Title: Frailty and potentially inappropriate medications using the 2019 Beers Criteria: Findings from the Australian Longitudinal Study on Women's Health (ALSWH)

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Acknowledgements

The authors thank Dominic Cavenagh and Peta Forder (Priority Research Centre for Generational Health and Ageing, University of Newcastle), and Natasha Weaver (School of Medicine and Public Health, University of Newcastle) for their statistical input. This research is based on a study conducted as part of the Australian Longitudinal Study on Women's Health by the University of Queensland and the University of Newcastle. The authors are grateful to the Australian Government Department of Health for funding and to all women who provided the survey data. The authors also acknowledge the Departments of Health and Veterans' Affairs, and Medicare Australia, for the provision of the PBS data, and the Australian Institute of Health and Welfare (AIHW) as the integrating authority.

Abstract

Background: Frailty is an essential consideration with potentially inappropriate medications (PIMs), especially among older women.

Aims: This study determined the use of potentially inappropriate medications according to frailty status using the Beers Criteria 2019, identified medications that should be flagged as potentially inappropriate and harmful depending on individual health factors, and determined the association between frailty and PIMs, adjusted for characteristics associated with PIMs.

Methods: This prospective longitudinal study included 9355 participants aged 77 to 82 years at baseline (2003). Frailty was measured using the FRAIL (Fatigue, Resistance, Ambulation, Illness, & Loss of Weight) scale. Generalised estimating equations using log-binomial regressions determined the association between frailty and risk of using PIMs.

Results: Among participants who were frail and non-frail at baseline, the majority used ≥3 PIMs (74.2% and 58.5%, respectively). At 2017, the proportion using ≥3 PIMs remained constant in the frail group (72.0%) but increased in the non-frail group (66.0%). Commonly prescribed medications that may be potentially inappropriate in both groups included benzodiazepines, proton-pump inhibitors and nonsteroidal anti-inflammatory drugs, and risperidone was an additional contributor in the non-frail group. When adjusted for other characteristics, frail women had a 2% higher risk of using PIMs (RR 1.02; 95% CI: 1.01, 1.03).

Conclusion: Given that the majority of frail women were using medications that may have been potentially inappropriate, it is important to consider both frailty and PIMs as indicators of health outcomes, and to review the need for PIMs for women aged 77 to 96 years who are frail.

Keywords: Frailty, older women, oldest old, potentially inappropriate medications

Introduction

Given the increased risk for adverse events such as delirium, falls, fractures, hallucination, confusion and mortality [1, 2], interdisciplinary expert panels regularly review, and update medications/medication classes deemed as potentially inappropriate medications (PIMs) for older adults [3]. The Beers Criteria are the longest standing list of PIMs and have been widely used in the last two decades to examine prescribing patterns within populations and cost and utilisation data, to evaluate health outcomes, and to educate clinicians [4]. First developed in 1991 by Dr Mark Beers, the Beers Criteria have undergone multiple revisions and updates; the American Geriatrics Society assumed the responsibility of three-yearly updates from 2012, with the latest version released in 2019 [3].

The Beers Criteria lists PIMs that should generally be avoided among older adults as the potential risks of adverse effects outweigh their benefits. The list also recommends the avoidance of some medications/medication classes on the basis of long duration, high doses, creatinine clearance, and certain diseases; it also includes PIMs that should be used with caution in all older people [3]. Although most health researchers and clinicians are able to identify the appropriateness of PIMs based on these pre-specified criteria, longitudinal studies may not have the same access to patient health data. However, longitudinal studies are increasingly popular [5] as they allow for repeated measures of the same individuals over time [6]. Therefore, longitudinal studies can flag medications that may be potentially inappropriate, and attention should be paid during the medication review process so as to determine their appropriateness among older people.

Frailty is an essential concept to consider in relation to PIM use. A geriatric syndrome triggered by multiple determinants, frailty is often characterised by reduced muscle endurance, strength and physiological function leading to higher dependency [7]. Frail older adults are more vulnerable to adverse events due to deficits in multiple physiological systems, and medication optimisation is crucial in this population. Optimisation may be challenging given the complexities associated with the presence of multiple morbidities, polypharmacy, and the potential for medication interactions, as well as a diverse and sometimes unpredictable response to medications [8].

Older women are at higher risk of using PIMs compared to older men [5]. Women represent a greater proportion of older adults due to longer life expectancy [6], and older women are more likely to have multiple morbidities, use more medications, obtain health care services and receive diagnoses [7]. However, there is a lack of evidence about the prevalence of PIMs according to frailty status, especially among older women in later life [9-11]. Although prevalence of PIMs among frail and non-frail women may provide insight into the association with frailty, most studies have not discerned the differences between the two populations [8, 9]. Therefore, despite the possible relationship between frailty and PIMs, there is a gap in the literature regarding their association, and a lack of information about other characteristics associated with PIM use among frail older adults. Two recent European studies determined the incidence of frailty and changes in frailty status but to the best of our knowledge, ours is the first to determine the prevalence of PIMs in the context of frailty in the southern hemisphere [12, 13].

In our study, we used longitudinal data to: (1) determine the use of PIMs according to frailty status using the 2019 Beers Criteria; (2) identify medications used by frail and non-frail women that should be flagged as potentially inappropriate and harmful depending on individual health factors; and (3) determine the association between frailty and PIMs, adjusted for other characteristics associated with PIMs.

Methods

Study population and linked data source

We included participants from the 1921 to 1926 cohort enrolled in the Australian Longitudinal Study on Women's Health (ALSWH); details about the cohort are provided elsewhere [14]. Participants were initially invited to complete three-yearly surveys from 1996 to 2011, and thereafter six-monthly surveys; the ALSWH is an on-going study. In our study, participants were followed over time from 2003 to 2017. Data of ALSWH participants were linked to data from the Pharmaceutical Benefits Scheme (PBS), Australia's government program for subsidised medications and health services for eligible citizens and permanent residents who have a Medicare card. The PBS has been widely used in medication utilisation studies and research purposes due to its informational benefits over self-reported data on medication use [15]. Participants were included in the study if they met the following criteria:

a) Alive at 1 January 2003, and

b) Had at least one medication record in the PBS in 2003, and

c) Had PBS records with complete Anatomic Therapeutic Chemical (ATC) codes (7 digits), and

d) Had self-reported frailty data in 2003, and

e) Did not withdraw consent to linking data to the PBS prior to 2017.

A stepwise flowchart of the inclusion process is included as a supplementary file (Online Resource 1).

Potentially inappropriate medication use

Participants were classified as PIM users if they used at least one PIM at each year. PIMs were examined using the 2019 Beers Criteria [3] using medication information from the PBS according to the ATC classification [16]. PIMs were identified based on the table '2019 American Geriatrics Society Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults', which included PIMs to avoid regardless of underlying diseases [3]. Although some PIMs were classified only as medication classes and not as individual medications in the table, we counted and presented PIMs as unique medications; all medications and medication classes from the table were included in the PIM count regardless of recommendations that may have included avoidance criteria. There were two categories of PIMs used in this study; the first considered use of ≥3 PIMs, 1-2 PIMs, or no PIMs, which was presented descriptively. The second included participants who used ≥1 PIM, or no PIMs, to determine medications used by frail and non-frail participants that should be flagged as potentially inappropriate and harmful depending on individual health factors, as well as in the regression analyses that determined the association between frailty and use of PIMs.

Frailty measure

Frailty status of participants was identified using the FRAIL (Fatigue, Resistance, Ambulation, Illness, & Loss of Weight) scale, which has previously been used with ALSWH participants and has been validated in the same cohort [17]. The FRAIL scale was developed by the Geriatric Advisory Panel of the International Academy of Nutrition, Health and Aging task force on frailty assessment among older adults [17]. The FRAIL scale categorises participants as frail or non-frail based on deficits in five

domains, i.e. ambulation (ability to walk at least 100m), resistance (ability to climb a flight of stairs), fatigue, presence of >5 pre-specified illnesses, and weight loss of ≥5% between consecutive surveys. Participants were scored positive if they had any deficit, and ranged from 0 for non-frail, to 5 for most frail; participants were considered frail if they scored >2 [17].

Explanatory variables

Explanatory variables included socio-demographic data (age at baseline, education level categorised as below Year 12, or Year 12 and above, and whether participants lived alone). Other variables included time (in years), whether participants had a Department of Veterans Affairs' coverage, number of general practitioner (GP) visits in the last 12 months categorised as ≤4 or >4, whether they had a hospital admission in the last 12 months, number of chronic diseases categorised as <4 and ≥4, if they had a fall in the last 12 months, and if they had continuous polypharmacy. If missing, data were carried forward where necessary. Continuous polypharmacy was defined as the same unique medication that was used in two periods at each year, 1 April to 30 June, and 1 October to 31 December, to capture medications taken on a regular basis; these months were selected to avoid underestimating medication use because stockpiling of medications has been reported to occur towards the end of each year in Australia [18]. Chronic diseases were deemed to be enduring if reported at any survey, and included hypertension, heart disease (myocardial infarction, angina or other heart problems), diabetes mellitus, stroke, respiratory disease (bronchitis, asthma or emphysema), cancer, mental illness (Alzheimer's disease/dementia, depression or anxiety/nervous disorder), arthritis (osteoarthritis and rheumatoid arthritis) and osteoporosis.

Statistical analyses

Stata® IC version 16 was used to perform all analyses [19]. Descriptive statistics were used to determine the proportion of participants using PIMs (≥3 PIMs, 1-2 PIMs, and no PIMs) for frail and non-frail participants, and to identify PIMs (≥1 PIM and no PIMs) used by both groups, from 2003 (age 77 to 82 years) to 2017 (age 91 to 96 years). Generalised estimating equations (GEEs) using log-binomial regressions with robust standard errors and an unstructured correlation matrix were used to determine the association between frailty and PIMs using longitudinal data. First, multicollinearity between variables was identified based on Pearson correlation coefficients greater than 0.8, and confirmed with

variance inflation factor values greater than 10 [20]; collinear variables were removed. Preliminary univariate regressions were then conducted, and variables significant at the 0.25 level were included in the first multivariable model [21]. A backward stepwise elimination method was used to obtain the final model, starting from removal of the least significant variable at the 0.05 level. Effect estimates are presented as risk ratios (RR) with confidence intervals of 95% (95% CI).

Ethics approval

The ALSWH has ongoing ethical approval from the University of Queensland (UQ) (reference 2004000224) and the University of Newcastle (UoN) (reference H-076-0795) Human Research Ethics Committees (HREC), and also for the health record linkage (UQ: reference 2012000132 and UoN: reference H-2011-0371). Our study was approved by the ALSWH Data Access Committee. Access to national data collections was approved by the Australian Institute of Health and Welfare HREC (reference EC2012/1/12).

Results

This study included 9355 participants aged 77 to 82 years in 2003. Participant characteristics at baseline (2003) are presented as a supplementary file (Online Resource 2). An additional 974 participants did not have frailty data and were excluded from analysis, but their characteristics were similar to those participants analysed. Compared to frail participants, non-frail participants had a lower median number of medications in 2003 (median=10, IQR: 7-15), which increased over time to 2017 (median=12, IQR: 8-15). These findings are detailed in Online Resource 3. The high prevalence of PIMs (≥1) among older women remained constant, as they aged from 77 to 82 years (76.2%) to 91 to 96 years (78.3%). The prevalence of frailty was fairly low and increased slightly as they aged, i.e. 22.8% to 29.5%. At baseline, PIM users accounted for the majority of frail (84.7%) and non-frail (73.6%) participants.

Fig.1 summarises the proportion of frail participants using PIMs overlayed by the median number of medications used each year; 84.8% of frail participants used ≥1 PIM at baseline. When participants were 77 to 82 years at 2003, the majority were using ≥3 PIMs (74.2%), followed by non-PIM users (15.3%), and users of 1-2 PIMs (10.6%); there were no discernible changes in proportion over time to

2017 when participants were aged 91 to 96 years. The median number of medications remained relatively constant: 14 in 2003 (interquartile range, IQR: 10-19), and 13 in 2017 (IQR: 10-17). Fig. 2 illustrates the proportion of non-frail participants using PIMs, with 73.7% who used ≥1 PIM at baseline. In comparison to those who were frail, there was a lower proportion of non-frail participants using ≥3 PIMs in 2003 (58.5%); the proportion of non-frail non-PIM users (26.4%) and non-frail users of 1-2 PIMs (15.2%) was higher. At 2017, the proportion of participants using ≥1 PIM remained fairly constant (76.7%) in comparison to 2003. However, there was an increase in the proportion of non-frail participants using ≥3 PIMs (66.0%) and a decrease in non-frail participants using 1-2 PIMs (10.7%). This information is summarised in Online Resource 4.

Fig. 3 and Fig. 4 depict medications used by frail and non-frail participants, respectively, that should be flagged as potentially inappropriate and harmful depending on individual health factors. These medications were included in the graphs provided they appeared in the top five at any year from 2003 to 2017. This resulted in a total of 12 medications for frail participants in 2003 which included: aspirin (31.3%; ATC codes: B01AC06, B01AC30), temazepam (24.7%; ATC code: N05CD07), omeprazole (24.5%; ATC code: A02BC01), digoxin (15.9%; ATC code: C01AA05), pantoprazole (11.0%; ATC code: A02BC02), esomeprazole (10.6%; ATC code: A02BC05), oxazepam (10.1%; ATC code: N05BA04), metoclopramide (9.1%; ATC code: A03FA01), diazepam (8.6%; ATC code: N05BA01), meloxicam (7.7%; ATC code: M01AC06), amitriptyline (6.4%; ATC code: N06AA09) and rabeprazole (5.0%; ATC code: A02BC04). In 2017, there was reduced use of aspirin (13.4%) and omeprazole (8.2%), and increased use of pantoprazole (27.6%), esomeprazole (27.4%) and metoclopramide (17.5%), compared to 2003. When compared to frail participants, two additional medications (diclofenac; ATC codes: M01AB05, D11AX18, M01AB55 and risperidone; ATC code: N05AX08) appeared in the top five for non-frail participants from 2003 to 2017. Despite a low prevalence in 2003 for diclofenac (6.9%) and risperidone (0.5%), the use of diclofenac decreased over time (to 1.1%) while that of risperidone increased over time (7.8%). There were no other discernible changes for the same medications from the frail group. This information is presented in the supplementary file (Online Resource 5).

In terms of the regression analyses, none of the explanatory variables were collinear. Univariate log-binomial regressions using GEEs indicated that there was no evidence for living alone and the use of PIMs (p=0.356), thus this variable was not included in subsequent models. Table 1 presents the

variables that were included in the final model. Frailty was associated with a 2% increase in risk of using PIMs (RR 1.02; 95% CI: 1.01, 1.03). Participants with ≥4 chronic diseases had a 6% higher risk of using PIMs (RR 1.06; 95% CI: 1.05, 1.07) compared to those with <4 chronic diseases. Participants with continuous polypharmacy had a 7% higher risk of using PIMs (RR 1.07; 95% CI: 1.06, 1.07). Hospital admissions and >4 GP visits in the last 12 months, and having DVA coverage were also associated with higher risk of using PIMs, while an education level of Year 12 and above was associated with a 3% lower risk of using PIMs (RR 0.97, 95% CI 0.95, 0.98). Age at baseline and time (in years) did not significantly contribute to the model.

Discussion

Almost 80% of women in our study used medications that could have been potentially inappropriate as according to the Beers Criteria 2019, and approximately one-third of these women were frail. Frail women had a 2% increased risk of using PIMs, when adjusted for other characteristics. Commonly used medications/medication classes that may have been potentially inappropriate among frail and non-frail women included benzodiazepines, proton-pump inhibitors, nonsteroidal anti-inflammatory drugs, aspirin and digoxin, and risperidone was an additional contributor among non-frail women.

When PIM use was determined in the context of frailty, use of one or more PIMs among frail (80%) and non-frail (75%) women remained constant as they aged from 77 to 82 years (in 2003) to 91 to 96 years (in 2017). Among non-frail PIM users, the proportion of women using three or more PIMs increased over time, while there was a decrease in the proportion of women who used one to two PIMs; this indicates a transition between these two groups of non-frail PIM users which occurred predominantly in their 80's. The higher number of women using more PIMs may reflect prescribing practices that are disease-specific and guideline-driven, increasing the risk of using PIMs. The use of PIMs estimated in our study approximated previous studies that used the Beers Criteria and reported prevalence of PIMs that ranged from 50% to 70% for frail women [22, 23]. However, prevalence in our study appeared higher than that reported by Maclagan et al. (2017), with 48% in the frail group, 39% in the non-frail group, and 43% in the pre-frail group [8]. Reasons for the variation in the prevalence of PIMs according to frailty is common across many studies; it could be due to the use of different tools to determine PIMs and frailty, and various study settings such as nursing homes or own homes, the availability of

medications across countries, prescribing habits, fear of discontinuing medications, and ideological and market pressures [9].

Frailty was associated with a 2% increased risk of using PIMs (RR 1.02; 95% CI: 1.01, 1.03) and although small it is nonetheless an important factor. Frailty is known to increase the risk of polypharmacy, which in turn increases the risk of using PIMs [24]. Polypharmacy is also a strong predictor of PIMs [25] thus increasing the association between frailty and PIMs. In our study, median medication use among frail women was higher than among non-frail women. Our study found that despite adjustment for other characteristics, continuous polypharmacy (medications taken on a regular basis) increased the risk of using PIMs by 7%. Although not a novel finding, this provides evidence that despite interventions, polypharmacy is still contributing to the use of PIMs among frail older adults.

The Asia-Pacific Clinical Practice Guidelines for the Management of Frailty recommend a careful approach to polypharmacy in order to reduce the prevalence of PIMs [26], indicating that frailty could be an important indicator of health outcomes. In the context of frailty, increase risk of using medications that may be potentially inappropriate in the context of frailty is clinically important for a few reasons. Pharmacokinetic and pharmacodynamic characteristics of older adults exacerbate adverse events in the presence of frailty [9, 27], further adding to the complexities and adverse events associated with the use of PIMs [1, 2]. Frail older adults suffer deterioration in balance, leading to walking impairment and increasing the risk of falls, which could be aggravated in those using PIMs that affect gait and balance. Falls is a major geriatric symptom among older adults and has been reported as the second leading cause of death globally, with over one-third of community-dwelling older adults falling annually [28].

In considering other characteristics associated with the use of PIMs, the findings of our study are generally consistent with literature. We observed that age at baseline and an increase in age only had a small effect on the risk of PIMs, which is similar to the findings by Miller et al. (2017) [29]; similar to our study, Miller et al. also reported that lower education level was associated with a lower risk of using PIMs. It is possible that literacy could improve the awareness and knowledge of disease symptoms, thus increasing the number of GP consultations and medications which make people more vulnerable to using PIMs [9, 29]. Having a DVA coverage increased the risk of polypharmacy and this could be due to a higher level of medical attention that DVA clients receive in comparison to other patients; veterans receive 1.5 additional consultations a year in comparison to their community counterparts,

whereas war widows receive 2.5 additional consultations a year [30]. Multimorbidity exhibited a strong association with use of PIMs, which is expected given that multimorbidity increases the risk of polypharmacy. The presence of four or more chronic diseases increased the risk of using PIMs by 6% in our study, similar to the findings by Bolina et al. (2019) [9]; as early as 2001 Fried et al. reported an association between frailty and multimorbidity among women [7]. Hospital admissions in the past year were also associated with a higher risk of using PIMs, consistent with the study by Bolina et al. [9]. Recently, a Canadian study by Weir et al. (2020) found that upon hospital discharge, two-thirds of older adults hospitalised for medical or surgical purposes were prescribed with at least one PIM upon discharge [31]. Finally, more than four GP visits in the past year was also associated with an increase in risk of using PIMs (5%) and may indicate the potential role that GPs can play in optimising medications for older adults.

Both frail and non-frail women used medications listed in the Beers Criteria 2019 that have frequently been reported in other studies [8, 10, 11], i.e. benzodiazepines, drugs for gastrointestinal disorders such as proton-pump inhibitors (PPIs) and metoclopramide, and nonsteroidal anti-inflammatory drugs (NSAIDs). Benzodiazepines should be avoided among older people according to the Beers Criteria, although benzodiazepine anxiolytics (e.g. oxazepam and diazepam) and benzodiazepine hypnotics (e.g. temazepam) were commonly used by women in our study. The incidence of benzodiazepine side effects, predominantly those of the central nervous system (CNS) such as fatigue, drowsiness, ataxia and confusion, increase with age in older adults [3]. Symptoms worsen in long-acting benzodiazepines, such as diazepam, and are dose-related. Amitriptyline was also commonly used in our study. Reports of an association between antipsychotics and tricyclic antidepressants, and an increased risk of hip fractures, are due to its anticholinergic properties, which increase in relation to dose [32]. However, the high use of these medications indicates a clinical need among women in our study. While symptomatic treatment with tricyclics may be considered provided non-pharmacological alternatives have been exhausted, it is important to consider a ‘drug holiday’, titrating doses starting from the lowest, and limited duration of use [32].

It was interesting to note that omeprazole, esomeprazole, pantoprazole and rabeprazole were chronically used by women in our study. High use of PPIs may be due to the frequent use of meloxicam and diclofenac which was evident. PPIs were reported as one of the most commonly used PIMs in other

studies using the Beers Criteria [33] and the Screening Tool of Older Person's potentially inappropriate Prescriptions (STOPP) criteria [34]. Although PPIs are well tolerated short-term, prolonged use may result in *Clostridium difficile*-associated diarrhoea, bone loss and fractures [3], increasing the risk of falls. It has been reported that patients are often advised to continue using PPIs indefinitely upon hospital discharge [33], and therefore it is important that the clinical need for PPIs be reviewed.

Risperidone was an additional PIM in the non-frail group. Higher plasma concentrations of risperidone are the result of its poor penetration of the blood brain barrier resulting in hyperprolactinemia and antipsychotic-induced osteoporosis [35]. Recent literature has presented compelling evidence that antipsychotic treatment results in decreases of bone mineral density which can be a characterisation of frailty [36]. Hyperprolactinemia occurs because antipsychotics block D2 dopamine receptors of the lactotrophs in the anterior pituitary [35] and may explain why risperidone was not used among frail women, as opposed to non-frail women. Nevertheless, caution should be taken when prescribing risperidone for any age but especially for long-term use in older people.

Clinical implications

Our study has several clinical implications. Acknowledging and understanding the characteristics associated with the use of PIMs in our study allows for improved assessment of healthcare amongst oldest old women [11]. Our findings that indicate almost one-third of women had frailty, highlights the importance of recognising frailty as an indicator of health outcomes, especially in the context of medication use. The decision-making process regarding medication use should be based on the individual's underlying comorbidities, functional status and treatment goals [8]. Frailty forms the basis of geriatric medicine, and geriatricians globally have advocated for the screening of frailty during health care access for older adults [37]. It is important to consider deprescribing for frail older adults, particularly those aged 75 years and over, and it is important to consider benefits versus risk. Medication optimisation is a pillar of patient-centred care and algorithms have been developed to identify PIMs [38] exclusively for frail older adults [39]. Patients' preferences and considerations should be taken into account, given the dynamic nature of frailty and the adverse events associated with PIMs that may vary between individuals.

The Beers Criteria identifies medications that are *potentially* inappropriate and that should *generally* be avoided, thus there is a need to emphasise that use of PIMs may be justified in some circumstances. It is neither intended to supplant clinical decisions and to be used punitively, nor override individual preferences and needs [3]. The use of the Beers Criteria to identify PIMs in our longitudinal study indicate that older women, particularly those aged 77 years and above, are prescribed medications that may be potentially inappropriate. For instance, aspirin is to be avoided at doses of more than 325mg/day, digoxin is to be avoided as first-line therapy as a rate control agent in atrial fibrillation and in heart failure, NSAIDs are to be avoided as chronic use except where other alternatives are not effective and the person is taking a gastro protective agent, and PPIs should not be used for more than eight weeks, unless indicated [3]. This highlights the importance of regularly reviewing medications for older people, and medication reviews should be aimed at ascertaining the appropriateness of medications listed as PIMs, particularly those identified in our study. The review process should be complemented by implicit interventions such as using a treatment algorithm to guide the decision-making process.

Finally, the majority of women in our study were community-dwelling, and this is comparable to the Australian Bureau of Statistics' Census of Population and Housing [40]. Most recent data in the Australian Bureau of Statistics (2016) indicate that 58% of older people resided in the community, while our study depicted that 58.26% of women were community-dwelling in the same year. It is known that older people prefer living in their homes rather than moving into frail care, a phenomenon that is encouraged by the Australian government [41]. Our finding is important because it draws attention to frailty among community-dwelling older people, and the increased awareness may stimulate development of additional home-care services specifically targeted for frail people, including an increase in regular medication reviews.

Strengths and limitations

There were limitations in our study. The majority of women in our study were community-dwelling and our findings may not be generalizable to older adults across Australia who may be living in aged care facilities. The lack of outcomes, such as increased risk of morbidity and mortality due to the association between frailty and PIMs, needs to be acknowledged; the clinical data required for such evaluations was not available in this study dataset. The PBS dataset does not include medications dispensed on

non-subsidised ‘private’ prescriptions, or medications that can be purchased without a prescription, therefore we may have underestimated use of PIMs. Although the ALSWH surveys may introduce recall bias due to its self-report nature, insights obtained from this large longitudinal study may take precedence over this limitation.

Conclusion

This study provides new insight regarding the use of PIMs among frail older women aged 77 to 96 years, and the characteristics associated with the use of PIMs. Overall, two-thirds of women in this study commonly used medications that may be potentially inappropriate, and approximately 80% of frail women used at least one PIM. Commonly used medications that may have been potentially inappropriate among frail and non-frail women were benzodiazepines, PPIs and NSAIDs, with risperidone as an additional contributor among non-frail women. Frailty was associated with a 2% increased risk of using PIMs. Characteristics such as continuous polypharmacy, four or more chronic diseases, having a DVA coverage, past hospital admissions and four or more GP visits in the past year increased the risk of using PIMs. Our study supports the need to consider these characteristics, and we recommend regular medication reviews to optimise medications for frail older women, particularly commonly used medications identified in our longitudinal study.

Declarations

Funding

This work was supported by the by the Australian Government Department of Health.

Conflicts of Interest

The authors have no conflicts of interest to declare that are relevant to the content of this article.

Ethics approval

The ALSWH has ongoing ethical approval from the University of Queensland (UQ) (reference 2004000224) and the University of Newcastle (UoN) (reference H-076-0795) Human Research Ethics Committees (HREC), and also for the health record linkage (UQ: reference 2012000132 and UoN: reference H-2011-0371). Our study was approved by the ALSWH Data Access Committee. Access to

national data collections was approved by the Australian Institute of Health and Welfare HREC (reference EC2012/1/12).

Availability of data and material

Use of the ALSWH dataset is subject to strict ethical conditions due to the personal nature of the data collected. The ethics committees that oversee the ALSWH are the Australian Government Department of Health Human Research Ethics Committee and the Human Research Ethics Committees at the University of Queensland and the University of Newcastle. Ethical approval of the ALSWH specifies that de-identified data are only available to collaborating researchers where there is a formal request to make use of the material, and that each request has to be approved by the ALSWH Data Access Committee. Further details can be found at http://alswh.org.au/for-researchers.

Code availability

Codes can be made available upon request.

Authors' Contributions

K.T. contributed to the design and conceptualization of the study, performed formal analysis, and wrote the first draft and made final corrections. J.B. contributed to the conceptualization of the study, reviewed and made final corrections to the manuscript. S.S.H. contributed to the conceptualization of the study and reviewed and made final corrections to the manuscript. N.E. contributed to formal analysis, reviewed and edited the manuscript. T.K. contributed to the conceptualization of the study and reviewed and edited the manuscript. All authors approved the final manuscript.

Acknowledgements

The authors thank Dominic Cavenagh and Peta Forder (Priority Research Centre for Generational Health and Ageing, University of Newcastle), and Natasha Weaver (School of Medicine and Public Health, University of Newcastle) for their statistical input. This research is based on a study conducted as part of the Australian Longitudinal Study on Women's Health by the University of Queensland and the University of Newcastle. The authors are grateful to the Australian Government Department of Health for funding and to all women who provided the survey data. The authors also acknowledge the Departments of Health and Veterans' Affairs, and Medicare Australia, for the provision of the PBS data, and the Australian Institute of Health and Welfare (AIHW) as the integrating authority.

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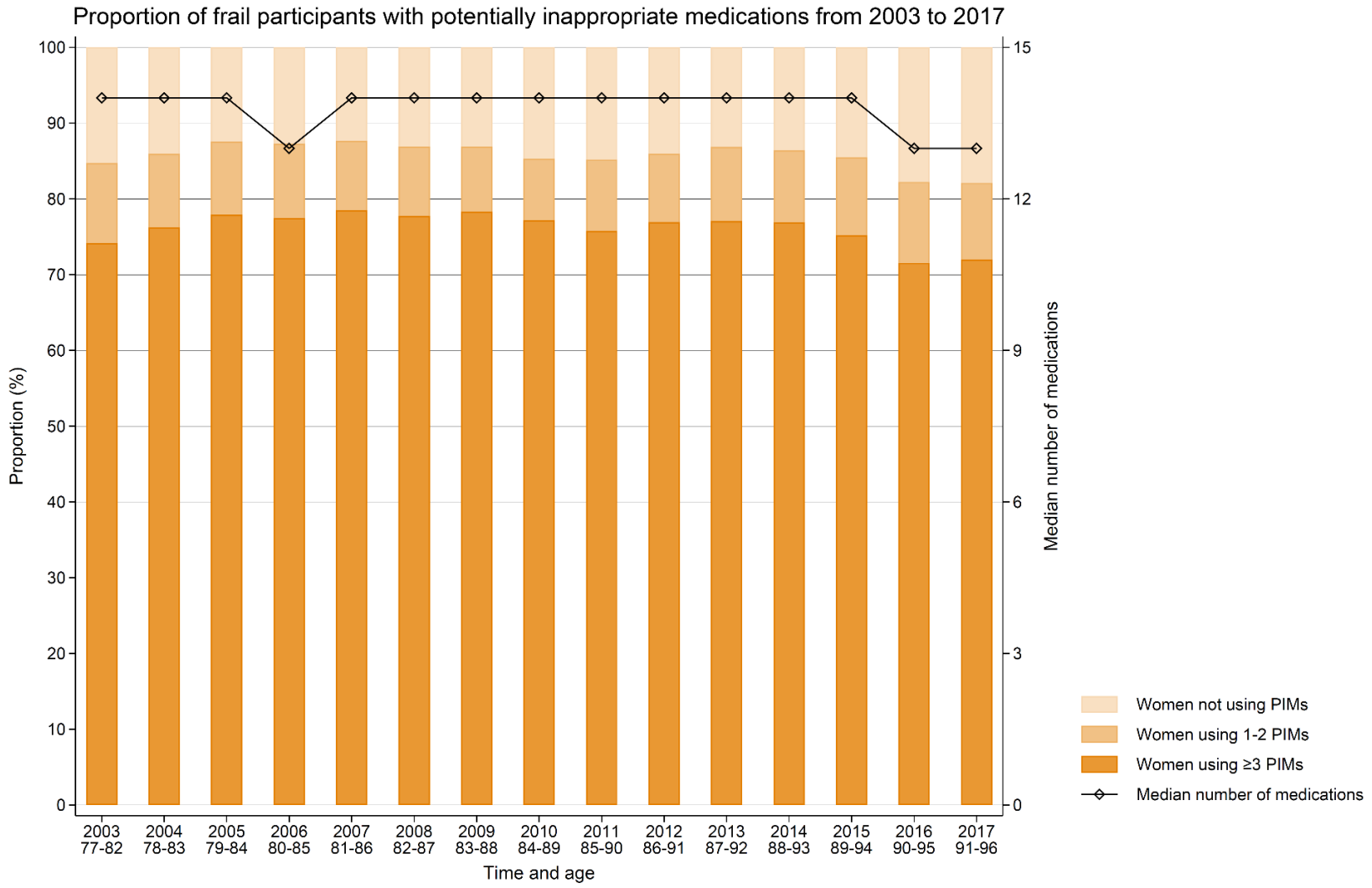

Fig. 1 Proportion of frail participants aged 77 to 96 years using potentially inappropriate medications overlayed by median number of medications from 2003 to 2017

PIMs: Potentially inappropriate medications

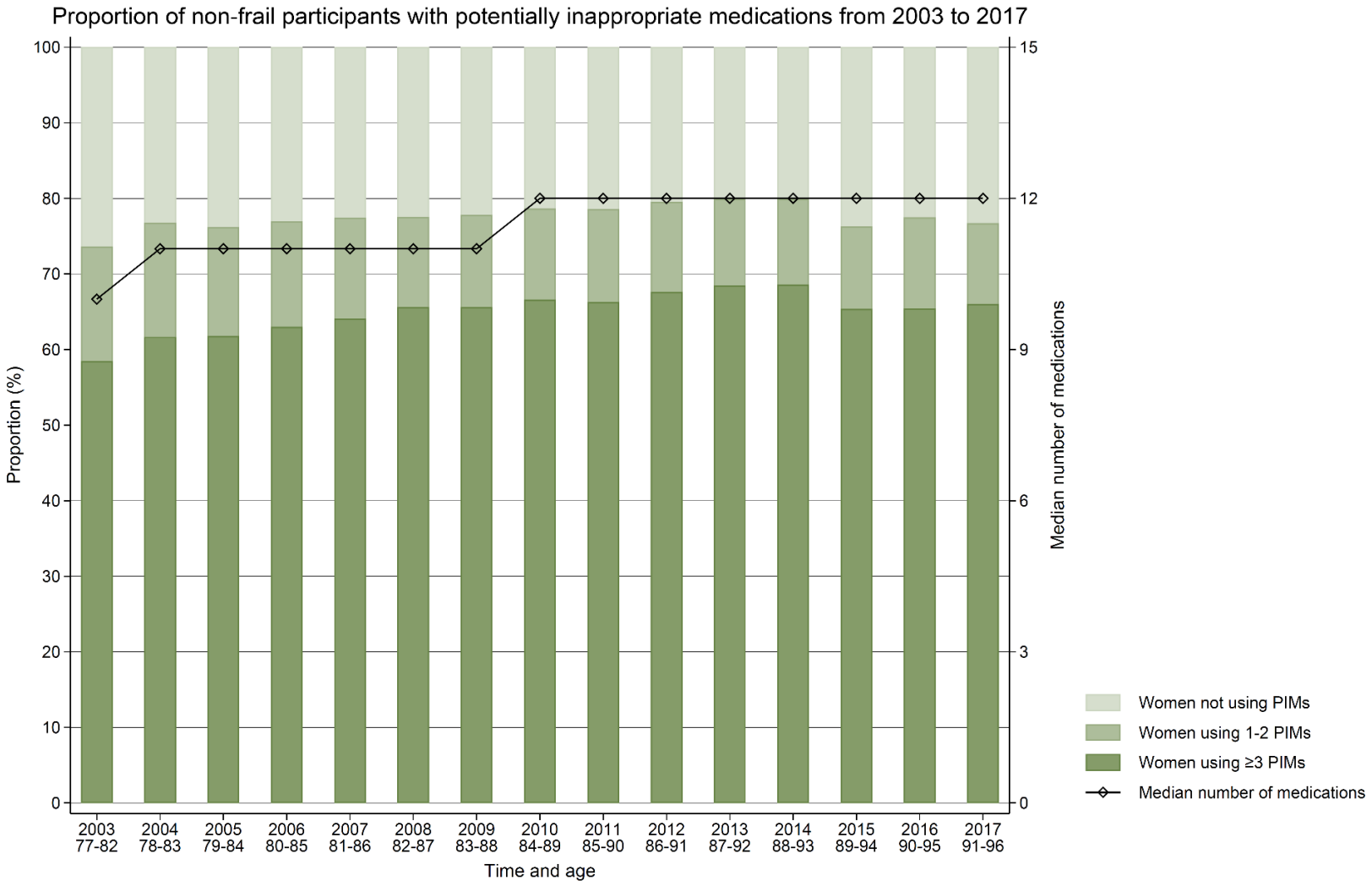

Fig. 2 Proportion of non-frail participants aged 77 to 96 years using potentially inappropriate medications overlayed by median number of medications from 2003 to 2017

PIMs: Potentially inappropriate medications

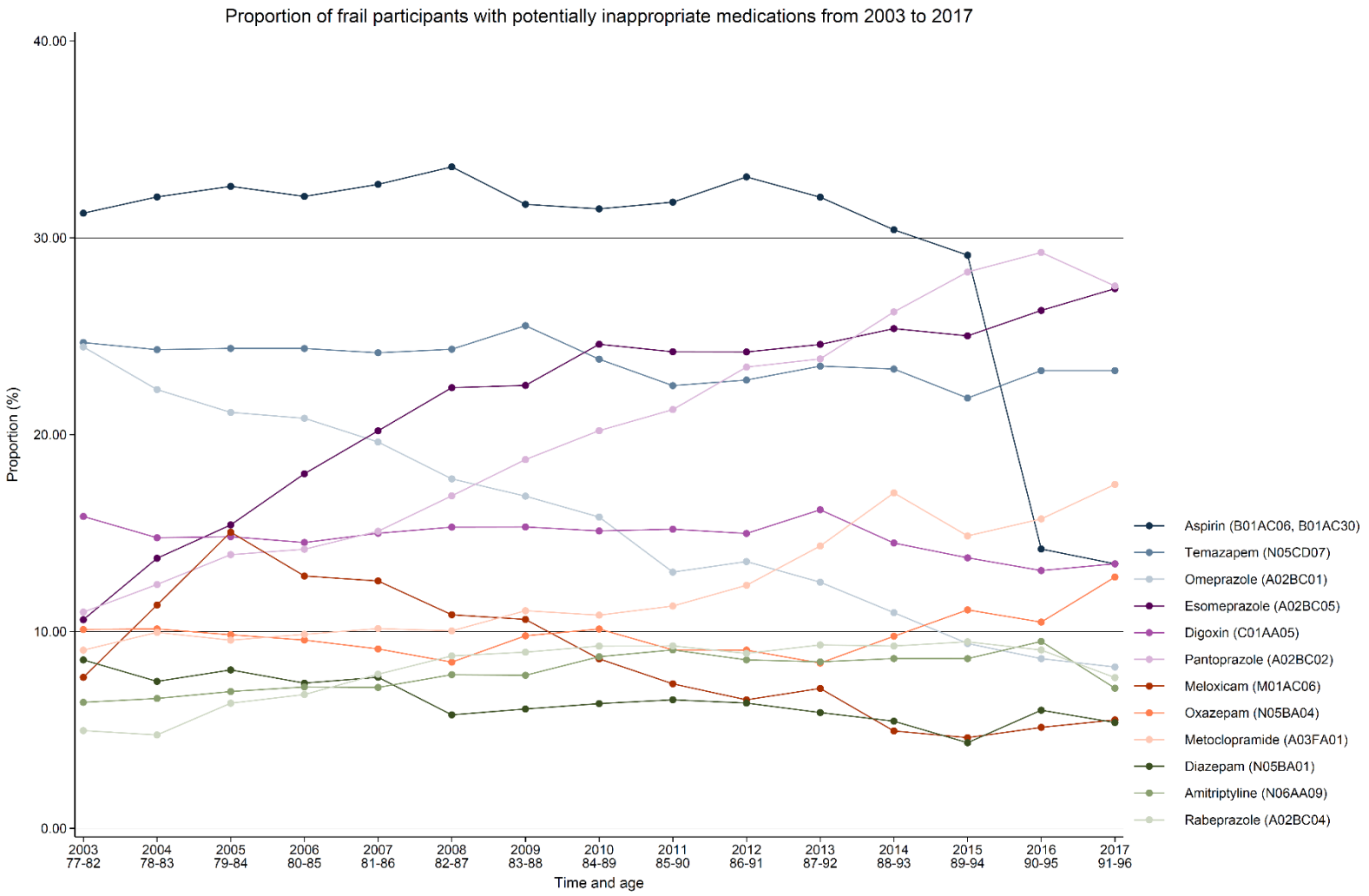

Fig. 3 Top five potentially inappropriate medications among frail participants aged 77 to 96 years from 2003 to 2017

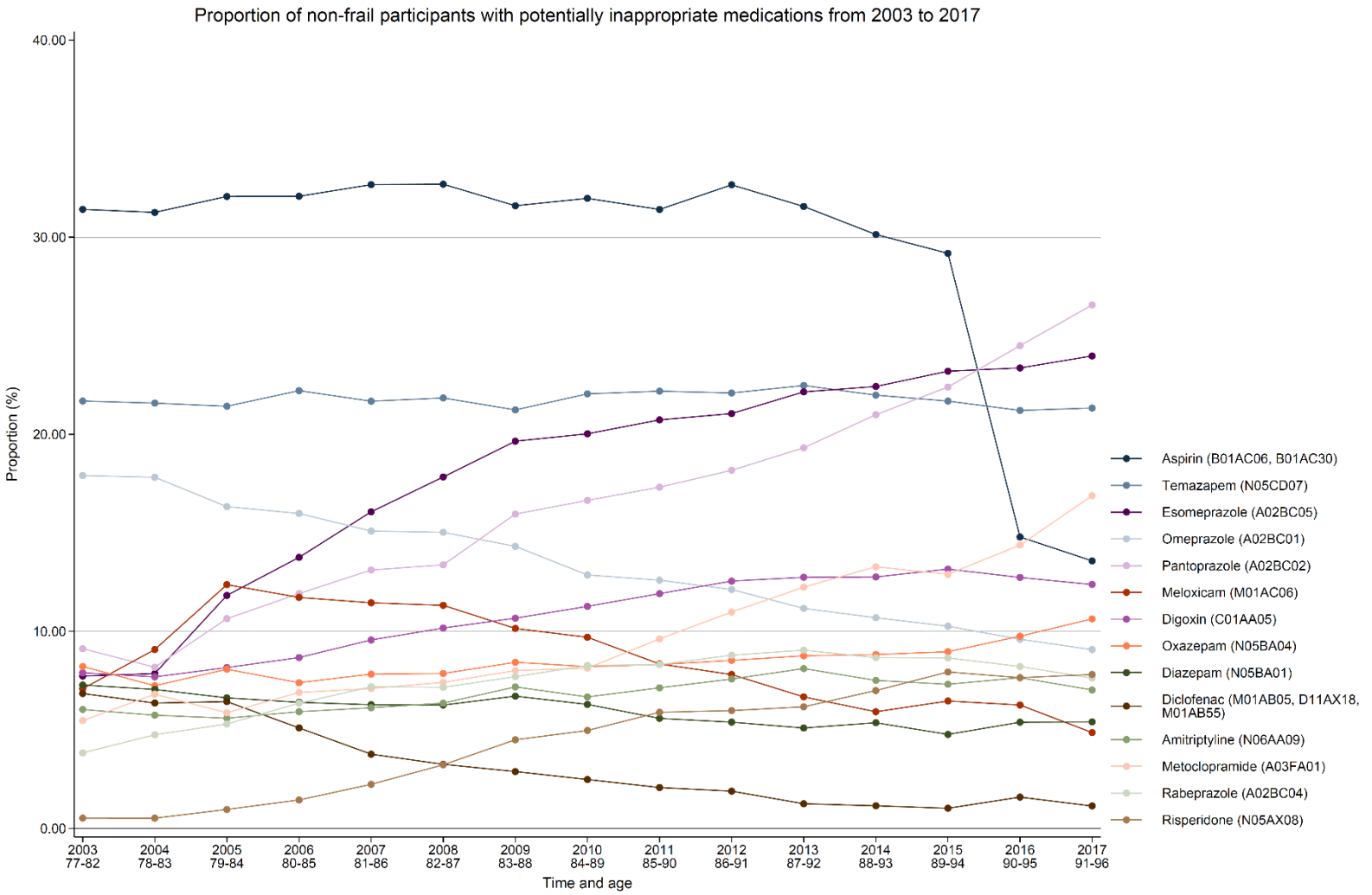

Fig. 4 Top five potentially inappropriate medications among non-frail participants aged 77 to 96 years from 2003 to 2017

Table 1 Adjusted and unadjusted results for the associations between frailty and potentially inappropriate medications (PIMs) from 2003 to 2017 using generalised estimating equations (GEEs) for log-binomial regressions

	Unadjusted models for women with PIMs [a]		**Adjusted model for women with PIMS**	
	Risk ratio (95% CI [b])	***p-value***	**Risk ratio (95% CI)**	***p-value***
Frailty status				
Non-frail	Reference		Reference	
Frail	1.05 (1.04, 1.06)	<0.001	**1.02 (1.01, 1.03)**	**<0.001**
Time (in years)	1.01 (1.00, 1.01)	<0.001	**1.00 (1.00, 1.00)**	**<0.001**
Age at baseline	1.00 (0.99, 1.01)	0.077	**1.00 (1.00, 1.01)**	**0.014**
Education level				
Below Year 12	Reference		Reference	
Year 12 and above	0.94 (0.93, 0.96)	<0.001	**0.97 (0.95, 0.98)**	**<0.001**
DVA [c] Status				
No	Reference		Reference	
Yes	1.05 (1.04, 1.06)	<0.001	**1.02 (1.01, 1.03)**	**0.004**
Number of GP [d] visits in the last 12 months				
≤4 visits	Reference		Reference	
>4 visits	1.08 (1.07, 1.09)	<0.001	**1.05 (1.04, 1.06)**	**<0.001**
Hospital admissions in the last 12 months				
No	Reference		Reference	
Yes	1.05 (1.04, 1.06)	<0.001	**1.02 (1.01, 1.02)**	**<0.001**
Number of chronic diseases				
<4	Reference		Reference	
≥4	1.11 (1.10, 1.12)	<0.001	**1.06 (1.05, 1.07)**	**<0.001**
Falls in the last 12 months				
No	Reference		Reference	
Yes	1.01 (1.00, 1.02)	0.042	0.99 (0.98, 1.00)	0.062
Presence of polypharmacy [e]				
No	Reference		Reference	
Yes	1.09 (1.09, 1.10)	<0.001	**1.07 (1.06, 1.07)**	**<0.001**

[a] Potentially inappropriate medications
[b] Confidence interval
[c] Department of Veterans Affairs
[d] General practitioner
[e] Polypharmacy defined as continuous polypharmacy, i.e. the use of 5 or more medications, where each medication is counted as one if it appears in two time windows at each year (1 Apr-30 Jun) & (1 Oct-31 Dec)

Note: The reference class was 'no PIMS'