Title: Prevalence and association of continuous polypharmacy and frailty among older women: A longitudinal analysis over 15 years

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Abstract

Objectives: This study aimed to determine the prevalence of continuous polypharmacy and hyperpolypharmacy, determine medications that contribute to continuous polypharmacy, and examine the association between frailty and continuous polypharmacy.

Study design: A prospective study using data from the Australian Longitudinal Study on Women's Health. Women aged 77 to 82 years in 2003, and 91 to 96 years in 2017 were analysed, linking the Pharmaceutical Benefits Scheme data to participants' survey data.

Main outcome measures: The association between frailty and continuous polypharmacy was determined using generalised estimating equations for log binomial regressions, controlling for confounding variables. Descriptive statistics were used to determine the proportion of women with polypharmacy, and medications that contributed to polypharmacy.

Results: The proportion of women with continuous polypharmacy increased over time as they aged. Among participants who were frail (n=833) in 2017, 35.9% had continuous polypharmacy and 1.32% had hyperpolypharmacy. Among those who were non-frail (n=1966), 28.2% had continuous polypharmacy, and 1.42% had hyperpolypharmacy. Analgesics (e.g. paracetamol) and cardiovascular medications (e.g. furosemide and statins) commonly contributed to continuous polypharmacy among frail and non-frail women. Accounting for time and other characteristics, frail women had an 8% increased risk of continuous polypharmacy (RR 1.08; 95% CI 1.05, 1.11) compared to non-frail women.

Conclusions: Combined, polypharmacy and frailty are key clinical and public health challenges. Given that one-third of women had continuous polypharmacy, monitoring and review of medication use among older women is important, and particularly among women who are frail.

Keywords: Aging; frailty; medication use; older adults, older women; polypharmacy

1. Introduction

Medications are important in maintaining quality of life for many older people. As people age, they tend to develop multiple comorbidities and often require several medications. The concomitant use of many medications- polypharmacy, is a common geriatric syndrome [1]. Although there does not seem to be any consensus regarding its definition, polypharmacy is commonly referred to as the use of five or more medications [2], with 10 or more medications sometimes referred to as hyperpolypharmacy [2]. Polypharmacy is associated with adverse outcomes such as serious drug-drug interactions, adverse drug reactions, hospitalisations, cognitive impairment, functional decline, falls, increased length of stay in hospitals, readmissions to hospitals soon upon discharge, and mortality [3,4].

Frailty is also a geriatric syndrome characterised by decreases in physiological reserves. There is general agreement that frailty is age-related, with operational definitions that aim to quantify vulnerabilities among older adults [5]. Frailty has garnered attention in the last few years based on its direct relationship with adverse health events including disability, falls, institutionalisation, hospitalisation, higher healthcare costs and increased mortality [5,6]. A systematic review reported that the prevalence of frailty among community-dwelling older people varied considerably from 4% to 59%, however overall weighted prevalence of frailty was 11%, which was higher in older women (9.6%) than in older men (5.2%), and increased with age [7]. Combined, polypharmacy and frailty are key clinical and public health challenges.

Understanding the association of frailty and polypharmacy could help identify a segment of the older population that could benefit from preventive actions. However, there is a lack of evidence about the prevalence of continuous polypharmacy amongst frail older women and the degree of association between frailty status and continuous polypharmacy. In this context, our study determined the prevalence of continuous polypharmacy and hyperpolypharmacy among older women according to frailty status, determined medications that contributed to continuous polypharmacy, and examined the association between frailty and continuous polypharmacy. To the best of our knowledge, our study is the first to use longitudinal data to determine the association between frailty and continuous polypharmacy, and how polypharmacy changes as women age.

2. Methods

2.1. Study population and data source

Participants included in our study were from the Australian Longitudinal Study on Women's Health (ALSWH). The ALSWH is an ongoing population-based survey which develops and informs public health and social policies. Our study included participants from the ALSWH 1921-1926 cohort, who completed a baseline survey in 1996, a second survey in 1998 and then surveys every three years until 2011, and abbreviated six-monthly surveys thereafter. A total of 12432 women (mean age=72.6,

SD=1.5) completed the first survey in 1996 and were determined to be largely representative of older Australian women in the same age group, when compared to the 1996 Australian National Census data [8]. Further information about the ALSWH are reported elsewhere [9].

2.2. Administrative data linkage

The ALSWH survey data were linked to the Pharmaceutical Benefits Scheme (PBS) dataset to obtain medication information. The PBS is a government program that provides access to a wide range of subsidised prescription medications to Australian citizens/permanent residents with a Medicare card. The PBS dataset used in our study includes medications in the Repatriation Pharmaceutical Benefits Scheme (RPBS) which subsidises medications for veterans, governed by the Department of Veterans Affairs (DVA). Medications below the PBS co-payment threshold prior to April 2012 are not included in the PBS data.

2.3. Eligible participants

Eligible participants fulfilled the following criteria:

i) Remained alive at 1 January 2003, and
ii) Eligible for and did not withdraw consent to PBS data linkage before 2017, and
iii) Had at least one PBS record in 2003 that contributed to polypharmacy in months of interest, and
iv) Had PBS records with complete ATC codes (7 characters), and
v) Had data on frailty in 2003

Supplementary Figure 1 represents a stepwise approach in deriving the final sample population for our study.

2.4. Assessment of polypharmacy

Medications in the PBS dataset are classified according to the Anatomic Therapeutic Chemical (ATC) classification system [10]. Polypharmacy was categorised using two different methods. The first categorisation of continuous polypharmacy was used in a line graph that differentiated the prevalence of participants using 5-9 unique medications (continuous polypharmacy) compared to those using ≥10 unique medications (continuous hyperpolypharmacy). The second categorisation was used to determine medications that contributed to continuous polypharmacy and in the regression analyses, which were continuous polypharmacy (≥5 unique medications) compared to no continuous polypharmacy (0-4 unique medications). In both categorisations, polypharmacy required that the same unique medication appeared in two time windows of the same year, 1 April to 30 June, and 1 October to 31 December. This avoided underestimating exposure to medications because some patients tend to stockpile medications towards the end of each year [11]. Combined formulations (more than one

active ingredient in a preparation) were treated as unique medications since we used the ATC classification which assigned combined medications with unique ATC codes. Medications excluded from the polypharmacy count are presented in **Supplementary Table 1**, and some of them include topical preparations, non-therapeutic agents, and vitamins and minerals. Topical preparations were excluded because consequences of polypharmacy are often a result of systemic absorption (e.g. oral dosage forms) of medications, leading to adverse outcomes. Vitamins and minerals (e.g. calcium and thiamine) were excluded to avoid under ascertainment of its contribution to polypharmacy as they may be obtained externally without prescriptions, and because they are only subsidised by the PBS under restricted benefits for certain groups of people.

2.5. Assessment of frailty

Frailty was determined based on the FRAIL (Fatigue, Resistance, Ambulation, Illness, & Loss of Weight) scale which was validated in the 1921-1926 cohort of ALSWH participants and with scores >2 being predictive of frailty [12]. Participants were scored 1 for each deficit and values ranged from 0 (non-frail) to 5 (most frail). Participants were indicated as being fatigued if they answered “a good bit of the time”, “most of the time” or “all of the time” to the questions “Did you feel worn out?” or “Did you feel tired?”, or if they answered “none of the time”, “a little of the time”, and “some of the time” to the question “Did you have a lot of energy?” Participants were scored positive for resistance and ambulation if they answered “limited a little” or “limited a lot” in being able to climb one flight of stairs or walk 100 metres, respectively. They were scored positive for the illness domain if they reported more than five of the following illnesses: angina pectoris or heart attack, Alzheimer’s disease or dementia, asthma, bronchitis or emphysema, arthritis which includes rheumatoid arthritis and osteoarthritis, hypertension, diabetes mellitus, stroke, depression and osteoporosis. Participants were indicated as having weight loss if self-reported weight loss was ≥5% between two consecutive surveys.

2.6. Explanatory variables

Survey 3 in 2002 was treated as the baseline survey for this study due to the lack of PBS data prior to 2002. Continuous variables include participants’ age at baseline and time (in years). Categorical variables included whether participants lived alone, their residential area (major cities in Australia, inner regional Australia and outer regional/remote/very remote Australia), DVA coverage, health status based on the question “In general, would you say your health is” from the SF-36 [13] and categorised as excellent/very good, good, and fair/poor, number of general practitioner (GP) visits in the last 12 months (≤4 times or >4 times which was categorised based on the median in 1996) [14], number of chronic diseases (0-1, 2-3, ≥4), BMI categories (underweight if <18.5 kg/m^2, healthy if 18.5 to <25 kg/m^2, overweight if 25 to <30kg/m^2, obese if ≥30 kg/m^2) [15], bodily pain categorised as none, very mild/mild, and moderate/severe/very severe, falls in the last 12 months, and the presence of potentially inappropriate medications (PIMS) determined from the Beers Criteria 2019 [16]. Missing data were carried forward from preceding surveys if available. Education level (below Year 12 and Year 12 and

above) was determined from Survey 1 in 1996 and age at baseline was determined as age of participants at Survey 3 in 2002 (age 77 to 82 years). Chronic diseases were considered enduring once reported at any survey.

2.7. Statistical analyses

Descriptive analyses determined the proportion of participants using medications at each year from 2003 (age 77 to 82 years) to 2017 (age 91 to 96 years). The association between continuous polypharmacy and frailty was determined using generalised estimating equations (GEE) for log binomial regressions with an unstructured correlation matrix and robust standard errors. GEE models allow for analysis of longitudinal data by accounting for the correlation between repeated measures on the same individual, thereby allowing accurate estimation of the relationship between continuous polypharmacy, frailty and other explanatory variables over time. This provides a distinct advantage over regression at a single time point, such as cross-sectional analysis.

First, univariate regressions were performed to examine the association between each of the explanatory variables, including frailty, and continuous polypharmacy. Multicollinearity among explanatory variables was identified using Pearson's correlation (values greater than 0.8) and variance inflation factor (values greater than 10), and these variables were removed in the adjusted models. The first multivariable model included variables that were significant at the 0.25 level in the univariate analyses. The final model was obtained using a backward stepwise elimination process, starting from the least significant variable at the 0.05 level. The regression results are presented as risk ratios (RR) with 95% confidence intervals (95% CI). All analyses were performed using Stata® IC version 16.

2.8. Ethics approval

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

3. Results

There were 8996 participants aged 77 to 82 years who met all eligibility criteria and were included in the study in 2003; their baseline characteristics are presented in **Table 1**. An additional 946 participants were missing frailty data; however, their characteristics did not substantially vary from those women included in the study.

3.1. Prevalence of continuous polypharmacy and hyperpolypharmacy according to frailty status

Based on **Supplementary Table 2** and summarised in **Fig. 1.**, most of the participants remained non-frail without continuous polypharmacy (0-4 medications). This proportion generally decreased from 2003 (5655, 81.80%) to 2015 (1688, 64.80%). Over time more participants became frail, and were classified as continuous polypharmacy/hyperpolypharmacy. From 2003 to 2015, there was an increasing trend for continuous polypharmacy (5-9 medications) among frail (749, 35.96% to 554, 43.21%) and non-frail (1216, 17.59% to 873, 33.51%) participants. Polypharmacy appeared to be less prevalent in 2016 and 2017, possibly due to changes in PBS listings although there was no discernible change in prevalence of hyperpolypharmacy for most of the period.

3.2. Medications that contributed to continuous polypharmacy according to frailty status

Fig. 2. represents seven medications that commonly contributed to continuous polypharmacy (≥5 medications) among frail participants, and includes medications which appeared in the top four in any year. Medications that most commonly contributed to continuous polypharmacy among frail participants in 2003 were paracetamol (37.44%), furosemide (26.10%), simvastatin (25.61%), omeprazole (21.46%), atorvastatin (17.20%), pantoprazole (9.88%) and esomeprazole (8.29%). The order for this list changed over time mostly due to reduction in prescriptions for paracetamol, simvastatin and omeprazole, and increased prescriptions for esomeprazole and pantoprazole. Similarly, **Fig. 3.** represents medications over time that contributed to continuous polypharmacy among non-frail participants. The medication list is similar to the list for frail participants, although with differing prevalences, and the addition of alendronate.

Expanding the list to include the top 10 medications for any year revealed that alendronate, warfarin, aspirin, isosorbide mononitrate, celecoxib, buprenorphine and Macrogol 3350 were common among women who were frail. Additional medications in the non-frail group were similar, with the exception of buprenorphine, while mirtazapine was observed as an additional contributor (see **Supplementary Table 3**).

3.3. The association between frailty and continuous polypharmacy

All variables were included in the first multivariable model, however after backward stepwise elimination, 9 variables, including frailty, were retained in the final model (**Table 2**). Frailty was associated with an 8% increase in the risk of continuous polypharmacy (RR 1.08; 95% CI: 1.05, 1.11). Participants using potentially inappropriate medications (PIMS) had a 50% higher risk of continuous polypharmacy (RR 1.50; 95% CI: 1.45, 1.55). The risk of continuous polypharmacy was 2.5 times higher among participants with ≥4 chronic diseases (RR 2.45; 95% CI: 2.25, 2.67) and 1.7 times higher among participants with 2-3 chronic diseases (RR 1.71, 95% CI: 1.58, 1.85) when compared to those with none or 1 chronic

diseases. For every 1 year increase in time, participants had a 1% increase in the risk of continuous polypharmacy (RR 1.01; 95% CI: 1.01, 1.01). Participants with >4 GP visits had a 23% higher risk of continuous polypharmacy (RR 1.23; 95% CI: 1.19, 1.27) compared to those who had ≤4 GP visits. Good and fair/poor health, moderate/severe or very severe pain, and overweight and obese BMI were also associated with higher risk of continuous polypharmacy. Higher education and underweight BMI were associated with lower risk of continuous polypharmacy.

4. Discussion

This study showed increases in the prevalence of hyper/polypharmacy and frailty as women age, and assessed the association between these two important health risks. The findings show that polypharmacy is common, affecting around one-third of women, and more common among frail women compared to non-frail women.

However, for most of the study the majority of women were neither frail nor using polypharmacy. The low prevalence of hyperpolypharmacy was also noted in a study by Page et al. (6%) [11] and in a 2012 study among older Australians who were community-dwelling (5%) [17]. The prevalence trends of polypharmacy and frailty in our study seem varied when compared to a study by Bonaga et al. (2018) whose study population included women with a mean age 78.5 years [18]. The variation is probably owing to differences in study settings, and lack of homogeneity regarding the definitions and assessments of frailty and polypharmacy.

In our study, the use of medications increased over time until 2015 likely due to aging and prescribing changes. Page et al. (2019) also found that continuous polypharmacy increased over time until 2015, even for women of the same age [11]. In 2016, low-cost medications such as paracetamol and aspirin were de-listed from the PBS and was reflected in a substantial decrease in our study from 2015 to 2017. It is unlikely that these essential medications were discontinued in later life; women would have continued taking them through ‘private’ prescriptions, i.e. not subsidised by the PBS [11,19].

In our study, medications contributing to polypharmacy among frail and non-frail women were taken on a continuous basis. The most common contributors were cardiovascular medications and analgesics, in line with a study in Malaysia [20], and consistent with age-associated increases in cardiovascular diseases and risks [21]. An increase in furosemide use could be associated with stricter management of hypertension, or as therapy in congestive heart failure. With respect to heart failure, the average prevalence increases with age, and has been reported to be highest in women aged 80 to 89 years, and over. Statin use also contributed to continuous polypharmacy, possibly because statins are commonly co-prescribed with other cardiovascular medications to reduce the risk of stroke [21].

Previous studies confirm that polypharmacy predicts use of PIMs. We identified that PIMs were associated with the highest increase in risk of continuous polypharmacy, and was higher than in a

Malaysian study by Lim et al. (30%) [22]. This may have been due to the inclusion of proton-pump inhibitors that could have contributed to high use of PIMs in our study. This is interesting because it could be indicative of a prescribing cascade, where a PIM is prescribed to curb adverse outcomes of other medications. In our study, this could be supported by a 34% increased risk of continuous polypharmacy among women with fair or poor health.

The main implication of our study is that frailty and polypharmacy co-occur, and each may magnify the risk of the other in terms of adverse events. The association between frailty and continuous polypharmacy is complex and bidirectional, and although they are independent risk factors for mortality, a 2015 study found that their combined effect multiplied the risk of death by 6.30 in a 2.6-year follow-up period [23]. It is important that in considering polypharmacy we need to consider frailty, and in considering frailty we need to consider polypharmacy. When an individual needs multiple medications, there is scope to emphasize strategies to protect against frailty and build resilience e.g. attention to diet control, exercise and social support. Equally when an individual is frail, medication reviews become particularly important to identify and avoid PIMs where possible, while considering medication interactions and adverse events.

Visits to GPs could be interpreted as a negative event, but it also means that GPs have the opportunity to regularly review medications in the context of frailty. This is where pharmacists play a key role, and the process is already established in many developed countries, known as pharmacist-led medication reviews [24-26]. Although it is inarguable that polypharmacy based on numerical counts is associated with a range of negative outcomes [27,28], it is important to consider adding medications for symptom control when appropriate, because quality of life for frail older people is often considered to be a more important therapeutic goal than prolongation of life [29]. For instance, should statin use be reduced in frail older people due to the risk of rhabdomylosis, muscle weakness and kidney failure, or should statins be used to reduce cardiovascular risk? This trade-off between quality of life and longevity needs to consider the range of associated risks as well as patient preferences and tolerance, focusing on patient-centred care as many older people themselves prioritize functional status and mobility as key rehabilitative goals [30].

Our study is limited by an exclusive observation of only women which may preclude generalisability of the findings to men. However, this may also be regarded as a strength as older women use more medications than older men [31], and data for older women with frailty and continuous polypharmacy are lacking. The self-report and longitudinal nature of the ALSWH surveys may subject participants to recall bias and survivor bias; nevertheless, insights obtained from this large longitudinal study of Australian women take precedence over these limitations.

5. Conclusions

Prevalence of continuous polypharmacy determined in our study could be a consequence of long-term use of preventive medications, which may be unavoidable among the oldest old, especially the frail. Given that one-third of women in our study have/had polypharmacy, there is still scope for improvement in appropriate prescribing for older people. There is potential for pharmacists and general practitioners, as members of healthcare inter-professional teams, to initiate and conduct regular medication reviews for older people, while considering frailty as an important indicator. The lack of homogeneity in the assessments of frailty and polypharmacy should not hinder decision-making; as a starting point, healthcare professionals should consider using established assessments of polypharmacy and frailty, to modify goals of care for frail older people.

Author contributions

Kaeshaelya Thiruchelvam contributed to conceptualization, methodology, formal analysis and writing the original draft.
Julie Byles contributed to conceptualization, methodology, and reviewing and editing the manuscript.
Syed Shahzad Hasan contributed to conceptualization, and reviewing and editing the manuscript.
Nicholas Egan contributed to formal analysis, methodology, and reviewing and editing the manuscript.
Therese Kairuz contributed to conceptualization and reviewing and editing the manuscript.

Conflicts of interest

The authors declare that they have no conflicts of interest with regards to this research, authorship and the publication of this article.

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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. However, codes can be made available upon request.

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References

1. N. Masnoon, S. Shakib, L. Kalisch-Ellett, G.E. Caughey, What is polypharmacy? A systematic review of definitions, BMC Geriatr. 17 (2017) 230. https://doi.org/10.1186/s12877-017-0621-2.

2. D. Gnjidic, S.N. Hilmer, F.M. Blyth, V. Naganathan, L. Waite, M.J. Seibel, 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. 65 (9) (2012) 989-995. https://doi.org/ 10.1016/j.jclinepi.2012.02.018.

3. G.E. Caughey, E.E. Roughead, N. Pratt, S. Shakib, A.I. Vitry, A.L. Gilbert, Increased risk of hip fracture in the elderly associated with prochlorperazine: is a prescribing cascade contributing? Pharmacoepidemiol. Drug. Saf. 19 (9) (2010) 977-982. https://doi.org/10.1002/pds.2009.

4. M.J. Rawle, R. Cooper, D. Kuh, M. Richards. Associations between polypharmacy and cognitive and physical capability: A British birth cohort study, J. Am. Geriatr. Soc. 66 (5) (2018) 916-923. https://doi.org/ 10.1111/jgs.15317.

5. L.P. Fried, C.M. Tangen, J. Walston, A.B. Newman, C. Hirsch, J. Gottdiener, et al., Frailty in older adults: evidence for a phenotype, J. Gerontol. A. Biol. Sci. Med. Sci. 56 (3) (2001) M146-M156. https://doi.org/ 10.1093/gerona/56.3.m146.

6. I. García-Nogueras, I. Aranda-Reneo, L.M. Peña-Longobardo, J. Oliva-Moreno, P. Abizanda, Use of health resources and healthcare costs associated with frailty: The FRADEA study, J. Nutr. Health. Aging. 21 (2) (2017) 207-214. https://doi.org/ 10.1007/s12603-016-0727-9.

7. R.M. Collard, H. Boter, R.A. Schoevers, R.C. Oude Voshaar, Prevalence of frailty in community-dwelling older persons: a systematic review, J. Am. Geriatr. Soc. 60 (8) (2012) 1487-1492. https://doi.org/ 10.1111/j.1532-5415.2012.04054.x.

8. W.J. Brown, A.J. Dobson, L. Bryson, J.E. Byles, Women's Health Australia: on the progress of the main cohort studies, J. Womens. Health. Gend. Based. Med. 8 (5) (1999) 681-688. https://doi.org/ 10.1089/jwh.1.1999.8.681.

9. A.J. Dobson, R. Hockey, W.J. Brown, J. Byles, D.J. Loxton, D. McLaughlin, et al., Cohort profile update: Australian Longitudinal Study on Women's Health, Int. J. Epidemiol. 44 (5) (2015) 1547-1547f. https://doi.org/10.1093/ije/dyv110

10. World Health Organization, Anatomical Therapeutic Chemical (ATC) classification. http://www.who.int/medicines/regulation/medicines-safety/toolkit_atc/en/, 2020 (accessed 18 April 2020).

11. A.T. Page, M.O. Falster, M. Litchfield, S.A. Pearson, C. Etherton-Beer, Polypharmacy among older Australians, 2006–2017: a population-based study, Med. J. Aust. 211 (2) (2019) 71-75. https://doi.org/10.5694/mja2.50244.

12. D. Lopez, L. Flicker, A. Dobson, Validation of the frail scale in a cohort of older Australian women, J. Am. Geriatr. Soc. 60 (1) (2012) 171-173. https://doi.org/ 10.1111/j.1532-5415.2011.03746.x.

13. J.E. Ware, C.D. Sherbourne, The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection, Med. Care. 30 (6) (1992) 473-483.

14. X. Dolja-Gore, M. Tavener, T. Majeed, B.R. Nair, J.E. Byles, Uptake, prevalence and predictors of first-time use for the 75+ Health Assessment Scheme, Aust. J. Prim. Health. 23 (5) (2017) 476-481. https://doi.org/10.1071/PY16108.

15. World Health Organization, Obesity: preventing and managing the global epidemic, (2000) 267.

16. 2019 American Geriatrics Society Beers Criteria® Update Expert Panel, American Geriatrics Society 2019 updated AGS Beers Criteria® for potentially inappropriate medication use in older adults, J. Am. Geriatr. Soc. 67 (4) (2019) 674-694. https://doi.org/10.1111/jgs.15767.

17. D. Gnjidic, S.N. Hilmer, F.M. Blyth, V. Naganathan, R.G. Cumming, D.J. Handelsman, et al., High-risk prescribing and incidence of frailty among older community-dwelling men, Clin. Pharmacol. Ther. 91 (3) (2012) 521-528. https://doi.org/10.1038/clpt.2011.258.

18. B. Bonaga, P.M. Sánchez-Jurado, M. Martínez-Reig, G. Ariza, L. Rodríguez-Mañas, D. Gnjidic, et al., Frailty, polypharmacy, and health outcomes in older adults: The frailty and dependence in Albacete Study, J. Am. Med. Dir. Assoc. 19 (1) (2018) 46-52. https://doi.org/ 10.1016/j.jamda.2017.07.008.

19. A. Kemp, E. Paige, E. Banks, Beginner's guide to using pharmaceutical benefits scheme data: tips and pitfalls. https://www.alswh.org.au/images/content/pdf/InfoData/linked-data/Guide_to_Using_PBS_Data_20131125.pdf, 2012 (accessed 20 April 2020).

20. S.M. Ong, Y.M.F. Lim, S. Sivasampu, E.M. Khoo, Variation of polypharmacy in older primary care attenders occurs at prescriber level, BMC. Geriatr. 18 (1) (2018) 59. https://doi.org/ 10.1186/s12877-018-0750-2.

21. J.B. Strait, E.G. Lakatta, Aging-associated cardiovascular changes and their relationship to heart failure, Heart. Fail. Clin. 8 (1) (2012) 143-164. https://doi.org/ 10.1016/j.hfc.2011.08.011.

22. L.M. Lim, M. McStea, W.W. Chung, N. Nor Azmi, S.A. Abdul Aziz, S. Alwi, et al., Prevalence, risk factors and health outcomes associated with polypharmacy among urban community-dwelling older adults in multi-ethnic Malaysia, PloS. One. 12 (3) (2017) e0173466. https://doi.org/10.1371/journal.pone.0173466.

23. M. Herr, J.M. Robine, J. Pinot, J.J. Arvieu, J. Ankri, Polypharmacy and frailty: prevalence, relationship, and impact on mortality in a French sample of 2350 old people, Pharmacoepidemiol. Drug. Saf. 24 (6) (2015) 637-646. https://doi.org/10.1002/pds.3772.

24. Pharmaceutical Society of Australia, Guidelines for pharmacists providing Home Medicines Review (HMR) services.https://www.ppaonline.com.au/wp-content/uploads/2019/01/PSA-Guidelines-for-Providing-Home-Medicines-Review-HMR-Services.pdf, 2011 (accessed 10 March 2020).

25. Government of Ontario M of H and L-TC, MedsCheck- Public Information - Ministry of Health and Long-term Care. http://www.health.gov.on.ca/en/public/programs/drugs/medscheck/, 2020 (accessed 10 March 2020).

26. Pharmacy Council of New Zealand, Medicines management: definition, levels, competence framework. http://www.pharmacycouncil.org.nz/cms_show_download.php?id=124, 2019 (accessed 12 February 2020).

27. A.T. Page, K. Potter, R. Clifford, C. Etherton-Beer, Deprescribing in older people, Maturitas. 91 (2016) 115-134. https://doi.org/10.1016/j.maturitas.2016.06.006.

28. A. Page, C. Etherton-Beer, Undiagnosing to prevent overprescribing, Maturitas. 123 (2019) 67-72. https://doi.org/10.1016/j.maturitas.2019.02.010.

29. R.E. Hubbard, M.S. O'Mahony, K.W. Woodhouse, Medication prescribing in frail older people, Eur. J. Clin. Pharmacol. 69 (3) (2013) 319-326. https://doi.org/ 10.1007/s00228-012-1387-2.

30. K. Rockwood, B. Joyce, P. Stolee, Use of goal attainment scaling in measuring clinically important change in cognitive rehabilitation patients, J. Clin. Epidemiol. 50 (5) (1997) 581-588. https://doi.org/10.1016/s0895-4356(97)00014-0.

31. E.A. Chrischilles, D.J. Foley, R.B. Wallace, J.H. Lemke, T.P. Semla, J.T. Hanlon, et al., Use of medications by persons 65 and over: data from the established populations for epidemiologic studies of the elderly, J. Gerontol. 47 (5) (1992) M137-M14. https://doi.org/ 10.1093/geronj/47.5.m1

Table 1

Baseline characteristics of study participants using their most recent data up to 2003

Participant characteristics	Frail (n=2083)		Non-frail (n=6913)	
	No continuous polypharmacy n (%)	Continuous polypharmacy n (%)	No continuous polypharmacy n (%)	Continuous polypharmacy n (%)
n	1263 (60.6)	820 (39.4)	5655 (81.8)	1258 (18.2)
Age at baseline, mean ± SD	79.68 ± 1.47	79.65 ± 1.46	79.50 ± 1.47	79.48 ± 1.47
Education level				
Below Year 12	891 (70.5)	592 (72.2)	3767 (66.6)	919 (73.1)
Year 12 and above	302 (23.9)	182 (22.2)	1603 (28.3)	276 (21.9)
Missing	*70 (5.5)*	*46 (5.6)*	*285 (5.0)*	*63 (5.0)*
Living alone				
No	684 (54.2)	419 (51.1)	3044 (53.8)	659 (52.4)
Yes	578 (45.8)	401 (48.9)	2610 (46.2)	598 (47.5)
Missing	*1 (0.1)*	*0 (0)*	*1 (<1)*	*1 (0.1)*
Residential area				
Major cities in Australia	519 (41.1)	366 (44.6)	2438 (43.1)	581 (46.2)
Inner regional Australia	493 (39.0)	315 (38.4)	2195 (38.8)	428 (34.0)
Outer regional/Remote/Very remote Australia	251 (19.9)	139 (17.0)	1022 (18.1)	249 (19.8)
Missing	*0 (0)*	*0 (0)*	*0*	*0 (0)*
DVA* coverage				
No	990 (78.4)	625 (76.2)	4466 (79.0)	961 (76.4)
Yes	230 (18.2)	155 (18.9)	912 (16.1)	228 (18.1)
Missing	*43 (3.4)*	*40 (4.9)*	*277 (4.9)*	*69 (5.5)*
Health status				
Excellent/Very good	107 (8.5)	42 (5.1)	2305 (40.8)	255 (20.3)
Good	487 (38.6)	203 (24.8)	2458 (43.5)	589 (46.8)
Fair/Poor	669 (53.0)	575 (70.1)	891 (15.8)	414 (32.9)
Missing	*0 (0)*	*0 (0)*	*1 (<1)*	*0 (0)*
Number of GP visits in the last 12 months				
≤4 visits	317 (25.1)	96 (11.7)	2624 (46.4)	240 (19.1)
>4 visits	946 (74.9)	724 (88.3)	3028 (53.5)	1018 (80.9)
Missing	*0 (0)*	*0 (0)*	*3 (0.1)*	*0 (0)*
Number of chronic diseases				
0-1	138 (10.9)	20 (2.4)	1618 (28.6)	93 (7.4)
2-3	641 (50.8)	231 (28.2)	2856 (50.5)	533 (42.4)
≥4	482 (38.2)	568 (69.3)	1179 (20.8)	632 (50.2)
Missing	*2 (0.2)*	*1 (0.1)*	*2 (<1)*	*0 (0)*
BMI categories				
Underweight	64 (5.1)	30 (3.7)	190 (3.4)	20 (1.6)
Healthy	440 (34.8)	271 (33.0)	2647 (46.8)	493 (39.2)
Overweight	367 (29.1)	240 (29.3)	1660 (29.4)	430 (34.2)
Obese	392 (31.0)	279 (34.0)	1158 (20.5)	315 (25.0)
Missing	*0 (0)*	*0 (0)*	*0 (0)*	*0 (0)*
Bodily pain				
None	97 (7.7)	41 (5.0)	1492 (26.4)	193 (15.3)
Very mild/Mild	325 (25.7)	139 (17.0)	2409 (42.6)	424 (33.7)
Moderate/Severe/Very severe	841 (66.6)	640 (78.0)	1753 (31.0)	640 (50.9)
Missing	*0 (0)*	*0 (0)*	*1 (<1)*	*1 (0.1)*
Falls in the last 12 months				
No	944 (74.7)	590 (72.0)	4789 (84.7)	1017 (80.8)
Yes	319 (25.3)	228 (27.8)	863 (15.3)	241 (19.2)
Missing	*0 (0)*	*2 (0.2)*	*3 (0.1)*	*0 (0)*
Presence of PIMS**				
No	270 (21.4%)	34 (4.1%)	1609 (28.5%)	84 (6.7%)
Yes	993 (78.6%)	786 (95.9%)	4046 (71.5%)	1174 (93.3%)
Missing	*0 (0)*	*0 (0)*	*0 (0)*	*0 (0)*

The frequencies represent number of people with continuous polypharmacy. In determining continuous polypharmacy, a medication is counted as one, only if it appears at two pre-specified time windows in each year (1 Apr-30 June) & (1 Oct-31 Dec), allowing for determination of medications taken on a long-term basis

*Department of Veterans Affairs

**Potentially inappropriate medications

Table 2

Adjusted and unadjusted results for the associations between frailty and continuous polypharmacy from 2003 to 2017 using generalised estimating equations (GEEs) for log binomial regressions

	Unadjusted models for women with continuous polypharmacy		Adjusted model for women with continuous polypharmacy	
	Risk ratio (95% CI)	***p-value***	**Risk ratio (95% CI)**	***p-value***
Frailty status				
Non-frail	Reference		Reference	
Frail	1.29 (1.25, 1.32)	<0.001	**1.08 (1.05, 1.11)**	**<0.001**
Time (in years)	1.03 (1.03, 1.03)	<0.001	**1.01 (1.01, 1.01)**	**<0.001**
Age at baseline	0.98 (0.97, 1.00)	0.019	0.99 (0.97, 1.00)	0.062
Education level				
Below Year 12	Reference		Reference	
Year 12 and above	0.84 (0.80, 0.88)	<0.001	**0.89 (0.85, 0.93)**	**<0.001**
Live alone status				
No	Reference		Reference	
Yes	1.08 (1.04, 1.11)	<0.001	1.03 (0.99, 1.07)	0.057
Residential area				
Major cities in Australia	Reference		Reference	
Inner Regional Australia	0.97 (0.93, 1.01)	0.176	1.01 (0.97, 1.05)	0.578
Outer regional/Remote/Very remote Australia	0.97 (0.92, 1.02)	0.228	0.98 (0.93, 1.03)	0.365
DVA* Status				
No	Reference		Reference	
Yes	1.13 (1.08, 1.18)	<0.001	1.02 (0.98, 1.06)	0.321
Health status				
Excellent/Very good	Reference		Reference	
Good	1.43 (1.38, 1.49)	<0.001	**1.21 (1.16, 1.27)**	**<0.001**
Fair/Poor	1.86 (1.78, 1.94)	<0.001	**1.34 (1.28, 1.41)**	**<0.001**
Number of GP visits in the last 12 months				
≤4 visits	Reference		Reference	
>4 visits	1.45 (1.41, 1.50)	<0.001	**1.23 (1.19, 1.27)**	**<0.001**
Number of chronic diseases				
0-1	Reference		Reference	
2-3	1.72 (1.62, 1.84)	<0.001	**1.71 (1.58, 1.85)**	**<0.001**
≥4	2.83 (2.65, 3.02)	<0.001	**2.45 (2.25, 2.67)**	**<0.001**
BMI categories				
Healthy	Reference		Reference	
Underweight	0.91 (0.83, 0.99)	0.022	**0.84 (0.77, 0.91)**	**<0.001**
Overweight	1.13 (1.09, 1.17)	<0.001	**1.08 (1.05, 1.12)**	**<0.001**
Obese	1.18 (1.13, 1.22)	<0.001	**1.11 (1.07, 1.14)**	**<0.001**
Bodily pain				
None	Reference		Reference	
Very mild/Mild	1.20 (1.15, 1.26)	<0.001	1.05 (0.99, 1.10)	0.061
Moderate/Severe/Very severe	1.50 (1.44, 1.57)	<0.001	**1.11 (1.05, 1.16)**	**<0.001**
Falls in the last 12 months				
No	Reference		Reference	

Yes	1.10 (1.07, 1.13)	<0.001	1.00 (0.98, 1.03)	0.763
Presence of PIMS**				
No	Reference		Reference	
Yes	1.51 (1.47, 1.55)	<0.001	**1.50 (1.45, 1.55)**	**<0.001**

*Department of Veterans Affairs
**Potentially inappropriate medications

The reference class was 'no polypharmacy'

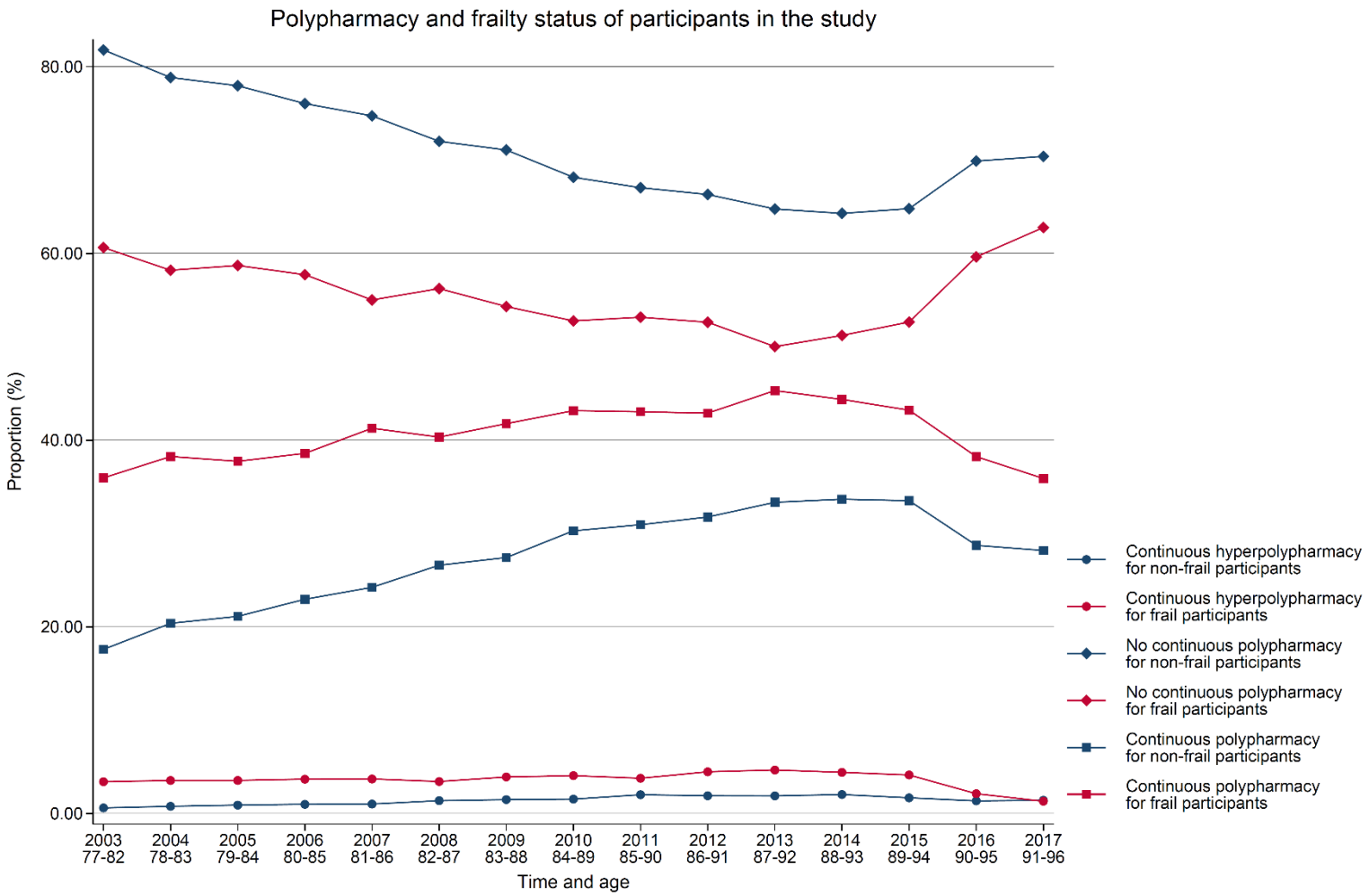

Fig. 1. Polypharmacy and frailty status of participants in the study from 2003 to 2017

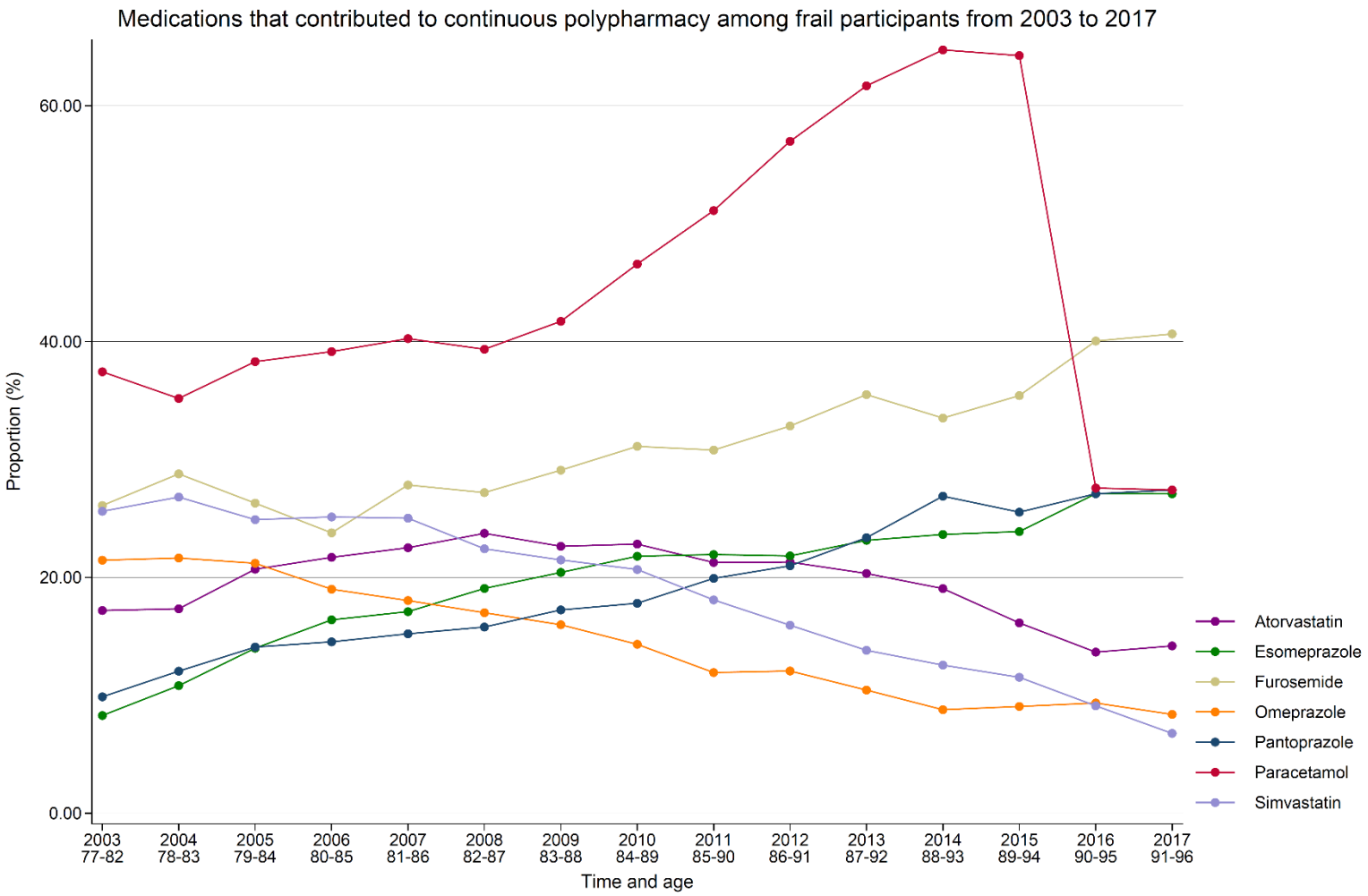

Fig. 2. Top 4 medications that contributed to polypharmacy from 2003 to 2017 among frail participants

As long as a unique medication appears in the 'top 4 medications that contribute to polypharmacy' at each year, it will be included along with its frequency in other years, to prevents breaks in the line graph

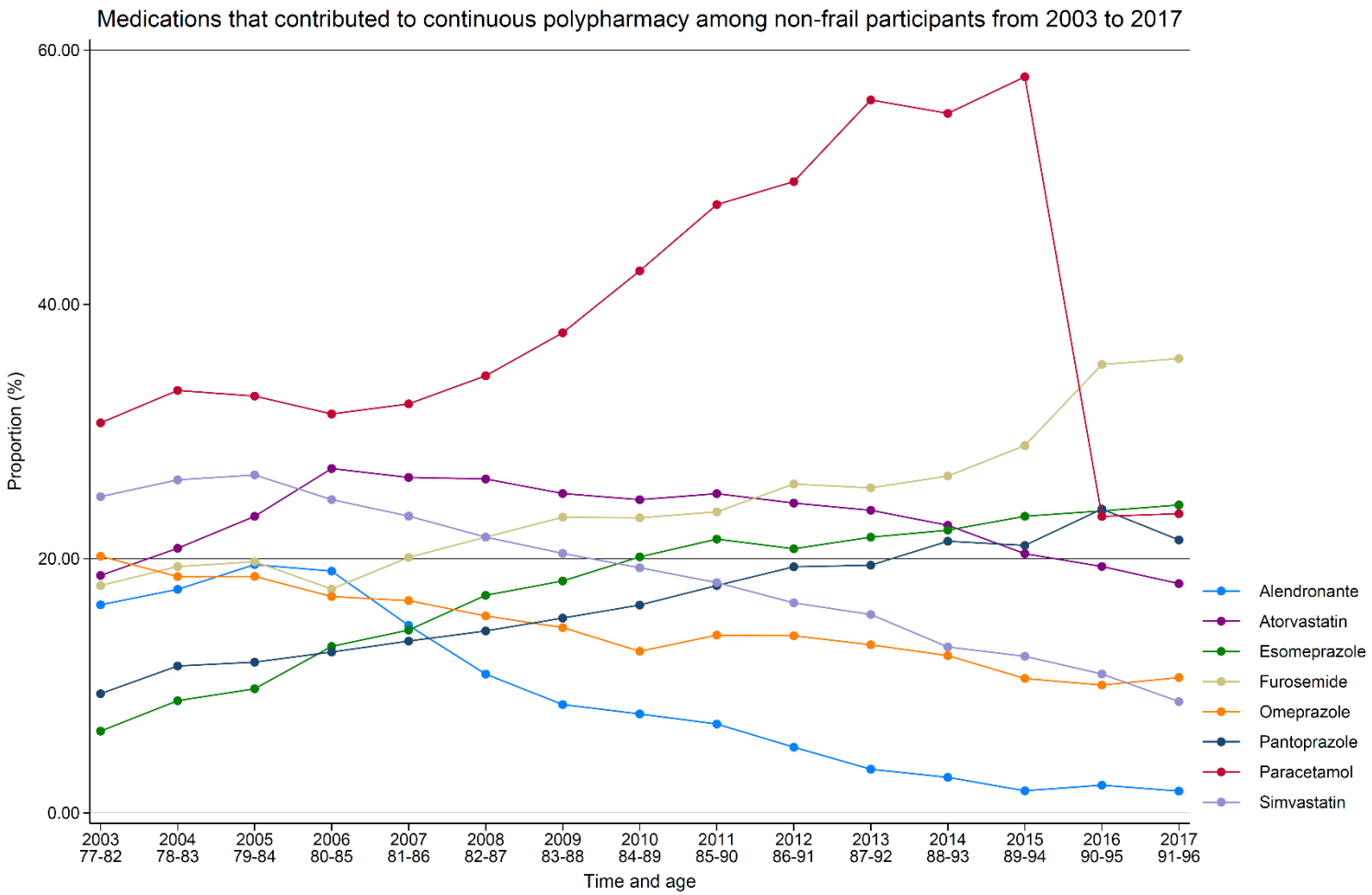

Fig. 3. Top 4 medications that contributed to polypharmacy from 2003 to 2017 among non-frail participants

As long as a unique medication appears in the 'top 4 medications that contribute to polypharmacy' at each year, it will be included along with its frequency in other years, to prevents breaks in the line graph