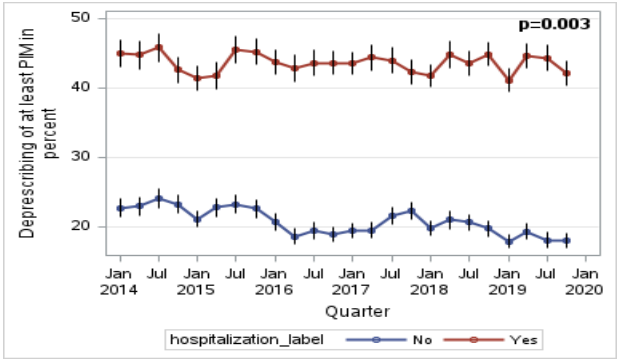


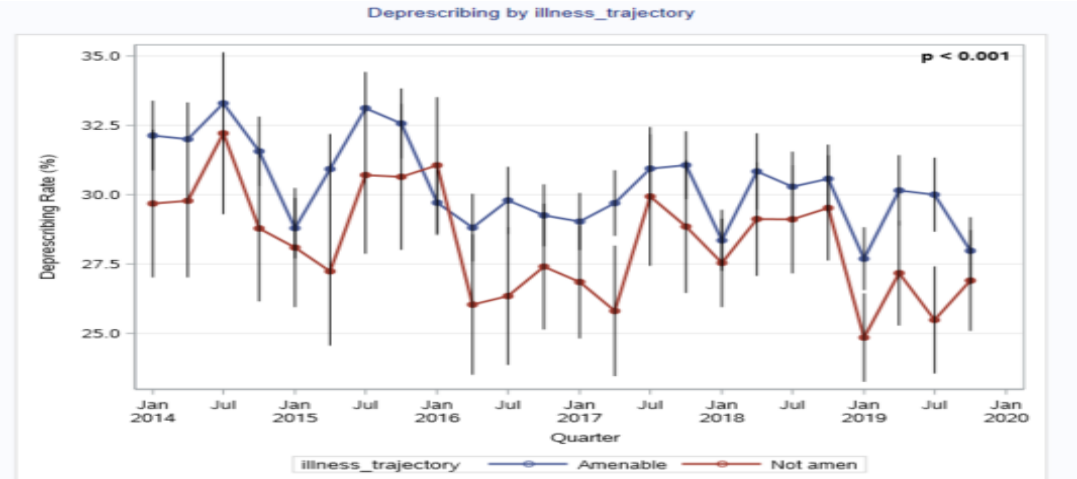












Chapter 4 supplementary materials

Supplementary file 4.1: demographic variables and eligibility screening questions (a qualtrics survey)

1. What is your name?
2. What is your gender?
3. What is your year of birth?
4. Do you come into contact with nursing home residents?
5. What profession do you currently practice?
6. In which region do you work?
7. What specialisation do you have?
8. Do you work with the Global Pharmaceutical Record?
9. Do you have regular/ chronic clients?
10. Are you involved in reviewing/re-evaluating patients' medication regimens?
11. Do you supply medications for nursing homes?
12. Have you ever attended any training related to palliative care?
13. In which setting do you work?
14. In what type of practice are you employed?
15. As a GP, are you also a Coordinating and Consulting Physician in a nursing home?
16. As a doctor, are you also a LEIF doctor?
17. Do you work with the Global Medical Record?
18. Do you have any other nursing role that you perform related to palliative care?
19. As a nurse, are you also a LEIF nurse?
20. How many years of work experience do you have?
21. Do you have experience of deprescribing at the end of life?
22. What form of interview do you wish to participate in?
23. What is your e-mail address?
24. What is your telephone number?
25. Do you have any additional information for us?

Supplementary file 4.2: Interview guide

Key questions	Probes
Are you familiar with the term deprescribing? What do you think about deprescribing for people with a limited life expectancy?	• How does this translate into the use of medicines? • Do you adjust the medication list when the end of life approaches? How? • In what circumstances do you make adjustments or not? • What is their role in the deprescribing process? • To what extent are you involved in this process and do you want to be involved? • Opportunities / difficulties for deprescribing • What do you need to make adjustments? • What's holding you back? • How can healthcare providers support deprescribing? • Barriers/facilitators in deprescribing • How do they feel about deprescribing? • What skills did you learn from your training in deprescribing? • What skills did you miss during your training?
When prescribing or deprescribing medicines for these patients, what factors play a role for you?	**Patient factors** (e.g. quality of life, benefit vs. risk, patient's condition, own wishes, values, norms, beliefs, cultural and existential factors): • Which specific patient group would you like to start prescribing with? • Do you come into contact with other beliefs/cultures/... When to prescribe medicines for patients? • Which values, norms and factors play an important role in patients? • How is the patient's quality of life discussed with the patient? • Do you think that deprescribing can cause harm to patients? **Physician factors** (e.g. prescribing habits, personal preference, past experiences, self-knowledge, self-confidence, expertise and skills, values, norms, beliefs): • Is there (multidisciplinary) collaboration in the deprescribing of medicines? • How do you see the collaboration on deprescribing medicines? **Other factors** (e.g.: care staff, other prescribers, patient and family wishes): • Do you also come into contact with other care staff when it comes to deprescribing? • Should deprescribing be part of your job? - Do patients and family members have a say when it comes to deprescribing medicines? • Who do you think should be involved when it comes to prescribing or withdrawing medicines? ➡ If they don't name the patient themselves, ask specifically what the role of patient and family is. – • To what extent does what other people think influence your decision to deny something?
How do you approach reducing or stopping medication at elderly people with a reduced life expectancy?	• Do they approve of this idea? Do they have concerns? (patient's point of view, family's point of view) • Do people with reduced life expectancy find it challenging to stop taking medicines? Why? • How often do they stop a medication? • What factors do you consider when making a decision about deprescribing? • When does the decision to deprescribing take place? • What factors are holding you back from deprescribing? • What do you think is feasible in practice?

What tools and guidelines to identify potentially inappropriate drugs (PIMS) and deprescribing are you aware of?	• Do you have access to tools and guidelines? • How do you get this information? • What tools and/or guidelines do you use in practice? • When do you use these guidelines/tools? • What are the advantages and disadvantages of these instruments? • What are you missing in these tools to use them? • How could you check that you are proactively withholding all unsuitable medicines?
What would the ideal scenario look like in practice and what can help you with that?	• What else could help with the process of reducing or discontinuing medicines? • What can make the process easier?

Chapter 5 supplementary materials

Supplementary file 5.1: List of conditions potentially amenable to palliative care and categorization into illness trajectories

Illness trajectory, conditions	ICD-10 codes
Cancer (trajectory of short decline with an evident terminal phase)	
Neoplasms and haematological malignancies	C00-C26, C30-C34, C37-C41, C43-C58, C60-C85, C88, C90-C97, D00-D09, D32, D33, D37-D48
Organ failure (trajectory of long-term limitations with intermittent acute episodes)	
Diabetes	E10-E14, G59.0, G63.2, H36.0, M14.2, N08.3
Other endocrinal diseases	E70-E72, E75-E77, E84-E85
Infectious and parasitic diseases	A520-A523, A527, A810, A812, B15-B19, B20-B24
Diseases of the blood	D60, D61, D69, D70, D752, D758, D86
Diseases of the cardiovascular system (incl. cerebrovascular disease)	I231-I233, I238, I25, I50, I60-I64, I67, I688, I69, G46, I65, I66, I680-I682, I27, I42, I43, I51, I520, I70, I73, I74, I792, I970, I971, I978, I980, I981, I988
Diseases of the respiratory system (incl. abnormalities of breathing)	J40-J44, J47, J60-J62, J66, J701, J80, J841, J951-J953, J96, J980-J984, R060, R062-R065, R068
Diseases of the digestive system (incl. liver diseases)	K70-K77, K44, K50, K51, K55, K56, K85, K86, K871, K90
Diseases of the skin	L305, L40-L42, L44, L93, L945
Diseases of the musculoskeletal system	M360, M361, M05, M06, M13, M15, M21, M30-M35, M40-M43, M45-M51, M53, M54, M638, M80, M81, M820, M821, M843, M844, M86-M88, M907,M961
Diseases of the genitourinary system (incl. renal failure)	N02-N05, N11, N12, N136, N160, N18, N19, N25, N312, N318, N319, N82
Other (incl. congenital conditions)	Q01-Q06, Q078, Q079, Q20-Q28, Q31, Q33, Q40-Q45, Q60-Q68, Q714, Q75-Q79, Q850, Q86-87, Q89-Q93, Q95-Q97, Q99
Prolonged dwindling (trajectory of progressive loss of physical and cognitive capacities)	
Alzheimer's disease	G30-G32
Mental and behavioural disorders	F00, F01, F02, F03, F05, F06, R54
Parkinson's disease	G20-G23
Multiple sclerosis	G35-G37
Other diseases of the nervous system	G10, G12, G70-G73, G03-G05, G07, G478, G518, G551, G608, G80-G83, G90-G99

Abbreviations: ICD-10, International Classification of Diseases 10th revision

Reference: Morin L, Aubry R, Frova L, et al. Estimating the need for palliative care at the population level: A cross-national study in 12 countries. Palliat Med. 2017;31(6):526–36.

Supplementary file 5.2: Identification of deaths related to acute and potentially unpredictable fatal events

ICD Chapter	Main criteria	Conditional argument
	ICD-10 codes listed as underlying cause of death	
Certain infectious and parasitic diseases	A00; A01; A02; A03; A04; A05; A06; A07; A08; A09; A39; A40; A41; A499; A80; A81; A87; B371; B375; B377; B440; B441; B448; B449; B99	
Diseases of the blood and blood-forming organs	D611; D619; D649	
Endocrine, nutritional and metabolic diseases	E86	
Diseases of the nervous system	G000; G001; G002; G003; G009; G039; G040; G048; G049; G060; G062; G931; G936	
Ischaemic and pulmonary heart diseases	I20; I21; I23; I25; I249; I255; I26; I28	No history of ischemic heart disease (I20-I25) or pulmonary embolism (I26)
Other forms of heart disease	I30; I33; I40; I461; I469	
Cerebrovascular diseases	I60; I61; I62; I63; I64; I65; I66; I67	No history of cerebrovascular disease (I60-I69)
Diseases of arteries, arterioles and capillaries	I71; I72; I74; I97	
Diseases of the respiratory system	J069; J09; J10; J11; J12; J13; J14; J15; J18; J22; J690; J81; J851; J852; J93; J958; J960	
Diseases of the digestive system	K250; K251; K252; K253; K254; K255; K256; K257; K259; K260; K261; K263; K264; K265; K266; K269; K550; K65; K720; K810; K859	
Diseases of the musculoskeletal system and connective tissue	M726	
Diseases of the genitourinary system	N00; N04; N10; N17; N390; N990; N998	No history of diabetes (E10-14) or renal failure (N18-19)
Symptoms, signs and abnormal clinical and laboratory findings, not elsewhere classified	R02; R572; R570; R571	
Injury, poisoning and certain other consequences of external causes	(codes start with) S%, T%	
External causes of morbidity and mortality	(codes start with) V%, W%, X%, Y %	

Supplementary file 5.3: Variable descriptions, nomenclature, and algorithms.

Variable	Dataset	Source of variable	Codes in SAS (nomenclature and algorithms)
Nursing home: RVT (rest and nursing homes)	IMA_health claim data	institution_site_cat	750, 751, 752, 753
Nursing home:ROB	IMA_health claim data	institution_site_cat	730, 731, 732, 734, 735, 737, 739, 740, 741, 743, 744, 745, 749, 760, 761, 762, 764, 765
Nursing home: RVT	IMA_Pharmanet	INSTITUTION_CAT	750, 751, 752, 753
Nursing home:ROB	IMA_Pharmanet	INSTITUTION_CAT	730, 731, 732, 735, 737, 739, 740, 741, 743, 744, 745, 749, 760, 761, 762, 765
Hospitalization	IMA-hospitalization	stay_cat	'ADM', 'JF', 'SP'
ICU admission	IMA-hospitalization	serv_adm serv_dis	serv_adm=490 or serv_dis=490
Emergency admission	IMA_health claim data	nomenclature codes (SS00020)	588151,590122, 590144, 590166,590181, 590225,590310, 590435, 590446, 590472, 590516,590531,590553, 590575, 590590,590612, 590634, 590656, 590671, 590693,590715, 590730, 590752,590774, 590796, 590811,590833,590855, 590870, 590892, 590914,590951, 590973,590995
Number of chronic medication	IMA_health claim data IMA_pharmanet	ATC_PROD_L SS00015_i	Number of medications prescribed at least 2 times at 3 months prior to death

Supplementary file 5.4: KatZ scale category and descriptions

KatZ category	Description
Category O	• Beneficiaries who are totally independent physically and mentally
Category A	• Beneficiaries who are physically dependent: ✓ they are dependent on washing and/or dressing themselves; • Beneficiaries who are psychically dependent: ✓ they are disoriented in time and space, and they are entirely physically independent;
Category B	• Beneficiaries who are physically dependent: ✓ they are dependent on bathing and dressing, and they are dependent for transfers and movements and/or going to the toilet, • Beneficiaries who are psychically dependent: - ✓ they are disoriented in time and space, and they are dependent on bathing and/or dressing
Category C	• Beneficiaries who are physically dependent: they are dependent on bathing and dressing, and ✓ they are dependent for transferring and moving and going to the toilet, and ✓ they are dependent for incontinence and/or eating
Category D (demented)	• Beneficiaries who have been diagnosed with dementia following a specialized diagnostic workup for dementia by a physician specializing in neurology, geriatrics or psychiatry
Category Cd (C demented)	• Beneficiaries who are psychically dependent: ✓ they are disoriented in time and space, and they are dependent on bathing and dressing, and ✓ they are dependent for incontinence, and ✓ they are dependent for transfers and movements and/or for going to the toilet and/or for eating.

Supplementary file 5.5: Sensitivity analysis by excluding unpredictable cause of death

Variable	Reinitiation (n= 1884, 16.78%)[a]			Initiation (n=38367, 29.65%)[b]		
	%	Univariate RR (95% CI)	Multivariate* RR (95% CI)	%	Univariate RR (95% CI)	Multivariate* RR (95% CI)
Age						
65-74	168 (19.74)	1.25 (1.08, 1.45)	1.01 (0.87, 1.16)	2937 (33.47)	1.18 (1.14, 1.21)	**0.94 (0.92, 0.97)**
75-84	622 (18.03)	1.14 (1.04, 1.25)	1.01 (0.92, 1.10)	11142 (31.68)	1.11 (1.09, 1.14)	**0.98 (0.96, 1.00)**
85 and over	1094 (15.79)	1.00	1.00	24288 (28.42)	1.00	1.00
Sex						
Female	1157 (15.96)	1.00	1.00	22495 (26.83)	1.00	1.00
Male	727 (18.26)	1.14 (1.05, 1.25)	1.05 (0.97, 1.14)	15872 (34.84)	1.30 (1.28, 1.32)	**1.19 (1.17, 1.21)**
Trajectory of illness						
Cancer	521 (21.04)	1.59 (1.42, 1.79)	**1.18 (1.04, 1.33)**	9653 (39.83)	1.73 (1.69, 1.77)	**1.34 (1.31, 1.37)**
Organ failure	955 (16.86)	1.28 (1.15, 1.42)	0.99 (0.89, 1.11)	19388 (29.97)	1.30 (1.27, 1.33)	**1.08 (1.06, 1.10)**
prolonged dwindling	408 (13.20)	1.00	1.00	9326 (23.05)	1.00	1.00
Educational status						
No formal education	173 (17.42)	1.00	1.00	3267 (28.67)	1.00	1.00
Primary education	781 (16.75)	0.96 (0.83, 1.12)	0.99 (0.85, 1.10)	15904 (29.61)	1.03 (1.00, 1.07)	**1.06 (1.03, 1.10)**
Secondary education	732 (16.08)	0.92 (0.79, 1.07)	0.93 (0.81, 1.09)	15477 (29.72)	1.04 (1.00, 1.07)	**1.04 (1.01, 1.07)**
Higher education	198 (19.35)	1.11 (0.92, 1.34)	1.13 (0.95, 1.36)	3719 (30.42)	1.06 (1.02, 1.10)	1.03 (0.99, 1.07)
Types of Nursing home						
ROB	1869 (16.79)	1.00	1.00	38094 (29.67)	1.00	1.00
RVT	15 (14.85)	0.88 (0.55, 1.41)	0.78 (0.46, 1.18)	273 (27.52)	0.93 (0.84, 1.02)	0.92 (0.83, 1.01)
Hospitalization (last 3 months) prior to death						
No	558 (10.03)	1.00	1.00	12142 (18.42)	1.00	1.00
Yes	1326 (23.40)	2.33 (2.13, 2.56)	**1.95 (1.77, 2.16)**	26225 (41.32)	2.24 (2.20, 2.29)	**2.09 (2.05, 2.13)**
Chronic medication use at 3 months prior to death)						
< 5	107 (8.69)	1.00	1.00	4868 (24.03)	1.00	1.00
5-9	538 (12.44)	1.43 (1.18, 1.75)	**1.30 (1.07, 1.59)**	14317 (25.95)	1.08 (1.05, 1.11)	0.99 (0.96, 1.01)
10 and above	1239 (21.84)	2.52 (2.08, 3.03)	**1.78 (1.47, 2.18)**	19182 (35.53)	1.48 (1.44, 1.52)	**1.04 (1.01, 1.07**)
Years of death						
2015	363 (16.43)	1.00	1.00	8271 (31.28)	1.00	1.00
2016	426 (17.92)	1.09 (0.96, 1.24)	1.07 (0.94, 1.21)	7780 (29.43)	0.94 (0.92, 0.97)	**0.94 (0.92, 0.96)**
2017	384 (16.60)	1.01 (0.89, 1.15)	0.97 (0.85, 1.10)	7948 (29.45)	0.94 (0.92, 0.97)	**0.93 (0.91, 0.96)**
2018	348 (16.15)	0.98 (0.86, 1.13)	0.94 (0.83, 1.08)	7201 (28.92)	0.92 (0.90, 0.95)	**0.92 (0.89, 0.94)**
2019	363 (16.68)	1.02 (0.89, 1.16)	0.97 (0.85, 1.11)	7167 (29.10)	0.93 (0.91, 0.96)	**0.93 (0.91, 0.95)**

[a]Among those discontinued their medications between 12 and 3 months prior to death, analysed based on those discontinuers where their educational status is known(N=11230).

[b] Among decedents for whom the medications were not prescribed between 12 and 3 months prior to death, irrespective of medication use in the year preceding their death, analysed based on those discontinuers where their educational status is known (N= 129400)

*Each of the listed variables included to mutually adjust in the final model

Supplementary file 5.6: Sensitivity analysis by the sub group of preventive medications

Variable	Reinitiation (n= 522, 10.72%)[a]			Initiation (n=9296, 6.68%)[b]		
	%	Univariate RR (95% CI)	Multivariate* RR (95% CI)	%	Univariate RR (95% CI)	Multivariate* RR (95% CI)
Age						
65-74	30 (11.28)	1.06 (0.75- 1.51)	0.84 (0.58- 1.16)	620 (6.65)	1.03 (0.95- 1.12)	**0.79 (0.73- 0.85)**
75-84	159 (10.84)	1.02 (0.85- 1.22)	0.88 (0.74- 1.05)	2737 (7.30)	1.14 (1.09- 1.19)	**0.96 (0.92- 1.00)**
85 and over	333 (10.61)	1.00	1.00	5939 (6.43)	1.00	1.00
Sex						
Female	357 (10.86)	1.00	1.00	5959 (6.60)	1.00	1.00
Male	165 (10.42)	0.96 (0.81-1.14)	0.88 (0.74- 1.05)	3337 (6.82)	1.03 (0.99- 1.08)	**0.88 (0.85- 0.92)**
Trajectory of illness						
Cancer	115 (11.60)	1.29 (1.01- 1.64)	0.86 (0.68- 1.09)	1914 (7.83)	1.65 (1.56- 1.76)	1.05 (0.99- 1.12)
Organ failure	286 (11.26)	1.25 (1.02- 1.53)	0.86 (0.71- 1.06)	5338 (7.46)	1.58 (1.50- 1.66)	**1.06 (1.01- 1.12)**
prolonged dwindling	121 (9.02)	1.00	1.00	2044 (4.73)	1.00	1.00
Educational status						
No formal education	51 (11.54)	1.00	1.00	820 (6.64)	1.00	1.00
Primary education	226 (11.10)	0.96 (0.72- 1.28)	1.08 (0.83- 1.45)	3785 (6.57)	0.99 (0.92- 1.07)	1.04 (0.97- 1.12)
Secondary education	187 (9.56)	0.83 (0.62- 1.11)	0.93 (0.70- 1.24)	3802 (6.78)	1.02 (0.95- 1.10)	1.07 (1.00- 1.15)
Higher education	58 (13.27)	1.15 (0.81- 1.64)	1.30 (0.92- 1.84)	889 (6.77)	1.02 (0.93- 1.12)	1.08 (0.99- 1.18)
Types of Nursing home						
ROB	518 (10.72)	1.00	1.00	9230 (6.68)	1.00	1.00
RVT	4 (10.81)	1.01 (0.40- 2.55)	0.84 (0.28- 1.76)	66 (6.01)	0.90 (0.70- 1.13)	0.87 (0.68- 1.08)
Hospitalization (last 3 months) prior to death						
No	75 (3.05)	1.00 (P<.0001)	1.00	957 (1.38)	1.00 (P<.0001)	1.00
Yes	447 (18.52)	6.05 (4.77- 7.73)	**5.18 (4.06- 6.70)**	8339 (11.93)	8.65 (8.07- 9.24)	**8.52 (7.97- 9.13)**
Chronic medication use at 3 months prior to death)						
< 5	16 (3.05)	1.00	1.00	947 (4.41)	1.00	1.00
5-9	130 (6.70)	2.20 (1.32- 3.66)	**1.68 (1.05- 2.90)**	2987 (5.07)	1.15 (1.07- 1.23)	0.96 (0.90- 1.03)
10 and above	376 (15.63)	5.13 (3.14- 8.38)	**2.46 (1.55- 4.22)**	5362 (9.12)	2.07 (1.93- 2.21)	1.05 (0.98- 1.13)
Years of death						
2015	97(10.17)	1.00	1.00	2044 (7.05)	1.00	1.00
2016	111 (10.49)	1.03 (0.80- 1.34)	0.99 (0.77- 1.27)	1890 (6.57)	0.93 (0.88- 0.99)	**0.93 (0.88- 0.99)**
2017	117 (11.50)	1.13 (0.88- 1.46)	1.01 (0.79- 1.29)	1945 (6.58)	0.93 (0.88- 0.99)	**0.92 (0.87- 0.98)**
2018	87 (9.70)	0.95 (0.73- 1.26)	0.91 (0.70- 1.19)	1688 (6.45)	0.92 (0.86- 0.98)	**0.92 (0.87- 0.98)**
2019	110 (11.64)	1.14 (0.88- 1.48)	1.06 (0.83- 1.36)	1729 (6.73)	0.95 (0.90- 1.02)	0.98 (0.92- 1.04)

[a] Among those who discontinued their preventive medications between 12 and 3 months prior to death, analysed based on those discontinuers where their educational status is known(N=4871).

[b] Among decedents for whom the medications (preventive) were not prescribed between 12 and 3 months prior to death, irrespective of medication use in the year preceding their death, analysed based on those discontinuers where their educational status is known (N= 139182)

*Each of the listed variables included to mutually adjust in the final model

Supplementary file 5.7: Sensitivity analysis by the sub-group of symptomatic medications

Variable	Reinitiation (n=1523, 20.32%)[a]			Initiation (n=35632, 25.60%)[b]		
	%	Univariate RR (95% CI)	Multivariate* RR (95% CI)	%	Univariate RR (95% CI)	Multivariate* RR (95% CI)
Age						
65-74	149 (23.35)	1.23 (1.06- 1.43)	1.03 (0.88- 1.20)	2733 (29.33)	1.19 (1.15- 1.23)	**0.96 (0.93- 0.99)**
75-84	512 (22.14)	1.17 (1.06- 1.29)	1.04 (0.95- 1.15)	10196 (27.21)	1.11 (1.08- 1.13)	**0.98 (0.96- 1.00)**
85 and over	862 (18.97)	1.00	1.00	22703 (24.58)	1.00	1.00
Sex						
Female	893 (19.02)	1.00	1.00	20231 (22.42)	1.00	1.00
Male	630 (22.50)	1.18 (1.08-1.29)	**1.10 (1.01- 1.21)**	15401 (31.47)	1.40 (1.38- 1.43)	**1.31 (1.28- 1.33)**
Trajectory of illness						
Cancer	411 (26.00)	1.62 (1.42-1.84)	**1.30 (1.14- 1.48)**	8711 (35.63)	1.76 (1.72- 1.81)	**1.43 (1.40- 1.47)**
Organ failure	786 (20.22)	1.26 (1.12- 1.41)	1.04 (0.93- 1.18)	18178 (25.42)	1.26 (1.23- 1.28)	**1.08 (1.06- 1.11)**
prolonged dwindling	326 (16.08)	1.00	1.00	8743 (20.24)	1.00	1.00
Educational status						
No formal education	137 (20.45)	1.00	1.00	3074 (24.88)	1.00	1.00
Primary education	615 (19.92)	0.97 (0.83- 1.15)	0.98 (0.84- 1.16)	14690 (25.49)	1.02 (0.99- 1.06)	**1.05 (1.02- 1.09)**
Secondary education	610 (20.01)	0.98 (0.83- 1.15)	0.98 (0.83- 1.16)	14395 (25.68)	1.03 (1.00- 1.07)	1.03 (1.00- 1.06)
Higher education	161 (23.37)	1.14 (0.93 -1.40)	1.15 (0.95- 1.41)	3473 (26.44)	1.06 (1.02- 1.11)	1.01 (0.97- 1.06)
Types of Nursing home						
ROB	1510 (20.35)	1.00	1.00	35374 (25.62)	1.00	1.00
RVT	13 (17.57)	0.86 (0.53- 1.42)	0.78 (0.45- 1.20)	258 (23.50)	0.92 (0.82- 1.02)	0.91 (0.82 - 1.01)
Hospitalization (last 3 months) prior to death						
No	514 (14.61)	1.00	1.00	11981 (17.30)	1.00	1.00
Yes	1009 (25.38)	1.74 (1.58- 1.91)	**1.45 (1.30- 1.61)**	23651 (33.83)	1.96 (1.92- 1.99)	**1.81 (1.78- 1.85)**
Chronic medication use at 3 months prior to death)						
< 5	97 (12.20)	1.00	1.00	4722 (22.00)	1.00	1.00
5-9	439 (16.06)	1.32 (1.07 -1.62)	**1.23 (1.01- 1.52)**	13475 (22.87)	1.04 (1.01- 1.07)	**0.97 (0.94- 0.99)**
10 and above	987 (24.89)	2.04 (1.68- 2.48)	**1.63 (1.34- 2.01)**	17435 (29.65)	1.35 (1.31- 1.39)	1.01 (0.98- 1.03)
Years of death						
2015	307 (20.60)	1.00	1.00	7850 (27.06)	1.00	1.00
2016	354 (21.88)	1.06 (0.93- 1.22)	1.04 (0.91- 1.19)	7308 (25.40)	0.94 (0.91- 0.96)	**0.93 (0.91- 0.96)**
2017	307 (19.48)	0.95 (0.82- 1.09)	0.92 (0.80- 1.06)	7558 (25.57)	0.94 (0.92- 0.97)	**0.93 (0.91- 0.96)**
2018	282 (19.94)	0.97 (0.84- 1.12)	0.94 (0.82- 1.09)	6469 (24.74)	0.91 (0.89- 0.94)	**0.90 (0.88- 0.93)**
2019	273 (19.54)	0.95 (0.82- 1.10)	0.91 (0.79- 1.05)	6447 (25.10)	0.93 (0.90- 0.95)	**0.92 (0.90- 0.95)**

[a] Among those who discontinued their symptom control medications between 12 and 3 months prior to death, analysed based on those discontinuers where their educational status is known(N=7495).

[b] Among decedents for whom the medications (symptom control) were not prescribed between 12 and 3 months prior to death, irrespective of medication use in the year preceding their death, analysed based on those discontinuers where their educational status is known (N= 139 171)

*Each of the listed variables included to mutually adjust in the final model

Chapter 6 supplementary materials

Supplementary file 6.1: Variable descriptions, nomenclature, and algorithms.

Variable	Dataset	Source of variable	Codes in SAS (nomenclature and algorithms)
Hospitalization	IMA-hospitalization	stay_cat	'ADM', 'JF', 'SP'
ICU admission	IMA-hospitalization	serv_adm serv_dis	serv_adm=490 or serv_dis=490
Emergency admission	IMA_health claim data	**Nomenclature codes (SS00020)**	588151,590122, 590144, 590166,590181, 590225,590310,590435, 590446, 590472, 590516,590531,590553, 590575, 590590,590612, 590634, 590656, 590671, 590693,590715, 590730, 590752,590774, 590796, 590811,590833,590855, 590870, 590892, 590914,590951, 590973,590995
Medications (Total, chronic, and potentially in appropriate)	IMA_health claim data IMA_pharmanet	ATC_PROD_L SS00015	ATCDDD - ATC/DDD Index

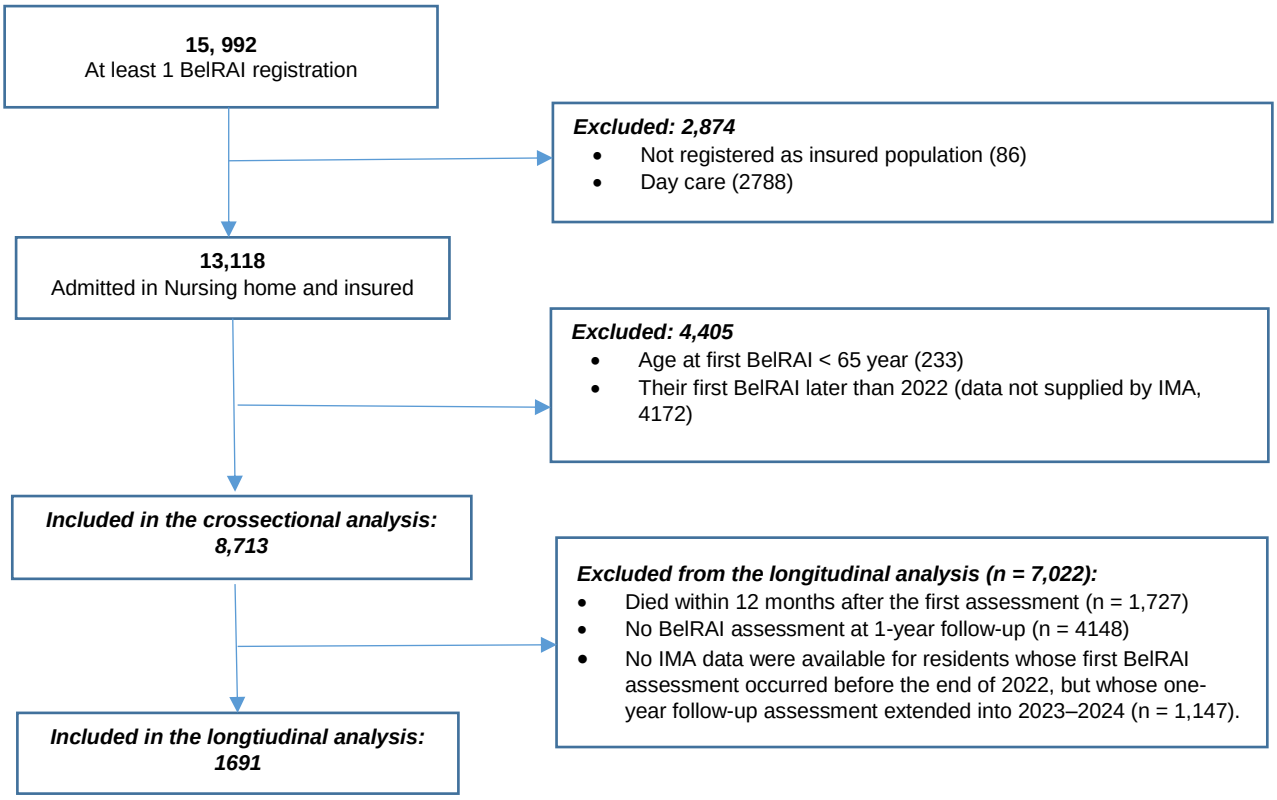
Supplementary file 6.2: Selected potentially inappropraite medication

	PIMs	***Duration to define PIMs***	***ATC code***
1	H2 receptor antagonist	≥8 weeks	A02BA
2	Proton pump Inhibitors	≥8 weeks	A02BC
3	Vitamin D	≥12 weeks	A11CC
4	Calcium supplement	≥12 weeks	A12A
5	Lipid-modifying agents	≥12 weeks	C10
6	Systemic corticosteroids	≥ 8 weeks	H02
7	Long-term oral NSAIDs	≥ 8 weeks	M01A
8	Anti-resorptive/bone anabolic drugs for osteoporosis	≥12 weeks	M05B
9	Antipsychotics	≥12 weeks	N05A
10	Tricyclic antidepressants	≥12 weeks	N06AA
11	Systemic drugs for obstructive airway diseases	≥12 weeks	R03DA04, R03DA05, R03DC01,R03DC03
12	Antihistamines for systemic use	≥12 weeks	R06A
13	Anti-dementia drugs	≥12 weeks	N06D

Supplementary file 6.3: Predefined list of comorbidities available in the BelRAI dataset, used to calculate the total number of comorbid conditions per resident.

Number	Description of variable	BelRAI code
1.	Hip fracture in the last 30 days	ii1a
2.	Other fracture in the last 30 days	ii1b
3.	Alzheimers disease	ii1c
4.	Dementia other than Alzheimers disease	ii1d
5.	Hemiplegia	ii1e
6.	Multiple scleriosis (MS)	ii1f
7.	Paraplegia	ii1g
8.	Parkinsons disease	ii1h
9.	Quadriplegia	ii1i
10.	Stroke	ii1j
11.	Coronary artery disease	ii1k
12.	Chronic air way obstruction (COPD)	ii1l
13.	Heart failure (CHF)	ii1m
14.	anxiety	ii1n
15.	Bipolar syndrom	ii1w
16.	Depression	ii1o
17.	Schzopherenia	ii1p
18.	pnemonia	ii1q
19.	Urinary tract infection in the last 30 days	ii1r
20.	Cancer	ii1s
21.	Diabetes mellitus	ii1t
22.	cerebral palsy	ii1cc
23.	Septicemia	ii1dd/ii1xxxex

Supplementary file 6.4: Flow diagram illustrating the selection process of nursing home residents included in the study, based on BelRAI assessment data collected between 2016 and 2022.



Supplementary file 6.5: Long-term medication and PIM use for dementia cases

	Total baseline population 3974 (45.61%)	**Comparative populations (n=784, 46.36%)**			
		Baseline	**Year 1**	**Effect size**	**P-value**
Total medication (Median[IQR])					
Yes	7 (5-11)	7 (5-11)	8 (5-11)		<.0001
No	9 (6-14)	9 (6-12)	10 (7-14)		<.0001
Chronic medication (Mean[SD])					
Yes	5.4 (3.4)	5.3 (3.3)	5.5 (2.8)		0.045
No	6.5 (4.1)	6.3 (3.6)	6.6 (3.2)		0.039
At least one chronic medication (%)	3732 (93.91)	733 (93.49)	760 (96.94)		0.0002
Level of Polypharmacy (%)					
No polypharmacy (< 5)	1689 (42.50 %)	342 (43.62%)	302 (38.52%)		
Polypharmacy (5-9)	1862 (46.85%)	364 (46.43%)	419 (53.44%)	0.3874	0.0013
Hyperpolypharmacy (≥ 10)	423 (10.64%)	78 (9.95%)	63 (8.04%)		
At least one PIM	2939 (73.96%)	580 (73.98%)	458 (58.42%)		**<.0001**

Among residents with dementia, the median number of total medications was 7 (IQR, 5-11), 93.9% took at least one chronic medication, with a mean of 5.4 (SD, 3.4). Polypharmacy and excessive polypharmacy were observed in 46.85% and 10.64% of residents, respectively

Supplementary file 6.6: Transitions in PIM use between baseline and one year (N = 1,691)

Medications (Evolutions)	N (%)
Level of polypharmacy	
Escalated	218 (12.89)
Maintained	1338 (79.12)
De-escalated	135 (7.98)
Proton pump Inhibitors ≥8 weeks (A02BC)	
Not prescribed	802 (47.43)
Continued	678 (40.09)
Newly prescribed	141 (8.34)
Discontinued	70 (4.14)
Lipid-modifying agents (C10)	
Not prescribed	1215 (71.85)
Continued	321 (18.98)
Newly prescribed	72 (4.26)
Discontinued	83 (4.91)
Systemic corticosteroids ≥ 8 weeks (H02)	
Not prescribed	1599 (94.56)
Continued	28 (1.66)
Newly prescribed	36 (2.13)
Discontinued	28 (1.66)
Long-term oral NSAIDs ≥ 8 weeks (M01A)	
Not prescribed	1644 (97.22)
Continued	6 (0.35)
Newly prescribed	16 (0.95)
Discontinued	25 (1.48)
Anti-resorptive/bone anabolic drugs for osteoporosis (M05B)	
Not prescribed	1628 (96.27)
Continued	37 (2.19)
Newly prescribed	18 (1.06)
Discontinued	8 (0.47)
Antipsychotics ≥12 weeks (N05A)	
Not prescribed	1168 (69.07)
Continued	290 (17.15)
Newly prescribed	153 (9.05)
Discontinued	80 (4.73)
Benzodiazepines (N05BA, N05CD, N05CF)	
Not prescribed	1596 (94.38)
Continued	4 (0.24)
Newly prescribed	23 (1.36)
Discontinued	68 (4.02)
Tricyclic antidepressants (N06AA)	
Not prescribed	1630 (96.39)
Continued	33 (1.95)
Newly prescribed	17 (1.01)
Discontinued	11 (0.65)
Antihistamines for systemic use (R06A)	
Not prescribed	1546 (91.43)
Continued	68 (4.02)
Newly prescribed	44 (2.60)
Discontinued	33 (1.95)
Anti-dementia drugs (N06D)	
Not prescribed	1596 (94.38)
Continued	43 (2.54)
Newly prescribed	13 (0.77)
Discontinued	39 (2.31)

Supplementary file 6.7: Transitions in physical and psychosocial health between baseline and one year

Changes in physical and psychosocial health	N (%)
ADL performance (N=1610)	
Deteriorated	148 (9.19)
Improved	46 (2.86)
No change	1416 (87.95)
Health instability (N=1509)	
Deteriorated	356 (23.59)
Improved	100 (6.63)
No change	1053 (69.78)
Pain (N=1606)	
Deteriorated	155 (9.65)
Improved	118 (7.35)
No change	1333 (83.00)
Cognitive status (N=1592)	
Deteriorated	216 (13.57)
Improved	35 (2.20)
No change	1341 (84.23)
Mood status (N=1616)	
Deteriorated	295 (18.25)
Improved	132 (8.17)
No change	1189 (73.58)
Aggressive behaviour (N=1621)	
Deteriorated	201 (12.40)
Improved	116 (7.16)
No change	1304 (80.44)
Comorbidity (N=1691)	
Decrease	111 (6.56)
Increase	250 (14.78)
Same	1330 (78.65)
Fall (N=1622)	
Deteriorated	208 (12.82)
Improved	185 (11.41)
No change	1229 (75.77)
Social Engagement (N=1601)	
Deteriorated	228 (14.24)
Improved	200 (12.49)
No change	1173 (73.27)

Supplemenary file 6.8. Changes in medication use by socio-demographic characteristics and health changes

	Level of polypharmacy							Potentially inappropriate medications							
	Escalated	*Maintained*	*De-escalated*	*Total*	*Effect Size ǂ (Cramer's V)*	*P-value*	*Somers' D (C|R)*	*No PIM*	*Discontinued*	*New PIM*	*Continued*	*Total*	*Effect size ǂ (Cramer's V)*	*P-value*	*Somers' D (C|R)*
Age	***218 (12.89)***	***1338 (79.12)***	***135 (7.98)***	***1691***				***330 (19.52)***	***414 (24.48)***	***131 (7.75)***	***816 (48.26)***	***1691***			
65-74	23 (10.55)	174 (13.00)	17 (12.59)	214 (12.66)		0.6621	0.0107	35 (10.61)	41 (9.90)	16 (12.21)	122 (14.95)	214(12.66)	0.1027	**<.0001**	**0.1224**
75-84	93 (42.66)	550 (41.11)	52 (38.52)	695 (41.10)	0.0210			107 (32.42)	161 (38.89)	56 (42.75)	371 (45.47)	695(41.10)			
85 and above	102 (46.79)	614 (45.89)	66 (48.89)	782 (46.24)				188 (56.97)	212 (51.21)	59 (45.04)	323 (39.58)	782(46.24)			
Sex	***218 (12.89)***	***1338 (79.12)***	***135 (7.98)***	***1691***				***330 (19.52)***	***414 (24.48)***	***131 (7.75)***	***816 (48.26)***	***1691***			
Male	60 (27.52)	341 (25.49)	42 (31.11)	443 (26.20)	0.0364	0.3272		76 (23.03)	83 (20.05)	30 (22.90)	254 (31.13)	443 (26.20)	0.1109	**<.0001**	
Female	158 (72.48)	997 (74.51)	93 (68.89)	1248 (73.80)				254 (76.97)	331 (79.95)	101 (77.10)	562 (68.87)	1248 (73.80)			
Dementia	***218 (12.89)***	***1338 (79.12)***	***135 (7.98)***	***1691***				***330 (19.52)***	***414 (24.48)***	***131 (7.75)***	***816 (48.26)***	1691			
Yes	108 (49.54)	608 (45.44)	68 (50.37)	784 (46.36)	0.0362	0.3664		145 (43.94)	181 (43.72)	59 (45.04)	399 (48.90)	784 (46.36)	0.0495	0.2465	
No	110 (50.46)	730 (54.56)	67 (49.63)	907 (53.64)				185 (56.06)	233 (56.28)	72 (54.96)	417 (51.10)	907 (53.64)			
ADLH scale score	***20 (12.61)***	***1279 (79.44)***	***128 (7.95)***	***1610***				***317 (19.69)***	***394 (24.47)***	***122 (7.58)***	***777 (48.26***	***1610***			
Deteriorated	30 (14.78)	109 (8.52)	9 (7.03)	148 (9.19)	0.0602	**0.02**	0.0577	27 (8.52)	22 (5.58)	19 (15.57)	80 (10.30)	148 (9.19)	**0.0728**	**0.009**	**0.0437**
No change	164 (80.79)	1137 (88.90)	115 (89.84)	1416 (87.95)				283 (89.27)	363 (92.13)	97 (79.51)	673 (86.62)	1416 (87.95)			
Improved	9 (4.43)	33 (2.58)	4 (3.13)	46 (2.86)				7 (2.21)	9 (2.28)	6 (4.92)	24 (3.09)	46 (2.86)			
DRS scale score	***203 (12.56)***	***1287 (79.64)***	***126 (7.80)***	***1616***				***320 (19.80)***	***395 (24.44)***	***121 (7.49)***	***780 (48.27)***	***1616***			
Deteriorated	40 (19.70)	232 (18.03)	23 (18.25)	295 (18.25)	0.0252	0.7256	0.0143	63 (19.69)	75 (18.99)	24 (19.83)	133 (17.05)	295 (18.25)	0.0330	0.7422	-0.0376
No change	146 (71.92)	954 (74.13)	89 (70.63)	1189 (73.58)				237 (74.06)	284 (71.90)	87 (71.90)	581 (74.49)	1189 (73.58)			
Improved	17 (8.37)	101 (7.85)	14 (11.11)	132 (8.17)				20 (6.25)	36 (9.11)	10 (8.26)	66 (8.46)	132 (8.17)			
CPS scale score¥	***198 (12.44)***	***1269 (79.71)***	***125 (7.85)***	***1592***			**0.0226**	***314 (19.72)***	***390 (24.50)***	***122 (7.66)***	***766 (48.12)***	***1592***			
Deteriorated	29 (14.65)	174 (13.71)	13 (10.40)	216 (13.57)	**0.0559**	**0.04**		48 (15.29)	45 (11.54)	19 (15.57)	104 (13.58)	216 (13.57)	0.0438	0.4124	-0.0267
No change	161 (81.31)	1074 (84.63)	106 (84.80)	1341 (84.23)				263 (83.76)	337 (86.41)	99 (81.15)	642 (83.81)	1341 (84.23)			
Improved	8 (4.04)	21 (1.65)	6 (4.80)	35 (2.20)				3 (0.96)	8 (2.05)	4 (3.28)	20 (2.61)	35 (2.20)			
CHESS scale score	***178 (11.80)***	***1216 (80.58)***	***115 (7.62)***	***1509***			0.0139	***296 (19.62)***	***370 (24.52)***	***110 (7.29)***	***733 (48.58)***	***1509***			
Deteriorated	42 (23.60)	290 (23.85)	24 (20.87)	356 (23.59)	0.0203	0.8719		74 (25.00)	79 (21.35)	26 (23.64)	177 (24.15)	356 (23.59)	0.0436	0.4533	-0.0091
No change	125 (70.22)	847 (69.65)	81 (70.43)	1053 (69.78)				208 (70.27)	263 (71.08)	80 (72.73)	502 (68.49)	1053 (69.78)			
Improved	11 (6.18)	79 (6.50)	10 (8.70)	100 (6.63)				14 (4.73)	28 (7.57)	4 (3.64)	54 (7.37)	100 (6.63)			
ABS scale score	***204 (12.58)***	***1291 (79.64)***	***126 (7.77)***	***1621***			0.0245	***319 (19.68)***	***397 (24.49)***	***123 (7.59)***	***782 (48.24)***	***1621***			
Deteriorated	23 (11.27)	160 (12.39)	18 (14.29)	201 (12.40)	0.0315	0.5232		47 (14.73)	30 (7.56)	14 (11.38)	110 (14.07)	201 (12.40)	**0.07**	**0.01**	**0.0553**
No change	165 (80.88)	1044 (80.87)	95 (75.40)	1304 (80.44)				242 (75.86)	339 (85.39)	101 (82.11)	622 (79.54)	1304 (80.44)			
Improved	16 (7.84)	87 (6.74)	13 (10.32)	116 (7.16)				30 (9.40)	28 (7.05)	8 (6.50)	50 (6.39)	116 (7.16)			
Pain scale score	199 (12.39)	1279 (79.64)	***128 (7.97)***	***1606***				***317 (19.74)***	***393 (24.47)***	***121 (7.53)***	***775 (48.26)***	***1606***			
Deteriorated	15 (7.54)	126 (9.85)	14 (10.94)	155 (9.65)	0.0230	0.7901	- 0.0167	22 (6.94)	42 (10.69)	15 (12.40)	76 (9.81)	155 (9.65)	0.0599	0.0733	0.0347
No change	169 (84.92)	1061 (82.96)	103 (80.47)	1333 (83.00)				274 (86.44)	312 (79.39)	102 (84.30)	645 (83.23)	1333 (83.00)			
Improved	15 (7.54)	92 (7.19)	11 (8.59)	118 (7.35)				21 (6.62)	39 (9.92)	4 (3.31)	54 (6.97)	118 (7.35)			
Co-morbidity	***218 (12.89)***	***1338 (79.12)***	***135 (7.98)***	***1691***				***330 (19.52)***	***414 (24.48)***	***131 (7.75)***	***816 (48.26)***	***1691***			
Increased	30 (13.76)	208 (15.55)	12 (8.89)	250 (14.78)	0.0430	0.1804	0.0236	40 (12.12)	47 (11.35)	14 (10.69)	149 (18.26)	250 (14.78)	**0.0713**	**0.008**	**0.0792**
No change	173 (79.36)	1047 (78.25)	110 (81.48)	1330 (78.65)				267 (80.91)	343 (82.85)	110 (83.97)	610 (74.75)	1330 (78.65)			
Decreased	15 (6.88)	83 (6.20)	13 (9.63)	111 (6.56)				23 (6.97)	24 (5.80)	7 (5.34)	57 (6.99)	111 (6.56)			

ǂCramer's V for variables with more than two categories (negligible <0.1, small = 0.10–0.29, medium = 0.30–0.49, large ≥0.50)

¥fisher exact test

Abbreviations: ABC – Aggressive Behaviour Scale; ADLH – Activities of Daily Living Hierarchy Scale; CHESS – Changes in Health, End-Stage Disease, and Signs and Symptoms Scale; CPS – Cognitive Performance Scale; DRS – Depression Rating Scale; PIM – Potentially Inappropraite Medications

Supplemenary file 6.9: Changes in medication use (PPI and antipsychotics) in relation to changes in health

	Proton pump inhibitors							**Antipsychotics**						
	Not prescribed	Dis-continued	Newly prescribed	Continued	Total	Pvalue/ Cramer's V	Somers' D (C|R)	Not prescribed	Dis-continued	Newly prescribed	Continued	Total	Pvalue/ Cramer's V	Somers' D (C|R)
Age	***802 (47.43)***	***70 (4.14)***	***141 (8.34)***	***678 (40.09)***	***1691***			***1168(69.07)***	***80 (4.73)***	***153 (9.05)***	***290 (17.15)***	***1691***		
65-74	98 (12.22)	8 (11.43)	17 (12.06)	91(13.42)	214(12.66)	0.2089		132(11.30)	13(16.25)	21(13.73)	48(16.55)	214(12.66)	**0.0077**	
75-84	329(41.02)	19(27.14)	59 (41.84)	288(42.48)	695 (41.10)		0.0209	463(39.64)	34(42.50)	62(40.52)	136(46.90)	695(41.10)		0.0799
85 and above	375(46.76)	43(61.43)	65 (46.10)	299 (44.10)	782 (46.24)	0.0499		573(49.06)	33(41.25)	70(45.75)	106(36.55)	782(46.24)	**0.0719**	
Sex	***802 (47.43)***	***70 (4.14)***	***141(8.34)***	***678 (40.09)***	***1691***			***1168(69.07)***	***80(4.73)***	***153(9.05)***	***290(17.15)***	***1691***		
Male	221(27.56)	18(25.71)	39(27.66)	165(24.34)	443(26.20)	0.5429		273(23.37)	23(28.75)	53(34.64)	94(32.41)	443(26.20)	**0.0009**	
Female	581(72.44)	52(74.29)	102 (72.34)	513(75.66)	1248 (73.80)	0.0356		895(76.63)	57(71.25)	100(65.36)	196(67.59)	1248(73.80)	**0.0989**	
ADLH scale score	***762(47.33)***	***69(4.29)***	***127(7.89)***	***652(40.50)***	***1610***			***1106(68.70)***	***78(4.84)***	***146(9.07)***	***280(17.39)***	***1610***		
Deteriorated	85(11.15)	1(1.45)	22(17.32)	40(6.13)	148(9.19)	**0.0002**		95(8.59)	8(10.26)	19(13.01)	26(9.29)	148(9.19)	0.3696	0.0190
No change	656(86.09)	66(95.65)	100(78.74)	594(91.10)	1416(87.95)		**-0.1189**	976(88.25)	69(88.46)	126(86.30)	245(87.50)	1416(87.95)		
Improved	21(2.76)	2(2.90)	5(3.94)	18(2.76)	46(2.86)	**0.0911**		35(3.16)	1(1.28)	1(0.68)	9(3.21)	46(2.86)	0.0449	
DRS scale score	***761(47.09)***	***69(4.27)***	***131(8.11)***	***655(40.53)***	***1616***			***1114(68.94)***	***77(4.76)***	***146(9.03)***	***279(17.26)***	***1616***		
Deteriorated	143(18.79)	14(20.29)	23(17.56)	115(17.56)	295(18.25)	0.9799		211(18.94)	14(18.18)	25(17.12)	45(16.13)	295(18.25)	0.2489	
No change	557(73.19)	51(73.91)	97(74.05)	484(73.89)	1189(73.58)		-0.0105	811(72.80)	57(74.03)	109(74.66)	212(75.99)	1189(73.58)		-0.0285
Improved	61(8.02)	4(5.80)	11(8.40)	56(8.55)	132(8.17)	0.0188		92(8.26)	6(7.79)	12(8.22)	22(7.89)	132(8.17)	0.0213	
CPS scale score	***755(47.42)***	***69(4.33)***	***128(8.04)***	***640(40.20)***	***1592***			***1094(68.72)***	***78(4.90)***	***145(9.11)***	***275(17.27)***	***1592***		
Deteriorated	103(13.64)	8(11.59)	18(14.06)	87(13.59)	216(13.57)	0.8793		142(12.98)	13(16.67)	25(17.24)	36(13.09)	216(13.57)	0.0537	0.0450
No change	637(84.37)	59(85.51)	105(82.03)	540(84.38)	1341(84.23)		-0.0005	934(85.37)	60(76.92)	115(79.31)	232(84.36)	1341(84.23)		
Improved	15(1.99)	2(2.90)	5(3.91)	13(2.03)	35(2.20)	0.0275		18(1.65)	5(6.41)	5(3.45)	7(2.55)	35(2.20)	0.0624	
CHESS scale score	***713(47.25)***	***59(3.91)***	***121(8.02)***	***616(40.82)***	***1509***			***1037(68.72)***	***74(4.90)***	***132(8.75)***	***266(17.63)***	***1509***		
Deteriorated	173(24.26)	9(15.25)	33(27.27)	141(22.89)	356(23.59)	0.3252		234(22.57)	20(27.03)	37(28.03)	65(24.44)	356(23.59)	0.2519	0.0422
No change	492(69.00)	49(83.05)	79(65.29)	433(70.29)	1053(69.78)		-0.0179	741(71.46)	46(62.16)	83(62.88)	183(68.80)	1053(69.78)		
Improved	48(6.73)	1(1.69)	9(7.44)	42(6.82)	100(6.63)	0.0480		62(5.98)	8(10.81)	12(9.09)	18(6.77)	100(6.63)	0.0509	
ABS scale score	***763(47.07)***	***68(4.19)***	***131(8.08)***	***659(40.65)***	***1621***			***1116(68.85)***	***78(4.81)***	***146(9.01)***	***281(17.33)***	***1621***		
Deteriorated	105(13.76)	11(16.18)	17(12.98)	68(10.32)	201(12.40)	**0.0045**		119(10.66)	9(11.54)	22(15.07)	51(18.15)	201(12.40)	**0.0002**	**0.1256**
No change	594 (77.85)	56(82.35)	97(74.04)	557(84.52)	1304(80.44)		**-0.0955**	931(83.42)	57(73.08)	110(75.34)	206(73.31)	1304(80.44)		
Improved	64(8.39)	1(1.47)	17(12.98)	34(5.16)	116(7.16)	**0.0815**		66(5.91)	12(15.38)	14(9.59)	24(8.54)	116(7.16)	**0.0910**	
Pain scale score	***758(47.20)***	***69(4.30)***	***129(8.03)***	***650(40.47)***	***1606***			***1105(68.80)***	***79(4.92)***	***144(8.97)***	***278(17.31)***	***1606***		
Deteriorated	68(8.97)	3(4.35)	12(9.30)	72(11.08)	155(9.65)	**0.0465**	**0.0761**	103(9.32)	14(17.72)	12(8.33)	26(9.35)	155(9.65)	0.9520	
No change	644(84.96)	59(85.51)	109(84.50)	521(80.15)	1333(83.00)			918(83.08)	56(70.89)	118(81.94)	241(86.69)	1333(83.00)		-0.0039
Improved	46(6.07)	7(10.14)	8(6.20)	57(8.77)	118(7.35)	**0.0537**		84(7.60)	9(11.39)	14(9.72)	11(3.96)	118(7.35)	0.0682	
Co-morbidity	***678(40.09)***	***70(4.14)***	***141(8.34)***	***678(40.09)***	***1691***			***1168(69.07)***	***80(4.73)***	***153(9.05)***	***290(17.15)***	***1691***		
Increased	101(12.59)	10(14.29)	25(17.73)	114(16.81)	250(14.78)	0.2487	0.0516	165(14.13)	15(18.75)	30(19.61)	40(13.79)	250(14.78)	0.4146	0.0211
No change	649(80.92)	53(75.71)	106(75.18)	522(76.99)	1330(78.65)			928(79.45)	61(76.25)	110(71.90)	231(79.66)	1330(78.65)		
Decreased	52(6.48)	7(10.00)	10(7.09)	42(6.19)	111(6.56)	0.0482		75(6.42)	4(5.00)	13(8.50)	19(6.55)	111(6.56)	0.0424	

‡Cramer's V for variables with more than two categories (negligible <0.1, small = 0.10–0.29, medium = 0.30–0.49, large ≥0.50)

Abbrevations: ABC – Aggressive Behaviour Scale; ADLH – Activities of Daily Living Hierarchy Scale; CHESS – Changes in Health, End-Stage Disease, and Signs and Symptoms Scale; CPS – Cognitive Performance Scale; DRS – Depression Rating Scale; PIM – Potentially Inappropriate Medications

Chapter 7 supplementary materials

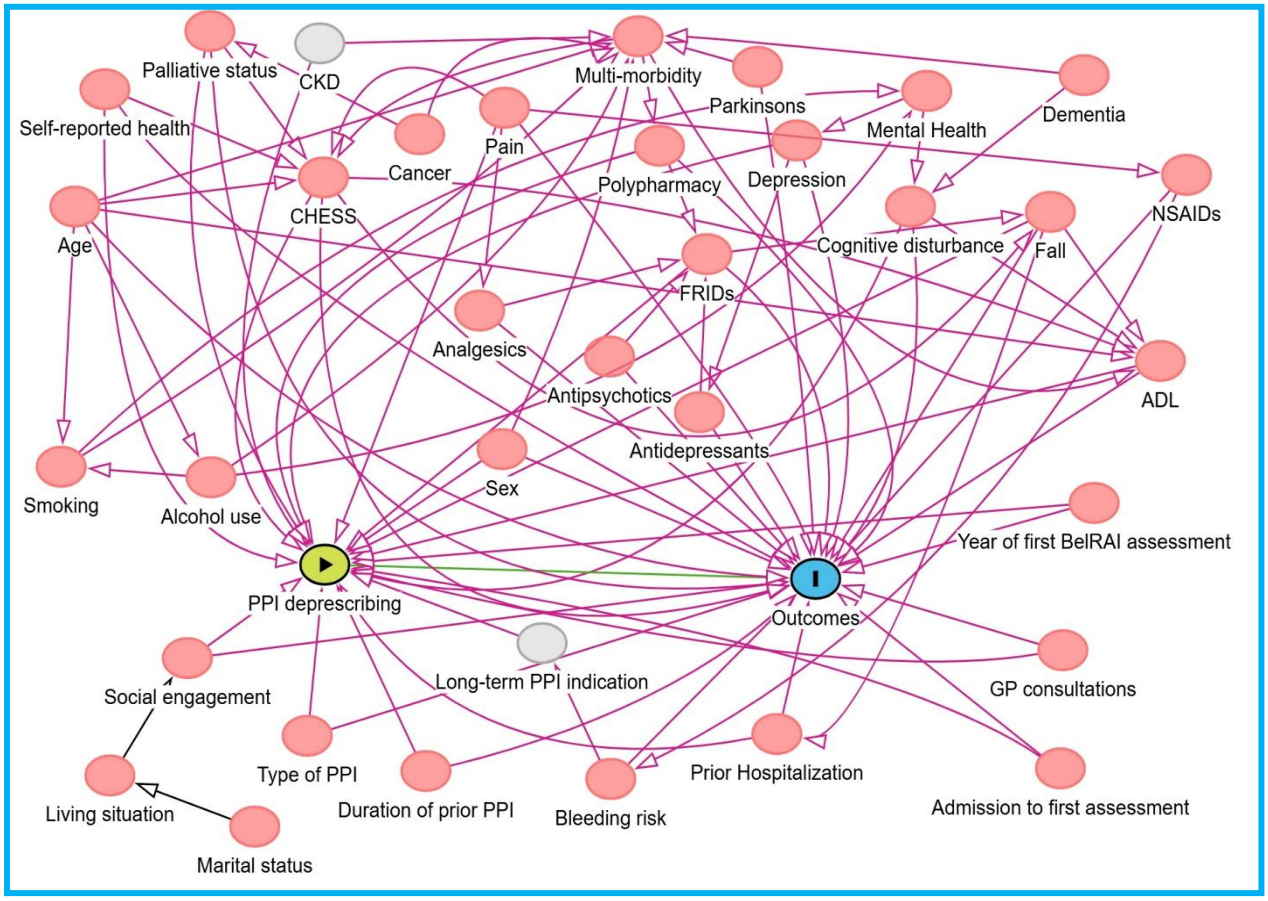
Supplemenary file 7.1: The items used to define the InteRAI scales

Scales	***Items for evaluation***	***code***
Activities of Daily Living Hierarchy Scale [ADLH]	Personal Hygiene Locomotion Toilet use Eating	iG2b iG2f iG2h iG2j
Cognitive Performance Scale [CPS]	Decision-making Short-term memory Understood Eating	iC1 iC2a iD1 iG2j
Depression Rating Scale[DRS]	Negative statements Persistent anger Unrealistic fears Repetitious health complaints Repetitious anxious complaints Sad, worried face expression Crying	iE1a iE1b iE1c iE1d iE1e iE1f iE1g
Pain Scale	Pain Frequency Pain Intensity	iJ5a iJ5b
Falls	Falls	iJ1
Revised index of social engagement [RISE])	At ease interacting with others At ease doing planned activities Accepts invitations Pursues involvement in life of facility Initiates interactions Reacts positively to interactions	iF5a iF5b iF5c iF5d iF5e iF5e
The Changes in health, End-stage disease, Signs, and Symptoms (CHESS) scale	Estimated survival Change in decision making Change in ADL status Health condition - Vomiting Health condition - Peripheral edema Health condition - Dyspnea End-stage disease Weight loss Insufficient fluid Dehydrated One or fewer meals Decrease in food or fluid Fluid output exceeds input	iA16a iC5 iG8a2 iJ2n iJ2s iJ3 iJ6c iK2a iK2b iK2c iK2e iK2g iK2h
Aggressive Behavior Scale [ABS]	Verbal abuse Physical abuse Socially inappropriate Resists care	iE3b iE3c iE3d iE3e
self-reported health	self-reported health	iJ7

Supplemenary file 7.2: List of fall risk increasing drugs (FRIDs) medications based on STOPPFALL criteria

	Medications	ATC code
CNS-active medications	Opioids	N02A
	Antipsychotics	N05A
	Anxiolytics	N05B
	Hypnotics and sedatives	N05C
	Antidepressants	N06A
	Antiepileptics	N03
Cardiovascular medications	Vasodilators used in cardiac diseases	C01D
	Antihypertensive	C02
	Diuretics	C03
	Beta blocking agents	C07
	Calcium channel blockers	C08
	Renin–angiotensin system inhibitors	C09

Supplemenary file 7.3: Causal directed acyclic graph (DAG) used to identify the minimum sufficient adjustment set for estimating the total effect of PPI deprescribing on quality-of-life–related patient outcomes, hospitalization, and all-cause mortality.



Minimum sufficent ajustment set for estomating total effect of PPI deprescribing on outcomes

Set1: ADL, Admission to first assessment, Age, Bleeding risk, CHESS, Cognitive disturbance, Depression , Duration of prior PPI, FRIDs, Fall, GP consultations, Pain, Palliative status, Parkinsons, Polypharmacy, Prior Hospitalization, Self-reported health, Sex, Social engagement, Type of PPI, Year of first BelRAI assessment

Supplemenary file 7.4: Description of each variables level how to handle for imputation and modelling in the propensity score model

Variable (for imputations)	Level	Missing frequency (%)	Selected for PS (DAG) (Yes/No)	Categorization of variable after imputation	Remark
Demographics / social factors					
Age in year	14→ (65-69)	0	Yes	65-74	Orginally delivered in category Name: AGE05_CAT to Age_category
	15→ (70-74)				
	16→ (75-79)			75-84	
	17→ (80-84)				
	18→ (85-89)			≥85	
	19→ (90-94)				
	20→ (95-99)				
	21→ (≥100)				
Sex	1→ Male	0	Yes	Male	Name: pp0020 to Sex
	2→ Female			Female	
Marital status	1→ Never married		No	Never married	Name: 'Marital Status'n to Marital_status
	2→Married			Married/partner	
	3→ Living together with partner				
	4→ Widow/widower			Widowed	
	5→Factually separated			Separated	
	6→ legally separated				
Living situation before admission to nursing homes	1→ alone		No	A lone	Name: LivingSituation_seq to Living_situation
	2→ with spouse or partner			With others	
	3→ with spouse or partner and others				
	4→ with childrens				
	5→ with parents or guardian				
	6→ with brothers or sisters				
	7→ with other relatives				
	8→ with non-verants				
	9→ in residential care or other institutionalized care settings				
Social engagement	0–6; lower scores indicate higher engagement, and higher scores indicate lower or no engagement (0 = *high engagement;* 6 = *no engagement*).		Yes	0: No engagement 1-2: Low engagement 3-4: Moderate engagement 5-6: High engagement	At baseline Name: IndexOfSocial Engagement_seq to Social_engagement
Smoking	0→ No		No	Same	
	1→Yes				
Alcohol use	0→ No		No	Same	
	1→ Yes				
Health and morbidity					
Baseline self-reported health	0→ Excellent		Yes	Good health	Self-reported health is an outcome, so only the baseline measurement is
	1→ Good				
	2→ Fair			Poor health	

	3→ Bad 8→ would not answer				included as a covariate in the models. 8 recode to missing Name: SelfRatedHealth to Self_Rated_Health to Self_Reported_Health
Mental health	0→ No 1→ Yes		No	Same	Name: Mental_Health
Pain	0→ No pain 1→Less than daily pain 2→ Daily pain but not severe 3→Daily severe pain 4→Daily excruciating pain		Yes	No daily pain Daily pain	Pain is an outcome so only baseline included in the covariate Name: PainCalculated_seq to Daily_Pain
CHESS	0-5		Yes	0→ No health instability 1-2→ Minimal/low health instability ≥3→ health instability	Name: ChessRecalculated_seq to CHESS
Baseline ADL	0-6		Yes	0-2→ No extensive assistance for ADL ≥3→ extensive assistance for ADL	ADL is an outcome so only baseline included in the covariate Name: ADLHierarchy_seq to Extensive_assistance_for_ADL
Baseline cognitive performance	0-6		Yes	0-2→ No Significant_ congitive_impairment ≥3→ Significant_ congitive_impairment	Cognitive preformance is an outcome so only baseline included in the covariate Name: CPSCalculated_seq to Significant_congitive_impairment
Baseline mood disturbance	0-14		Yes	0-2→ No daily depressive symptoms ≥3→ daily depressive symptoms	Cognitive preformance is an outcome so only baseline included in the covariate Name: depressionScale_seq to Daily depressive symptoms
Fall (last 90 days)	0→ No in 90 days 1→ No in last 30 days but fell 31-90 days ago 2→ One in last 30 days 3→2+ in last 30 days		Yes	0→ No fall in 90 days 1→ Fall in 90 days	Fall is an outcome so only baseline included in the covariate Name: FallScale_seq to Fall
Dementia	No Yes		No	Same	Name: Dementia
Cancer	0→ No		No	0→ No	

	1→ Primary diagnosis/diagnosis for current care period 2→Diagnosis present, active treatment 3→ Diagnosis present, being followed up, but no active treatment			1→ Yes	Name: Cancer to Cancer_cat
Parkinsons disease	0→ No 1→ Primary diagnosis/diagnosis for current care period 2→Diagnosis present, active treatment 3→ Diagnosis present, being followed up, but no active treatment			0→ No 1→ Yes	Name: = ParkinsonsDisease_seq to Parkinsons
Number of Morbidity	Count	0	No	0→0 1→1 2→2 3→ ≥3	Name: NumberOfComorbidities_seq to Number_of_morbidities
Palliative status	0→ No palliative care 1→ Recieving/planned		Yes	Same	Name: Palliative to Palliative_care_status
Medication burden & treatment context					
Number of chronic medications	Count	0	Yes	0-4: No polypharmacy 5-9: Polypharmacy ≥ 10: Excessive polypharmacy	Baseline_chronicMed_count to ChronicMedication_class
FRIDs	0→No 1→Yes	0	Yes	Same	Name: FRIDs
Number of FRIDS	Count	0	Yes	Same	Name: Num_FRIDs
Antidepressants	0→No 1→Yes	0	No	Same	Name: chronicUseN06A
Antipsychotics	0→No 1→Yes	0	No	Same	Name: chronicUseN05A
Analgesics	0→No 1→Yes	0	No	Same	Name: ChronicAnalgesic_N02
NSAIDS	0→No 1→Yes	0	No	Same	Name: chronicUseM01
PPI indication & GI risk					
Bleeding risk	0→No 1→Yes	0	yes	Same	Name: Bleeding
Duration of PPI use at time zero (days)	Number of days	0	Yes	90-179 (3-6 months) 180-269 (6-9 months) 270-359 (9-12 months) 360-719 (12-24months) ≥ 720 (24 month+)	Name: change DurationPPI_Pre180 to Duration_PPI_use
Type of PPI	Omeprazole (A02BC01) Pantoprazole (A02BC02) Lansoprazole (A02BC03)	0	Yes	Omeprazole Pantoprazole others	Name: Type_PPI to Types_of_PPI

	Rabeprazole (A02BC04) Esomeprazole (A02BC05)				
Health care utilization & system factors					
Prior Hospitalizations (3months)	0→ No hospitalization 1→31-90 days 2→15-30 days 3→8-14 days 4→in the last 7 days 5→Now in the hospital		Yes	0→ No hospitalization 1→ Hospitalized	Number of hospitalization is an outcome Name: HospitalazationBel_seq to Prior_Hospitalization_90days
Number of GP consulations	Count		Yes	0→0 1→1 2→2 3→ ≥3	Name: Number_of_consulting_Physician to Number_of_GP_consulations
Year of first BelRAI assessment	2016-2022	No	Yes	2016-2019 2020-2022	Name: Year_BelRAI_reg to Years_of_first_BelRAI_assessment
Duration admission → assessment	1 →< 180 days 2→180-359 3→360-719 4→≥ 720	No	Yes	Same	Name: NHDays_BeforeBelRAI to Duration_admission_assessment
Assessment follow-up	0,3,6,12 months			Same	Time_Months
Exposure					
PPI Exposure	0→ Continued 1→ Discontinued 2→ Intermitent/on-demand use			0 - Continued 1 - Deprescribing	For sensitivity analysis 0, and 1 excluded Intermitent/on-demand use
Outcomes (by scales)					
Activities of Daily Living Hierarchy Scale	0 to 6			≥3 indicates extensive assistance of ADL	
Cognitive Performance Scale	0 to 6			≥3 indicates significant cognitive impairment	
Depression Rating Scale	0 to 14;			≥3 indicates daily depressive symptoms	
Daily pain	0 to 4			≥2 indicates daily pain	
Self reported health	0 to 3;			≤1 indicates good health and ≥2 indicates poor health	
Number of Hospital admission after intervention (12 months)	Count per resident per 12 months or death if died before 1 year	No		Number of hospitalizations until death among residents who died within 12 months, and during 12 months of follow-up among those who did not die.	Number_of_HospitalAdm0_360

Death Time to death	0→No 1→Yes Days after the intervention	No		Time until event (death)/censored end of follow up (360 days)	Death Time_to_Death
Fall	0 to 3;			0 indicates no fall and ≥1 indicates at least one fall in the last 90 days	
Repeated measure of primary outcomes					
Visit	(1, 2, 3, 4)				
Time in month since the baseline (crosponding to each visit)	(0, 3, 6, 12)				

Supplemenary file 7.5: Pooled Odds Ratios from Multiple Imputation Analysis

Variable	*Level*	*Log(OR)*	*SE*	*95% CI Lower*	*95% CI Upper*	*P value*	*OR*	*OR Lower*	*OR Upper*
ADL_Baseline	Yes	-0.000327	0.088145	-0.1731	0.1724	0.9970	0.99967	0.84106	1.18820
Age_category	75-84	-0.125434	0.107521	-0.3362	0.0853	0.2434	0.88211	0.71450	1.08905
Age_category	>=85	-0.333731	0.113189	-0.5556	-0.1119	**0.0032**	0.71625	0.57374	0.89415
Alcohol_use	Yes	0.033483	0.091849	-0.1466	0.2135	0.7155	1.03405	0.86368	1.23802
Analgesics	Yes	0.078954	0.082277	-0.0823	0.2402	0.3372	1.08215	0.92099	1.27152
Antidepressants	Yes	-0.144348	0.081466	-0.3040	0.0153	0.0764	0.86559	0.73785	1.01544
Antipsychotics	Yes	0.027527	0.093651	-0.1560	0.2111	0.7688	1.02791	0.85554	1.23501
Baseline_depression	Yes	-0.063497	0.084735	-0.2296	0.1026	0.4536	0.93848	0.79487	1.10803
Bleeding_risk	Yes	-0.089063	0.255131	-0.5892	0.4111	0.7270	0.91479	0.55475	1.50850
CHESS	Minimal/low health instability	0.189747	0.078413	0.0360	0.3434	**0.0155**	1.20894	1.03671	1.40979
CHESS	Moderate to severe health instability	0.288890	0.164243	-0.0331	0.6108	0.0786	1.33495	0.96748	1.84199
Cancer	Yes	-0.129186	0.124052	-0.3723	0.1140	0.2977	0.87881	0.68912	1.12072
Cognition_Baseline	Yes	0.144408	0.094399	-0.0406	0.3294	0.1261	1.15536	0.96020	1.39018
Dementia	Yes	-0.025736	0.088004	-0.1982	0.1467	0.7699	0.97459	0.82019	1.15806
Duration_PPI_use	12-24 months	-0.008288	0.186442	-0.3737	0.3571	0.9645	0.99175	0.68818	1.42922
Duration_PPI_use	6-9 months	0.249370	0.262293	-0.2647	0.7635	0.3417	1.28322	0.76742	2.14568
Duration_PPI_use	9-12 months	-0.120096	0.264619	-0.6387	0.3985	0.6499	0.88684	0.52796	1.48966
Duration_PPI_use	>=24 months	0.006596	0.222177	-0.4289	0.4421	0.9763	1.00662	0.65125	1.55590
Duration_admission_a	12-24 months	-0.356767	0.127711	-0.6071	-0.1065	**0.0052**	0.69994	0.54494	0.89901
Duration_admission_a	6-12 months	-0.418740	0.131361	-0.6762	-0.1613	**0.0014**	0.65788	0.50854	0.85106
Duration_admission_a	>=24 months	-0.651576	0.111213	-0.8695	-0.4336	**<.0001**	0.52122	0.41914	0.64817

Variable	*Level*	*Log(OR)*	*SE*	*95% CI Lower*	*95% CI Upper*	*P value*	*OR*	*OR Lower*	*OR Upper*
Fall_Baseline	Yes	0.114045	0.085801	-0.0541	0.2822	0.1838	1.12080	0.94731	1.32607
Hospitalization_Base	Yes	-0.082661	0.106584	-0.2916	0.1262	0.4380	0.92066	0.74709	1.13456
Intercept		-1.055904	0.318726	-1.6806	-0.4312	0.0009	0.34788	0.18626	0.64972
Living_situation	live with others	-0.110750	0.087013	-0.2813	0.0598	0.2031	0.89516	0.75480	1.06162
Marital_status	Never married	-0.035800	0.166352	-0.3619	0.2903	0.8296	0.96483	0.69638	1.33677
Marital_status	Separated	-0.210690	0.194050	-0.5911	0.1697	0.2776	0.81003	0.55373	1.18495
Marital_status	Widowed	-0.004419	0.115156	-0.2301	0.2213	0.9694	0.99559	0.79443	1.24769
Mental_Health	Yes	-0.127210	0.121755	-0.3659	0.1114	0.2961	0.88055	0.69360	1.11788
NSAIDs	Yes	0.076108	0.252322	-0.4184	0.5707	0.7629	1.07908	0.65808	1.76942
Number_of_FRIDs		-0.060002	0.033019	-0.1247	0.00471	0.0692	0.94176	0.88275	1.00473
Number_of_GP_consula	1	0.070237	0.078675	-0.0840	0.2244	0.3720	1.07276	0.91945	1.25163
Number_of_GP_consula	2	0.351231	0.155936	0.0456	0.6569	**0.0243**	1.42082	1.04663	1.92878
Number_of_GP_consula	>=3	0.152656	0.219835	-0.2783	0.5836	0.4875	1.16492	0.75707	1.79251
Number_of_chronic_me		0.020494	0.014155	-0.00725	0.0482	0.1477	1.02071	0.99278	1.04942
Number_of_morbiditie	1	0.117926	0.114491	-0.1065	0.3423	0.3030	1.12516	0.89900	1.40822
Number_of_morbiditie	2	0.065825	0.121284	-0.1719	0.3035	0.5873	1.06804	0.84207	1.35464
Number_of_morbiditie	>=3	-0.026840	0.125454	-0.2727	0.2190	0.8306	0.97352	0.76130	1.24489
Pain_Baseline	Yes	-0.003077	0.102115	-0.2032	0.1971	0.9760	0.99693	0.81609	1.21783
Palliative_care_stat	Receiving / Planned palliative care	-0.110706	0.214930	-0.5321	0.3107	0.6065	0.89520	0.58737	1.36437
Parkinsons	Yes	0.056347	0.139329	-0.2167	0.3294	0.6859	1.05796	0.80513	1.39019
Self_Reported_Health	Poor health	-0.072721	0.085456	-0.2403	0.0948	0.3948	0.92986	0.78642	1.09947
Smoking	Yes	0.186198	0.102172	-0.0141	0.3865	0.0684	1.20466	0.98604	1.47175
Social_engagement	Low engagement	0.386627	0.103245	0.1843	0.5890	**0.0002**	1.47201	1.20233	1.80217
Social_engagement	Moderate engagement	0.226011	0.092059	0.0456	0.4064	**0.0141**	1.25359	1.04663	1.50148
Social_engagement	No engagement	0.367558	0.128501	0.1157	0.6194	**0.0042**	1.44420	1.12265	1.85786
Types_of_PPI	Omeprazole	0.276323	0.108270	0.0641	0.4885	**0.0107**	1.31827	1.06622	1.62992
Types_of_PPI	Other PPIs	0.006097	0.151635	-0.2911	0.3033	0.9679	1.00612	0.74744	1.35432
Years_of_first_BelRA	2020-2022	0.878814	0.126572	0.6307	1.1269	**<.0001**	2.40804	1.87900	3.08604
sex	Female	-0.026095	0.086033	-0.1947	0.1425	0.7617	0.97424	0.82307	1.15318

Supplemenary file 7.6: Number of residents with observed, missing, and truncated outcome status by death at each visit windows

Outcomes	**Visits**	**N= 3604**			**Remark**
		Outcome measure observed n (%)	***Outcome measure is missing n (%)***	***Outcome measure is truncated n (%) ****	
Extensive assistance for ADL	Baseline	3427 (95.09)	177 (4.91)	0 (0)	To estimate a marginal treatment effect, baseline outcome values were included as confounders. We assumed that the baseline status of the outcome may influence the decision to discontinue treatment and is also predictive of future outcome trajectories. Therefore, adjusting for baseline outcome helps control for confounding and improves comparability between treatment groups.
	3 months	452 (12.54)	2984 (82.80)	168 (4.66)	
	6 months	774 (21.48)	2443 (67.79)	387 (10.74)	
	12 months	1142 (31.69)	1773 (49.20)	689 (19.12)	
Significant Congitive impairment	Baseline	3377 (93.70)	227 (6.30)	0 (0)	
	3 months	444 (12.32)	2989 (82.94)	171 (4.74)	
	6 months	773 (21.45)	2443(67.79)	388 (10.77)	
	12 months	1141 (31.66)	1774 (49.22)	689 (19.12)	
Daily Pain	Baseline	3395 (94.20)	209 (5.80)	0 (0)	
	3 months	450 (12.49)	2985 (82.82)	169 (4.69)	
	6 months	774 (21.48)	2443 (67.79)	387 (10.74)	
	12 months	1143 (31.71)	1772 (49.17)	689 (19.12)	
Daily depressive symptoms	Baseline	3440 (95.45)	164 (4.55)	0 (0)	
	3 months	449 (12.46)	2985 (82.82)	170 (4.72)	
	6 months	771 (21.39)	2444 (67.81)	389 (10.79)	
	12 months	1142 (31.69)	1773 (49.20)	689 (19.12)	
Fall	Baseline	3428 (95.12)	176 (4.88)	0 (0)	
	3 months	456 (12.65)	2979 (82.66)	169 (4.69)	
	6 months	776 (21.53)	2441 (67.73)	387 (10.74)	
	12 months	1144 (31.74)	1771 (49.14)	689 (19.12)	
Self-Reported Health	Baseline	2965 (82.27)	639 (17.73)	0 (0)	
	3 months	392 (10.88)	3024 (83.91)	188 (5.22)	
	6 months	663 (18.40)	2538 (70.42)	403 (11.18)	
	12 months	986 (27.36)	1905 (52.86)	713 (19.78)	
Death	Time to death (until 12 month)				There was no competing risk because death itself was the outcome of interest.
Number of hospitalization	Until 12 months				Cumulated number of hospitalization was complete until death (770) or administrative censoring at the end of the study period.

*Total death is 770 in the last year but as we, use a time window of assessment only, truncated may be those not having completed assessment [death in the first 3 month=240 (6.66), 6 month=437 (12.13) and 12 month= 770 (21.37)]

Supplemenary file 7.7: RMST Summary: Discontinuation vs Continuation (Mortality)

τ (days)	*ΔRMST (difference)*	*ΔRMST 95% CI*	*p (ΔRMST)*	*RMST ratio*	*Ratio 95% CI*	*p (ratio)*
Main analysis						
90	1.80	0.85 to 2.75	0.0002	1.021	1.010 to 1.032	0.0002
180	4.41	1.97 to 6.85	0.0004	1.027	1.012 to 1.042	0.0004
270	-4.77	-9.22 to -0.32	0.0358	0.981	0.963 to 0.999	0.036
360	-16.01	-22.78 to -9.23	0.0001	0.950	0.930 to 0.971	0.0001
Sensitivity analysis						
90	-15.38	-21.20 to -9.57	<.0001	0.821	0.759 to 0.889	<.0001
180	-31.57	-43.02 to -20.12	<.0001	0.810	0.744 to 0.882	<.0001
270	-49.08	-68.51 to -29.65	<.0001	0.801	0.732 to 0.876	<.0001
360	-63.77	-90.30 to -37.24	<.0001	0.802	0.726 to 0.885	<.0001

Footnote: Weighted by IPTW (SW); MI-pooled across 90 imputations. RMST Difference is in days; RMST ratio is unit less. 95% CIs and two-sided p-values are shown.

Supplemenary file 7.8: Detailed results for the main and sensitivity analyses of the effect of PPI deprescribing on hospitalizations

Measure	**Main analysis**	**Sensitivity analysis ***
Incidence rate ratio (Discontinued vs Continued)	0.81	0.24960
95% CI	0.69 – 0.94	0.12780 – 0.48749
E value (point estimate)	1.78	7.48
E value (95% CI limit closest to 1)	1.32	3.52
Daily rate: Continued	0.00116 (95% CI: 0.00106 – 0.00126)	0.001148 (95% CI: 0.001051 – 0.001254)
Daily rate: Discontinued	0.00093 (95% CI: 0.00073 – 0.00119)	0.000287 (95% CI: 0.000134 – 0.000611)
Yearly rate: Continued	0.416 (95% CI: 0.380 – 0.455)	0.416 (95% CI: 0.379 – 0.451)
Yearly rate: Discontinued	0.335 (95% CI: 0.263 – 0.428)	0.104 (95% CI: 0.049 – 0.220)

Footnote: IRR estimated from an IPTW-weighted negative-binomial GEE model using a while-alive strategy. E-values quantify the minimum strength of association that an unmeasured confounder would need with both exposure and outcome to fully explain the observed association.

*****In the IPTW weighted negative binomial model restricted to person time alive, the deprescribed group experienced substantially fewer hospitalizations per unit of person time than the continued therapy group. The incidence rate ratio (IRR) was 0.25 (95% CI: 0.13–0.49, p < .0001), indicating that deprescribing was associated with a 75% lower hospitalization rate relative to continued PPI use.

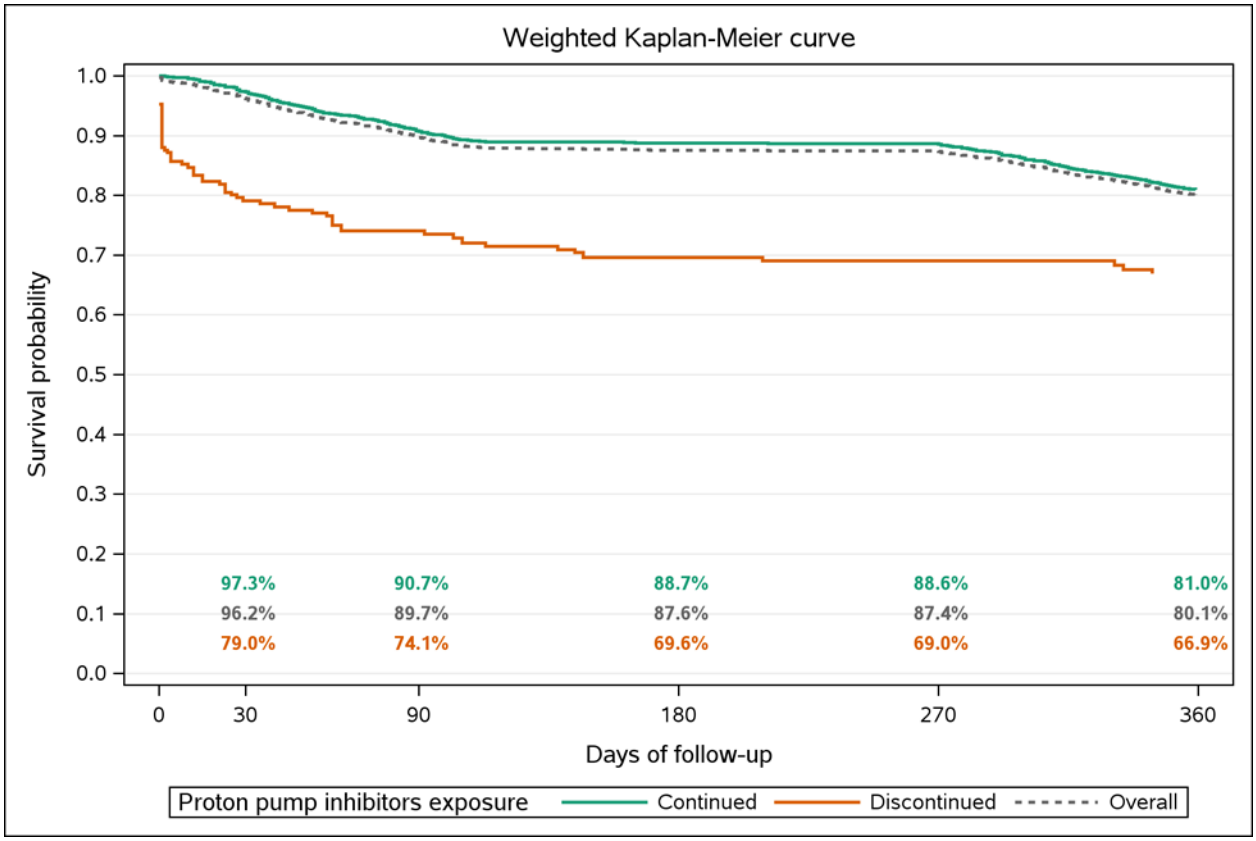
Daily hospitalization rates were 0.00115 (95% CI: 0.00105–0.00125) in the continued group and 0.00029 (95% CI: 0.00013–0.00061) in the deprescribed group. When expressed at the yearly scale, these correspond to 0.416 hospitalizations per resident year in the continued group compared with 0.103–0.220 hospitalizations per resident year in the deprescribed group.

Clinically, this means that for every 100 residents alive per year, we would expect approximately 42 hospitalizations among those who continued PPI therapy versus 10–22 hospitalizations among those who were deprescribed. The large separation in rates and the narrow uncertainty bounds suggest a robust reduction in hospitalization incidence associated with deprescribing within this weighted, MI pooled negative binomial framework.

Supplemenary file 7.9: Estimates of quality-of-life–related patient outcomes based on different estimands and alternative definitions of deprescribing.

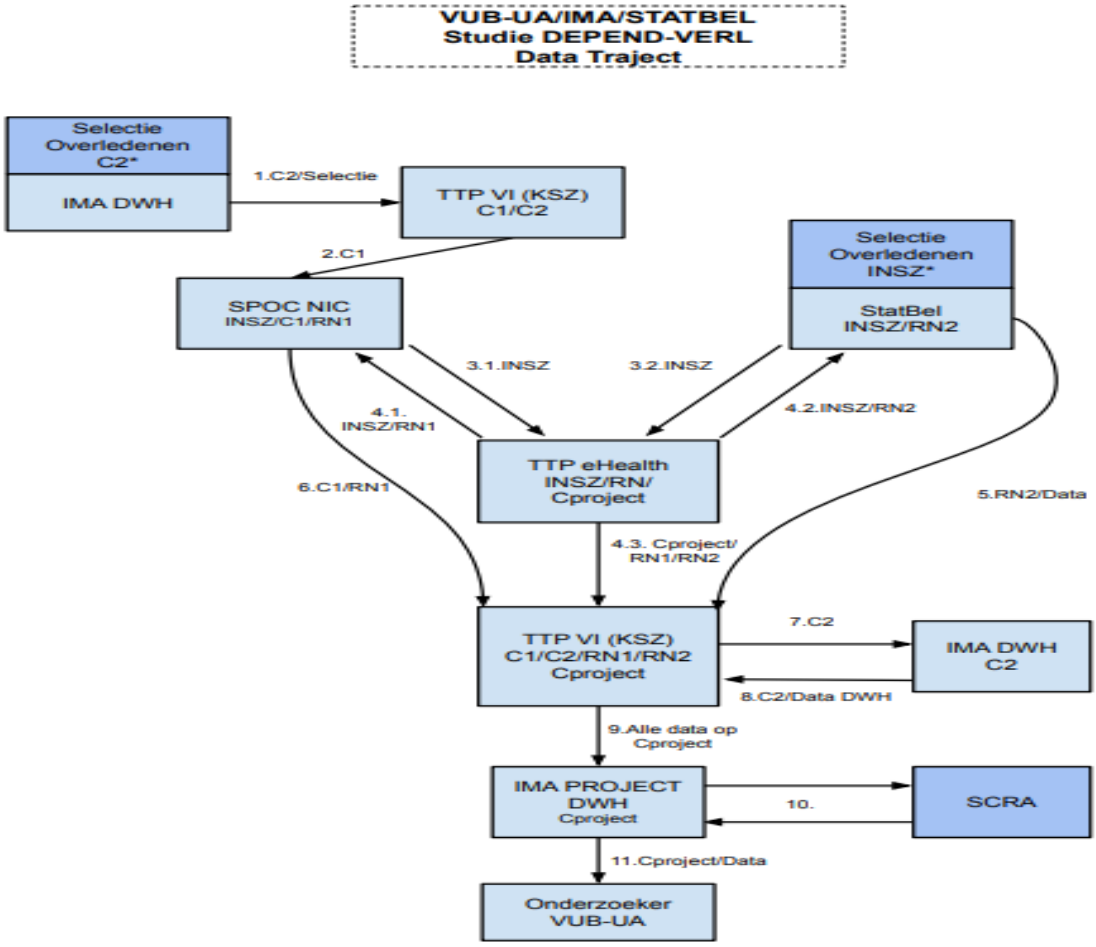
Strategy for handling death (Analysis)	Estimands	**Outcomes**	Estimate (95% CI) (Time*PPI exposure)	P-value	Fraction of missing informations
Main effect					
While-alive: summarize only while alive	What is the marginal difference in the outcome, averaged over the follow-up period while individuals were alive up to 360 days, when comparing PPI discontinuation with continuation?	Extensive assistance for ADL	0.992 (0.982, 1.002)	0.1224	0.175778
		Significant congitive impairment	0.996 (0.986, 1.005)	0.3650	0.238875
		Daily Pain	0.996 (0.978–1.013)	0.6335	0.273607
		Daily depressive symptoms	1.004 (0.990–1.018)	0.6015	0.331696
		Fall	1.004 (0.983–1.028)	0.7238	0.438752
		Self Reported Health	1.002 (0.981–1.024)	0.8448	0.708220
Sensitivity analysis: with different estimand					
Hypothetical: remove death conceptually	What is the effect on the outcome at 360 days when comparing PPI discontinuation with continuation, in a hypothetical scenario where all individuals would have survived to have the outcome measured?	Extensive assistance for ADL	0.994 (0.985, 1.003)	0.1782	0.244825
		Significant congitive impairment	0.996 (0.987, 1.005)	0.3573	0.237462
		Daily Pain	0.998 (0.981, 1.015)	0.7931	0.351522
		Daily depressive symptoms	1.005 (0.992, 1.017)	0.4458	0.354852
		Fall	1.006 (0.983, 1.028)	0.6299	0.491235
		Self Reported Health	0.996 (0.978, 1.015)	0.6985	0.710289
Composite: death = worst outcome	What is the marginal effect at 360 days on the composite of death or the outcome when comparing PPI discontinuation with continuation, treating death as the worst possible outcome state?	Extensive assistance for ADL	1.007 (0.995, 1.019)	0.2595	0.116008
		Significant congitive impairment	1.033 (1.020, 1.045)	<.0001	0.070314
		Daily Pain	1.060 (1.041–1.078)	<.0001	0.101605
		Daily depressive symptoms	1.032 (1.018–1.047)	<.0001	0.192838
		Fall	1.054 (1.033–1.075)	<.0001	0.321423
		Self Reported Health	1.045 (1.025–1.066)	<.0001	0.493652
Principal stratum: restrict to always-survivors	What is the effect on the outcome at 360 days when comparing PPI discontinuation with continuation in the sub-population of individuals who would survive to 360 days under either treatment strategy?	Extensive assistance for ADL	0.991 (0.982, 1.001)	0.0760	0.177941
		Significant congitive impairment	0.996 (0.986, 1.007)	0.4893	0.200660
		Daily Pain	0.994 (0.976-1.013)	0.5527	0.243830
		Daily depressive symptoms	1.007 (0.992–1.021)	0.3527	0.307654
		Fall	1.004 (0.980–1.029)	0.7408	0.432541
		Self Reported Health	1.002 (0.983–1.021)	0.8759	0.642516
Sensitivity analysis by redefining exposure: excluding the intermittent/on-demand PPI use (for the main analysis)					
While-alive: excluding intermitent use	What is the effect on the outcome at 360 days when comparing PPI discontinuation(not including intermittent use) with continuation, in a hypothetical scenario where all individuals would have survived to have the outcome measured?	Extensive assistance for ADL	0.993 (0.982–1.003)	0.1833	0.178213
		Significant congitive impairment	0.995 (0.985–1.004)	0.2791	0.244316
		Daily Pain	0.996 (0.978–1.014)	0.6592	0.255992
		Daily depressive symptoms	1.000 (0.986–1.015)	0.9598	0.349183
		Fall	1.002 (0.978–1.027)	0.8704	0.444215
		Self Reported Health	1.002 (0.979–1.024)	0.8817	0.702875

Supplemenary file 7.10: Kaplan-Meier curve for sustaind deprescribing versus continued use



Chapter 8 supplementary materials

Supplemenatry File 8.1A: ***Step-by-step overview of linkage procedure for cohort 1***



Abbreviations:

IMA DWH: InterMutualistic Agency Data Warehouse;

TTP VI KSZ: Trusted Third Party Crossroads Bank for Social Security;

SPOC NIC: Single Point of Contact National InterMutualistic College;

TTP eHealth: Trusted Third Party eHealth;

StatBel BE: Statistics Belgium;

SCRA: Small Cells Risk Analysis;

SSN: Social Security Number; C1/C2: coding 1/2;

Both IMA and StatBel make a selection of deceased from their DWH.

1. IMA does the selection of the deceased from the DWH at C2. This list is transmitted to TTP VI (KSZ).

2. The TTP VI (KSZ) converts C2 to C1 and sends the list on C1 to DPO NIC.

3.1. The DPO NIC converts the C1 to INSZ and transfers the list with INSZ to TTP-eHealth;

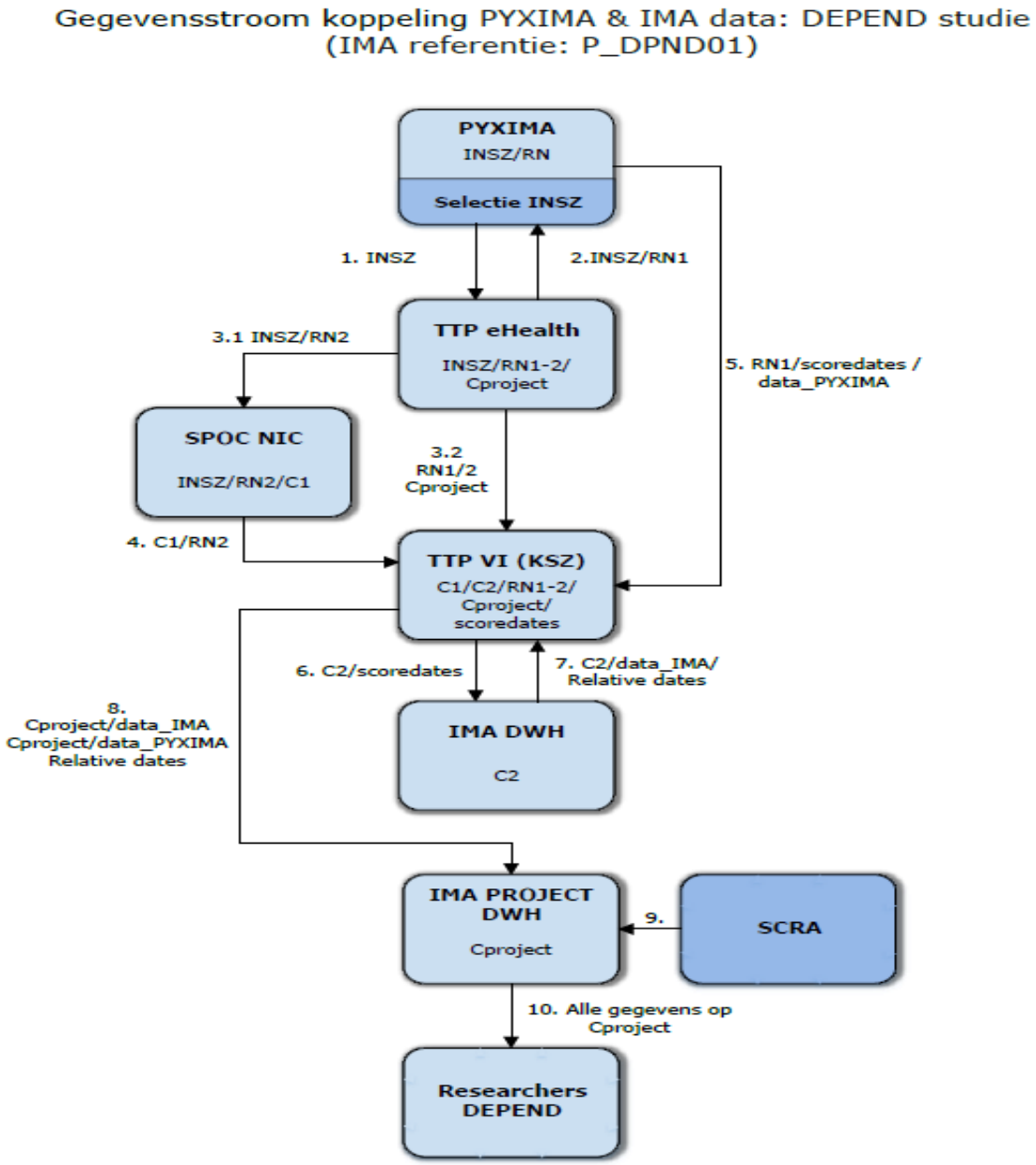
3.2. For the purpose of this study, StatBel makes a selection from the DWH and transfers the list of INSZ to TTP-eHealth;

Upon receipt of both lists (3.1 & 3.2), TTP-eHealth assigns an RN to each unique INSZ;

4.1. eHealth sends the INSZ/RN1 back to the DPO NIC;

4.2. eHealth sends the INSZ/RN2 list to the responsible StatBel;
4.3. eHealth sends the RN1/RN2/Cproject list to the TTP-VI (KSZ);
5. The responsible StatBel forwards this data on RN2 to the TTP VI (KSZ);
6. The DPO NIC transmits the list of persons to the TTP VI (KSZ) on C1/RN1;
7. Based on a second pseudonymisation (C1 → C2), the data are selected from IMA's data warehouse (DWH IMA);
8. Data is delivered back to TTP VI (KSZ) at C2;
9. The TTP VI (KSZ) replaces the C2 in the data with the Cproject, and also puts the received data (Statistics Belgium) on Cproject. All data are placed on Cproject in the IMA DWH;
10. A Small Cells Risk Analysis will be performed;
11. The datasets will be made available to researchers on Cproject.

Supplementary file 8.1B: ***Step-by-step overview of linkage procedure for cohort 2***



Abbreviations:

IMA DWH: InterMutualistic Agency Data Warehouse;
TTP VI KSZ: Trusted Third Party Crossroads Bank for Social Security;
SPOC NIC: Single Point of Contact National InterMutualistic College;
TTP eHealth: Trusted Third Party eHealth;
SCRA: Small Cells Risk Analysis; (by KCE)
SSN: Social Security Number; C1/C2: coding 1/2;
Data flow coupling PYXIMA & IMA data: DEPEND study (IMA reference: P_DPND01)

In the context of this study:

Step 1: From PYXIMA's data warehouse (DWH), all individuals registered since 2016 are selected. PYXIMA hereafter transfers this list of unique INSZ to the TTP eHealth for coding.

TTP eHealth will create a unique C-project code for each INSZ along with 2 random identifiers (RN1/RN2). After this, the TTP eHealth will take the following steps:

- Step 3.1: the correspondence list INSZ/RN1 is transferred to the responsible PYXIMA.
- Step 3.2: the correspondence list INSZ/RN2 will be transferred to the unique point of contact at the National Intermutual College (NIC SPOC)
- Step 3.3: the correspondence list RN1/RN2/C project is transferred to the Trusted Third Party of Insurance Institutions (TTP VI (KSZ)).

Step 4: SPOC NIC replaces each INSZ from the list INSZ/RN2 with the unique code (C1) of the insurance institutions and transfers the new list C1/RN2 to the TTP VI (KSZ).

Step 5: PYXIMA transmits the registration data including score dates to the TTP VI (KSZ).

Step 6: The TTP VI (KSZ) converts each C1 from the C1/RN2 list to the InterMutualistic Agency (IMA) code C2 and makes the exhaustive list of C2 codes including associated score dates (C2/scoredate) available in the IMA Data Warehouse. The score dates are replaced in the final dataset by relative dates where the first score date is the reference.

Step 7: The IMA selects all necessary data on C2 (data_IMA) and transforms all absolute dates of requested performance into number of days relative to the first score date (0) of each patient. In the process, the sequence of score moments per patient is not lost given that the sequence and duration between score moments is preserved.

After this, the data are transferred to the TTP VI (CSF).

Step 8: All data are placed on C-project and transferred to the IMA Project DWH.

Step 9: A Small Cells Risk Analysis (SCRA) is performed before making the data available if deemed necessary by the Information Security Committee (IVC).

Step 10: The data is made available to researchers in the IMA Project DWH.

List of abbreviations

ARIMA: Autoregressive Integrated Moving Average

ATC: Anatomical Therapeutic Chemical

BCT: Behavior Change Techniques

DDD: Defined Daily Dose

EHDS: European Health Data Space

HDA: Health Data Agency

ICD-10: International Classification of Diseases, 10th Revision

IMA-AIM: InterMutualistisch Agentschap-Agence InterMutualiste

ISC: Information Security Committee

KCE: Belgian Health Care Knowledge Center

LTCF: Long Term Care Facility

PIMs: Potentially Inappropriate Medications

PPI: Proton Pump Inhibitor

SCRA: Small Cell Risk Analysis

STOPPFrail: Screening Tool of Older Persons' Prescriptions in Frail adults with limited life expectancy

TDF: Theoretical Domains Framework

TTPs: Trusted Third Parties

Curriculum Vitae

Personal informations:

Name: Anlay
Given Name: Degefaye Zelalem
Nationality: Ethiopian
Work email: degefaye.zelalem.anlay@vub.be
degefayezelalem.anlay@uantwerpen.be
Private email: degefaye@gmail.com
Phone: +32497272696

Education:

Degree	Institution	Period
Master of Epidemiology	University of Antwerpen, Belgium	09/2019-09/2021
Master of clinical tropical infectious disease & HIV Medicine	University of Gondar, Ethiopia	01/2013-06/2015
Bachealors in Nursing	University of Gondar, Ethiopia	12/2006-07/2009

Research experience

Since July 2022, I have been working as a doctoral researcher at the End-of-Life Care Research Group at the Vrije Universiteit Brussel and the Centre for Research and Innovation in Care at the University of Antwerp. My PhD research focuses on strengthening the evidence on the effects of deprescribing medications and investigating the real world implementation of deprescribing in nursing homes. Using large scale linked administrative data, including healthcare reimbursement records, statistical agency data, and patient level clinical data from the BelRAI long term care facility assessment, I apply a range of epidemiological and advanced statistical methods. These include interrupted time series analysis and target trial emulation to estimate the causal effects of deprescribing on quality of life related outcomes. My research also addresses challenges in accessing and analysing large health datasets.

Prior to my current position, I gained research experience in the field of clinical infectious diseases, with a particular focus on drug related problems in HIV and tuberculosis, as well as treatment failure in resource limited settings. In addition, I was involved in clinical research focusing on clinical risk prediction.

Publications

Peer reviewed articles

- More than 30 articles indexed in ISI web of Science
- **ORCID code:** https://orcid.org/0000-0002-7566-9548

Publications as part of PhD:

Anlay DZ, Paque K, Van Leeuwen E, Cohen J, Dilles T. Tools and guidelines to assess the appropriateness of medication and aid the deprescribing: an umbrella review. Br J Clin Pharmacol. 2023 Sep 11. doi: 10.1111/bcp.15906 [2022 IF 3.4; Ranking Q2; ranking 126/277 PHARMACOLOGY & PHARMACY]

Anlay DZ, Paque K, Van den Eynden B, Dilles T, Cohen J. International Deprescribing Guidelines Did Not Impact Actual Practice in Deprescribing of Potentially Inappropriate Medications for Nursing Home Residents: An Interrupted Time Series Analysis. Drugs & Aging. 2025 May;42(5):485-499. 105122. doi: 10.1007/s40266-025-01197-2 [2023 IF 3.4; Ranking Q2; ranking 22/73 GERIATRICS & GERONTOLOGY]

Anlay DZ, Peremans L, Cohen J, Dilles T, Paque K. Deprescribing for nursing home residents with limited life expectancy: A qualitative study to identify barriers and enablers for healthcare professionals. Geriatr Nurs. 2025 Feb 4;62(Pt B):1-11. doi: 10.1016/j.gerinurse.2025.01.049 [2023 IF 2.5; Ranking Q1; ranking 33/193 NURSING]

Anlay DZ, Paque K, Brys ADH, Cohen J, Dilles T. Balancing palliative care needs and medication appropriateness: Initiation and reinitiation of medications at the end of life. Arch Gerontol Geriatr. 2025 Aug 23;139:105994. doi: 10.1016/j.archger.2025.105994. Epub ahead of print. PMID: 40916322. [2024 IF 3.8; Ranking Q2; ranking 22/73 GERIATRICS & GERONTOLOGY]

Anlay DZ, de Almeida Mello J, Declercq A, Van Leeuwen E, Paque K, Cohen J, Dilles T. Evolution of Health and Medication Use in a Cohort of Nursing Home Residents: A Data Linkage Study. J Am Med Dir Assoc. 2026 Jul 2;27(8):106300. doi: 10.1016/j.jamda.2026.106300. Epub ahead of print. PMID: 42391777. [2025 IF 3.4; Ranking Q2; ranking 33/72 GERIATRICS & GERONTOLOGY in SCIE edition]

Anlay DZ, Paque K, Sabbe K, Miranda R, Dilles T, Cohen J. Structural challenges in accessing and using big data in health care: A case study based on palliative care research. Int J Med Inform. 2026 Jul 6;220:106593. doi: 10.1016/j.ijmedinf.2026.106593. Epub ahead of print. PMID: 42413364. [2025 IF 5; Ranking Q1; ranking 25/194 HEALTH CARE SCIENCES & SERVICES in SCIE edition]

Anlay DZ, Paque K, de Almeida Mello J, Declercq A, Van Leeuwen E, Dilles T, Cohen J. (submitted) The effect of deprescribing proton pump inhibitors on quality-of-life related patient outcomes among nursing home residents: a target trial emulation.

Other publications:
Anlay DZ. (2026) Wat elke verpleegkundige moet weten over 'deprescribing': van kennis naar actie in de dagelijkse praktijk. Netwerk verpleegkunde magazine

Anlay DZ.(2025) Data linkages in Belgian (administrative) RWD: the missing link. Available from: https://academy.hda.belgium.be/pluginfile.php/1001/mod_resource/content/1/artikel%208_BMT-HDTS%20-%20Data%20linkages%20in%20Belgian.pdf

---

Presentations
'Deprescribing for older nursing home residents: Linked big-data evidence on the implementation and effects of deprescribing on outcomes relevant to End-of-Life Care'. NuPhaC international board meeting (2026) [virtual oral presentation]

'International Deprescribing Guidelines Did Not Impact Actual Practice in Deprescribing of Potentially Inappropriate Medications for Nursing Home Residents: An Interrupted Time Series Analysis.' European Drug Utilization Conference 2025, Uppsala, Sweden [poster presentation]

'Balancing Palliative Care Needs and Medication Appropriateness: Initiation and Reinitiation of Medications at the End of Life.' European Drug Utilization Conference 2025, Uppsala, Sweden [oral presentation]

'International Deprescribing Guidelines Did Not Impact Actual Practice in Deprescribing of Potentially Inappropriate Medications for Nursing Home Residents: An Interrupted Time Series Analysis.' 19th World Congress of the European Association for Palliative Care (2025), Helsinki, Finland [oral presentation]

'Deprescribing for nursing home residents with limited life expectancy: a qualitative study to identify barriers and enablers for healthcare professionals.' 2nd International Conference on Deprescribing (ICOD2, 2024), Nantes, France [poster presentation]

'Impact of deprescribing Guidelines on Trends in Deprescribing for Nursing Home Residents with Limited Life Expectancy in Belgium.' NuPhaC Winter Conference 2024: Integrated care for high quality and safe medicines use (2024), Antwerp, Belgium [oral presentation]

'Impact of International Deprescribing Guidelines on Trends in Deprescribing for Nursing Home Residents with Limited Life Expectancy in Belgium.' 1st Symposium on implementing deprescribing in routine practice in Belgium (2024), Brussel, Belgium [oral presentation]

'Tools and Guidelines Regarding the Appraisal of the Appropriateness of Medications and Deprescribing and its Applicability in Persons with Limited Life Expectancy: Umbrella Review.' 18th World Congress of the European Association for Palliative Care (2023), Rotterdam, The Netherlands [poster presentation]

Awards and grants

Certificate of Most Viewed Article (2023)

British Journal of Clinical Pharmacology

Anlay DZ, Paque K, Van Leeuwen E, Cohen J, Dilles T. 'Tools and guidelines to assess the appropriateness of medication and aid deprescribing: An umbrella review.'

Doctoral Scholarship (DOCPRO1), University of Antwerp (Nov 2025– Oct 2026)

FWO travel grant European Drug Utilization Conference 2025: Bridging Data, Policy & Patients in Drug Utilization Research, Uppsala (Zweden) - juli 2025

International Society for Pharmacology (ISPE) EuroDURG scholarships (travel and accommodation grant), European Drug Utilization Conference 2025, Uppsala, Sweden

FWO travel grant International Conference on Deprescribing 2026, Montreal (Québec) (Canada) - april 2026

Teaching experience

- NuPhaC Summer School (Uantwerpen, 2023/2024) - Deprescribing: When the benefits of medication are outweighed by the risks
- Annual NuPhaC lesson for nurse specialist students (2023, 2024, 2025)

Professional Activities

Review for international journals (palliative medicine, plos one, Journal of the American Medical Directors Association)

Member of NuPhaC Belgium

Skills:

Programming & Statistical Tools: SAS, R, NVivo.

Data Management Platforms: SQL, Redcap and Qualtrics.

Documentation & Analysis: Big data analysis, qualitative data analysis, trained medical writer with Emtex acadamy

Acknowledgements

Four years ago, I embarked on this PhD journey. Looking back, I realise that reaching this point would not have been possible without the support, guidance, and encouragement of many people. I would like to take this opportunity to express my sincere gratitude to all those who accompanied me along the way.

I would like to sincerely thank Prof. Dr. Katrien Beeckman for your willingness to chair my defence, a role that requires considerable time and effort. I am also grateful to the members of my doctoral jury, Prof. Dr. Petra Denig, Prof. Dr. Johan Wens, Dr. Maarten Wauters, Prof. Dr. Koen Putman, and Prof. Dr. Tinne Smets, for taking the time to read my doctoral thesis and for your thoughtful questions, constructive feedback, and engaging discussions.

I would now like to express my deepest gratitude to my promotors, Prof. Dr. Joachim Cohen, Prof. Dr. Tinne Dilles, and Dr. Kristel Paque. Thank you for believing in me and for giving me the opportunity to join the DepEND project. Throughout these four years, your guidance, commitment, and support have been invaluable. Despite your busy schedules, you always made time for discussions, feedback, and advice, often extending well beyond regular working hours. When challenges arose, particularly during delays in obtaining data access, your patience and practical solutions helped me maintain momentum and move forward. I greatly appreciated the openness with which you welcomed new ideas and discussions, always making me feel comfortable sharing my thoughts and exploring different perspectives. The postgraduate meetings were a particularly valuable source of insight, encouragement, and support. Your feedback consistently strengthened my work and helped me grow as a researcher.

Beyond the PhD itself, I am deeply appreciative of your genuine concern for my personal and family well-being. I also valued how you ensured that I could focus on my research without having to worry about financial uncertainty, allowing me to fully dedicate myself to the PhD. Looking back, I realise how fortunate I have been to work with such a collaborative and complementary supervisory team. I could not have wished for better supervisors throughout this journey.

Joachim, without your guidance, this PhD would have been difficult to imagine. The breadth of your knowledge and your ability to find solutions, whether discussing research methods, statistics, or entirely different topics, has always impressed me. Your comments consistently challenged me to think more critically, dig deeper, and improve my work. Although my deadlines sometimes felt ambitious, I was always amazed by how quickly detailed feedback would appear in my inbox, often late at night. Over the years, I learned not only how to conduct research, but also how to approach problems with curiosity, rigour, and a sense of humour. Thank you for the trust, freedom, and support you showed me throughout this journey.

Tinne, your ability to balance ambition with practicality has been a constant source of support. You always encouraged me to aim high while helping me stay focused on what was achievable and important. Your support was remarkably proactive. More often than not, you came to my office rather than me going to yours, sometimes making me wonder who the professor really was. During challenging periods, your encouragement, whether through a conversation, a quick visit, or an unexpected phone call, often provided exactly the confidence and reassurance I needed to move forward. I deeply appreciated your positive energy, kindness, and the many conversations that helped

me navigate both the challenges and opportunities of this PhD. Thank you for continually motivating me.

Kristel, thank you for your immense support as my daily supervisor. Your guidance was essential throughout many aspects of this project, particularly with data requests, study coordination, and the countless practical matters that arise during a PhD. Your feedback was always clear, constructive, and timely, helping me make steady progress. I am especially grateful for your accessibility, patience, and unwavering confidence in me. Having witnessed my growth from the beginning of this PhD journey, you continuously encouraged me to move forward. It has been a privilege to be your first PhD student, and I have no doubt that many others will benefit from your excellent supervision in the future.

No PhD is completed in isolation, and I was fortunate to be surrounded by colleagues at the University of Antwerp and Vrije Universiteit Brussel, particularly those in the Centre for Research and Innovation in Care (CRIC) and the End-of-Life Care Research Group in Ghent and Jette, who contributed to this journey in one way or another. Through your support, collaboration, insightful discussions, encouraging conversations, thoughtful emails, and genuine interest in my work, you helped make these four years both productive and enjoyable. The moments we shared during conferences, staff days, staff outings, meetings, lunches, and everyday conversations enriched this experience both professionally and personally.

Geertje, you deserve particular recognition for the exceptional support you provided from the very beginning of my PhD journey. As an international student, navigating visa procedures, residence permit renewals, administrative requirements, and countless practical matters can be challenging. You always helped with these processes willingly and with a smile. I am particularly grateful for your efforts in coordinating with VUB, UAntwerp, the Doctoral School, and many others to find suitable dates for both my internal and external defence. Without your persistence and support behind the scenes, reaching this day would have been much more difficult. You are a tremendous asset to the research group. You may not fully realise the positive impact you have on those around you, but I would like you to know how much I have appreciated it throughout these four years.

Joran, thank you for being my unofficial PhD buddy. I always knew I could reach out to you with questions, particularly during the final stages of my PhD. From thesis submission and publications to practical tips and advice, your support helped make a complex process much easier to navigate. Thank you for your guidance.

Noemi, from the beginning of my PhD journey, I could always count on your support. I am particularly grateful for your help in coordinating the final practical arrangements for my defence from the Antwerp side.

Elyne, you may not realise how much I appreciated our daily interactions. Even a brief greeting or conversation could brighten my day. Thank you for always being approachable and willing to help, not only with academic matters but also with practical aspects of life in Belgium, particularly those related to raising children. Your positive energy, kindness, and ability to connect people make a real difference within the research group.

Maarten, thank you for inviting me to present my research in the NuPhaC course. Beyond the opportunity to share my work, this presentation helped me fulfil the teaching and societal engagement requirements of my doctoral training.

Kelly, from organising nursing home visits and sharing useful resources to helping me better understand the Belgian nursing home sector and healthcare policy context, your guidance was invaluable. I also greatly appreciated your collaboration on the final chapter of this PhD and the many insights you shared along the way.

Laura and Senne, the final stages of a PhD come with countless practical details, and I greatly appreciated your help in managing them from the Antwerp side.

Yaël, thank you for the many conversations we shared and for occasionally serving as my live translator during Dutch discussions and PhD defences

Tine Averens, during some of the most difficult moments of this PhD journey, it was reassuring to encounter a familiar and caring face at Sint-Vincentius Hospital. The care you provided to Eyoab during his many hospital admissions, together with your support and encouragement, meant a great deal to me. I particularly remember the message you sent when his condition became more serious, reminding me to stay strong and of the remarkable resilience of children. Seeing a trusted colleague in such challenging circumstances brought comfort and reassurance when it was needed most. Your kindness, compassion, and care left a lasting impression, and I am deeply grateful for them.

I am indebted to the InterMutualistic Agency (IMA), Statbel, Pyxicare, and eHealth for enabling access to the data that formed the basis of this PhD. I also warmly acknowledge the teams at IMA (Jarmila, Anneke, Remi, David, Dirk, Montse, Xavier, Isaiah, El Maati Allaoui, and Sofie), Statbel (Elias, Cloë, and Patrick), and Pyxicare (Bert) for their valuable support and collaboration throughout the project.

As a researcher, I was fortunate to collaborate with many colleagues beyond my immediate research groups. Among these collaborations, I would like to highlight a few that particularly enriched this PhD. **Dr. Ellen Van Leeuwen** (Ghent University), thank you for your substantial contributions to three chapters of this thesis, for serving on my external advisory committee, and for the methodological and contextual insights you shared throughout the project. Your guidance and expertise were invaluable. I am also grateful to **Dr. Johanna De Almeida Mello** and **Prof. Dr. Anja Declercq** (KU Leuven) for introducing me to the BelRAI data and assessment instruments that were central to this research.

Prof. dr. Annelies Van Rie, this PhD journey may never have begun without you. By sharing the vacancy that led me to the DepEND project, you opened the door to this opportunity. I remain grateful for your guidance and support during my Master's in Epidemiology and for the role you played in shaping this path.

I am grateful to the **University of Gondar** for its strong commitment to staff development and for supporting me in pursuing my Master's degree and subsequently this PhD. Thank you for the opportunity and trust that made this journey possible.

To my **Ethiopian friends** in Antwerp, thank you for your friendship, support, and companionship throughout these years. Celebrating holidays together, sharing conversations, and being there for one another through life's challenges gave me and my family a strong sense of connection and belonging.

To **my parents**, thank you for your endless love, support, and encouragement. Growing up in a rural area, the opportunities that have led me to this moment were only possible because of your sacrifices, perseverance, and unwavering belief in the value of education. Although your own educational opportunities were limited, you always encouraged me to pursue mine. This achievement reflects not only my efforts but also the foundation you provided through your hard work, dedication, and constant support. I am profoundly grateful for everything you have done for me.

To my wife, Yeshiwork, and my son, Eyoab. This PhD is as much yours as it is mine. **Yeshi**, you carried far more than your share of the challenges that came with this journey. While I was focused on my PhD, you were often the one holding everything together and keeping our family moving forward. There were moments when I did not fully express how difficult this period was for you, but I want to acknowledge that now. Reaching this milestone would simply not have been possible without you. Thank you for your love, patience, and unwavering support throughout these four years. **Eyoab**, you arrived in the middle of my PhD and brought immense joy to our lives, alongside challenges that neither of us could have anticipated. The many hospital visits and difficult moments were not part of the plan, but they became part of our story. Watching you grow stronger over the past months has been one of the greatest sources of motivation and perspective throughout this journey. Completing this PhD feels a little like winning alongside you too.

Finally, I thank God for bringing me to this milestone.