Risk Factors for Potentially Inappropriate Medication Use in Older Adults: A 10-Year Cohort Study with Generalized Estimating Equation Models

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Abstract

Background

Much of the knowledge on the use of potentially inappropriate medications (PIM) in older adults is derived from cross-sectional studies, with little known about the risk factors over time.

Aim

Longitudinal analysis was applied to estimate the occurrence and risk factors of PIM use among older adults in a 10-year follow-up.

Methods

Longitudinal study with 418 older adult residents of a capital city of Central-West Brazil. The PIM were classified according to the Beers criteria 2019. The usage rate was calculated at baseline (2008) and at the 10-year follow-up moment (2018). Analysis of predictors (sociodemographic, self-rated health, hospitalization, number of comorbidities, polypharmacy, diabetes, hypertension, hypercholesterolemia and nutritional status) was performed using Generalized Estimating Equation (GEE) models.

Results

Mean age at baseline was 70.6 years (*SD* 7.1) and 76% were women; 221 older adults took part in the follow up. The rate of PIM use was 50.4% at baseline and 57.5% at the 10-year follow-up. Multiple analysis showed that PIM use in the cohort was statistically higher in the older adults with a history of hospitalization (RR_{adj}: 1.20; 95%CI: 1.01-1.40), with three or more diseases (RR_{adj}: 1.41; 95%CI: 1.14-1.74), with polypharmacy (RR_{adj}: 1.81; 95%CI: 1.47-2.24) and with diabetes mellitus (RR_{adj}: 1.24; 95%CI: 1.05-1.47).

Conclusion

A high level of potentially inappropriate medication use was observed, reaching 50% of the older adults, with a 7% increase in the prevalence over the 10-year follow-up period. Hospitalization, multimorbidities, polypharmacy and diabetes mellitus were associated with the use of these medications. Interventions for surveillance of the deprescribing process need to be encouraged to avoid potential harm caused by the use of medications.

Impact Of Findings On Practice Statement

- Hospitalization, multimorbidities, polypharmacy and diabetes mellitus were risk factors for an increase in the rate of PIM use over 10 years among older adults in the community.
- The prevalence of PIM use in the two stages of this cohort was above 40%, a high result, however, consistent with estimates that used versions of the AGS Beers criteria prior to 2019.

Introduction

The continuous use of medications has increased over recent decades, following the increase in non-communicable chronic diseases (NCDs) and life expectancy [1, 2]. Despite their benefits, some are considered potentially inappropriate medications (PIM) for older adults, since they can potentiate adverse events, thereby increasing costs with a negative economic impact on health services [3, 4].

The Beers criterion has been used worldwide for the classification of PIM, and its most recent update was carried out in 2019 by the American Geriatric Society (AGS) [3]. Cross-sectional studies published using versions prior to 2019 show wide variations in the prevalence of PIM use, ranging from 21 to 84% [5–10] in different care settings for older adults.

Some factors such as multimorbidities and polypharmacy have been associated with the use of PIM in previous studies on the subject [5, 6]. Certain specific health conditions such as diabetes mellitus, cardiovascular disease and mental disorders have also been associated with an increased use of PIM in older adults [9, 11–13]. However, studies analyzing whether these factors remain associated with the use of PIM over time are scarce. Only one recent study analyzed the persistence of PIM use over time and reported that 25.1% of the initially prescribed PIM continued to be used after one year [2]. In addition, few studies using the new classification of the AGS Beers criteria 2019 Beers criterion have been developed to date [4, 14, 15], and they continue to reinforce the need for surveillance of PIM use in older adults, and highlight the relevance of performing longitudinal analyses for a better understanding of PIM and risk factors [16]. Older adults are especially vulnerable to harm caused by medications and therefore it is necessary to determine risk factors associated with the use of PIM in this population in order to support decision-making by both healthcare providers and managers.

Aim

Considering the above, the aim of this study was to apply longitudinal analysis to estimate the rate of occurrence of PIM use and its risk factors among older adults in a 10-year follow-up.

Ethics approval

This research project was approved by the Research Ethics Committee (CEP) of the Hospital das Clínicas of the Universidade Federal de Goiás (UFG), under authorization number 2.500.0441/2018.

Method

Study design, population and data collection

This prospective cohort study is part of a larger research project entitled "Health conditions, health, frailty and body composition of older adults: Cohort of the Older Adult Project/Goiânia", performed in Goiânia, capital of the state of Goiás, located in the Central-West Region of Brazil.

This research began in 2008, with the baseline sample composed of 418 older adult users of the Brazilian National Health System (SUS) in Goiânia, capital of the State of Goiás, central region of Brazil. At baseline, the older adults were selected proportionally to represent the older adult population in the health regions of Goiânia. Details of the sampling procedures have already been published [15, 17, 18].

The target population of this study was composed of older adults at the baseline, denominated time 1 (t1), and the survivors after a period of ten years from the baseline evaluation, denominated (t2). Of the 418 older adults in the original sample, 34.9% died (*n*=146), 6% declined to answer the questionnaire (*n*=25) and 6% (*n*=25) were considered lost to follow-up, totaling a population of 221 older adults included in the follow-up for this study, who were interviewed between 2018 (August) and 2019 (March) (t2).

Data were collected at the homes of the older adults by trained researchers at t1 and t2. Before carrying out the data collection, a pilot study was performed to standardize the questionnaire and adapt the collection logistics. The participants were interviewed after reading and signing the consent form. The questionnaire variables consisted of demographic, socioeconomic, living and health conditions and medication use.

To identify the cohort survivors, the Brazilian Ministry of Health's Mortality Information System (SIM) was consulted to identify deaths during the period. Older adults not identified in the SIM (survivors) were located via telephone, using the database's address list. Those considered lost to follow-up were: older adults not found in their homes after five attempts; address not found on the visit and after consulting the SMS system; and those who had moved to another city.

Variables

The outcome variable was the rate of PIM use. First, to identify the medications in use, the following question was asked: "*Are you taking any medication?*", and in the case of a positive answer, the older adult was requested to present the prescription and/or packaging, if available at the time of the interview, in order to register the active ingredient and dosage on the questionnaire. Subsequently, based on the information collected on the use of medications, we classified PIM use according to AGS Beers criteria 2019 [3]. In this study, PIM were classified as inappropriate regardless of dosage and morbidity [3]. The rate of PIM use was calculated by dividing the number of PIM by the total number of medications used by the participant.

The sociodemographic variables investigated were gender, age group, marital status, education and economic class. The variables of marital status, education and income were evaluated descriptively. Socioeconomic status was determined using the Brazilian Economic Classification Criteria (CCEB) of the Brazilian Association of Research Companies (ABEP), composed by data including the educational level and items owned by the family. The economic classes were grouped into A/B, C and D/E [19].

The variables related to health conditions were the number of comorbidities reported, polypharmacy, hospitalization in the previous year, nutritional status, hypertension, self-assessment of health, Diabetes

mellitus and hypercholesterolemia.

The number of diseases was estimated through the question: "*Which diseases did the doctor say you already have?*", the health perception: "*What do you think about your health status in the last month?*" and hospitalization: "*Have you been hospitalized in the last year?*". For polypharmacy, the use of five or more drugs was considered, based on the presentation of a medical prescription and/or drug packaging [20]. The calculation of the body mass index (BMI) was estimated using the formula: weight (kg)/height² (m^2), with weight measured using an electronic scale (Tanita model, with a capacity of 200kg and precision of 100g) and height using a wall stadiometer (accuracy of 0.1cm). The following references were considered: underweight (≤ 22kg/m^2); eutrophic (between 22 and 26.9kg/m^2); and overweight (≥ 27kg/m^2) [21].

Systemic Arterial Hypertension (SAH) was defined considering the self-report, and/or SAH measure greater than the normality reference, systolic and diastolic pressure above 140mmhg and 90mmhg respectively, and/or use of medication. The Blood Pressure (BP) measurement was estimated from three measurements on the left arm, with the patient sitting without speaking, calculating the mean of the last two measurements. A semi-automatic device (OMRON brand) [22] was used.

Diabetes mellitus was determined by the self-report and/or the use of medication and/or glycemic control based on fasting blood glucose levels (≥ 126mg/dl) and/or glycated hemoglobin (≥ 7%) [23].

Data analysis

Longitudinal analysis of the predictors of PIM use was performed with the cohort. In this analysis, the dependent variable was the use of PIM (yes or no) at baseline (t1) and at 10 years (t2). The analysis of predictors was performed using generalized estimating equation (GEE) models. These models refer to an extension of the Generalized Linear Models (GLM), being appropriate for repeated measures in longitudinal studies. In the present study, GEE modeling was performed using Poisson regression. Initially, a bivariate analysis was carried out between the dependent variable and the independent variables. Next, variables with p value < .20 were inserted into a multiple regression model. The results of the bivariate analysis were presented as the Crude Rate Ratio (RR_c) and the multiple as the Adjusted Rate Ratio (RR_{adj}) and respective 95% CI. Values of $p < .05$ were considered statistically significant.

Results

At baseline (t1), 76% of the 418 older adults investigated were women, mean age was 70.6 (*SD*=7.1) years. From the total of 418 participants, in the 2019 follow-up, 34.9% had died (*n*=146), 6% refused to participate (*n*=25), and 6% were considered lost to follow-up (*n*=25). Of the remaining 221 participants in the 2019 follow-up (t2), 67.4% were women (*n*=149) and the mean age was 79.1 (*SD* 5.8) years, ranging from 70 to 99 years.

The prevalence of PIM use was 50.1% (95% CI=44.9-55.4) in 2008 (t1) and 57.5% (95% CI=50.6-64.2) in 2018 (t2). Of these 221 older adults, in 2019, 67 (36.6%) continued using some PIM. Among the 67 older adults who continued using PIM, 26 (38.8%) consumed the same PIM (Figure 1). In *t1* (2008), 40 different types of PIM were used by older adults, and the the most frequently consumed IPM were in this order: nifedipine (12.1%), glibenclamide (10.1%), sodium diclofenac (6.8%), amiodarone (5.7%) and amitriptyline (4.1%). Ten years over *(t2*) 38 types of PIM were identified, and the following were used more frequently: diclofenac sodium (9.8%), amiodarone (6.54%), scopalamine (6.1%), clonazepam (4.7%) and carisoprodol (3.8%).

In the longitudinal bivariate analysis using two moments (t1 – baseline and t2 – after 10 years) the following variables were statistically associated as a risk factor for PIM use: female gender, age between 70 and 79 years, hospitalization history, > 3 comorbidities, polypharmacy, diabetes mellitus, and hypertension. Eutrophy in the older adults was shown to be a protective factor against occurrence of problems related to PIM use. The rate of PIM use increased statistically over time (Table 1).

Table 1
Longitudinal bivariate analysis of potential predictors of PIM use in a cohort of older adults with a ten-year follow-up

Variables	RR_c	95% CI	*P*-value*
Sex			
Male	1.00		
Female	1.24	1.02-1.51	**.029**
Age range (yrs)			
60-69	1.00		
70-79	1.24	1.03-1.48	**.021**
≥ 80	1.11	0.88-1.41	.382
Skin color			
White	1.00		
Brown	0.88	0.73-1.07	.192
Black	1.08	0.85-1.39	.531
Years of school			
1-4	1.00		
> 4	0.90	0.84-1.10	.294
Economic class			
A/B/C	1.00		
D/E	1.13	0.95-1.34	.174
Lives with partner			
Yes	1.00		
No	1.13	0.95-1.33	.164
Hospitalization			
No	1.00		
Yes	1.36	1.15-1.60	**< .001**
Self-evaluation of health			
Very good/good/regular	1.00		

RR_c: Crude Rate Ratio; 95% CI: 95% Confidence Interval; * Wald's Chi-Square Test

Variables	RR_c	95% CI	*P*-value*
Poor/very poor	1.17	0.98-1.40	.081
Number of comorbidities			
1-2	1.00		
≥ 3	1.91	1.59-2.29	**< .001**
Polypharmacy			
No	1.00		
Yes	2.18	1.84-2.58	**< .001**
Arterial Hypertension			
No	1.00		
Yes	1.40	1.40-1.72	**.002**
Diabetes mellitus			
No	1.00		
Yes	1.72	1.48-2.00	**< .001**
Hypercholesterolemia			
No	1.00		
Yes	1.14	0.92-1.41	.230
Nutritional status			
Underweight	1.00		
Eutrophic	0.71	0.52-0.97	**.031**
Overweight	1.09	0.90-1.31	.371
Time	1.28	1.11-1.48	**.001**

RR_c: Crude Rate Ratio; 95% CI: 95% Confidence Interval; * Wald's Chi-Square Test

In the multiple analysis, the use of PIM was statistically higher in older adults with a history of hospitalization (RR_{adj}: 1.20; 95% CI: 1.01-1.40), with three or more comorbidities (RR_{adj}: 1.41; 95% CI: 1.14-1.74), with polypharmacy (RR_{adj}: 1.81; 95% CI: 1.47-2.24) and with a diagnosis of diabetes mellitus (RR_{adj}: 1.24; 95% CI: 1.05-1.47) (Table 2).

Table 2
Longitudinal multiple analysis of potential predictors of PIM use in a cohort of elderly people with ten-year follow-up

Variables	RR_{adj}	95% CI	*SD* robust	*P*-value*
Sex				
Female	1.00			
Male	1.05	0.86-1.29	0.10	.641
Age range (yrs)				
60-69	1.00			
70-79	1.05	0.86-1.29	0.10	.609
≥ 80	0.96	0.72-1.27	0.14	.774
Skin color				
White	1.00			
Brown	0.97	0.80-1.17	0.10	.743
Black	1.10	0.85-1.41	0.12	.472
Economic class				
A/B/C	1.00			
D/E	1.17	0.99-1.39	0.09	.071
Lives with partner				
Yes	1.00			
No	1.04	0.88-1.23	0.04	.640
Hospitalization				
No	1.00			
Yes	1.20	1.01-1.40	0.08	**.038**
Self-evaluation of health				
Very good/good/regular	1.00			
Poor/very poor	0.94	0.79-1.11	0.09	.469
Number of comorbidities				

RR_{adj}: Adjusted Ratio Rate; 95% CI: 95% Confidence Interval; * Wald's Chi-Square Test; ** GEE model adjusted for sex, age range, race/color, economic class, marital status, hospitalization, arterial hypertension, polypharmacy, number of comorbidities, diabetes mellitus, nutritional status and time

Variables	RR_{adj}	95% CI	*SD* robust	*P*-value*
1-2	1.00			
≥ 3	1.41	1.14-1.74	0.34	**.002**
Polypharmacy				
No	1.00			
Yes	1.81	1.47-2.24	0.10	**< .001**
Arterial hypertension				
No	1.00			
Yes	1.04	0.84-1.28	0.10	.730
Diabetes mellitus				
No	1.00			
Yes	1.24	1.05-1.47	0.09	**.013**
Nutritional status				
Underweight	1.00			
Eutrophic	0.79	0.60-1.06	0.14	.118
Overweight	0.82	0.83-1.16	0.09	.820
Time	0.89	0.73-1.08	0.10	.245

RR_{adj}: Adjusted Ratio Rate; 95% CI: 95% Confidence Interval; * Wald's Chi-Square Test; ** GEE model adjusted for sex, age range, race/color, economic class, marital status, hospitalization, arterial hypertension, polypharmacy, number of comorbidities, diabetes mellitus, nutritional status and time

Discussion

In this cohort, it was found that hospitalization, multimorbidities, polypharmacy and diabetes mellitus increased the rate of PIM use over 10 years among the older adults in the community. The high usage of PIM in the cohort at the two moments analyzed can also be highlighted. The findings are relevant since they are in line with the World Health Agenda, in that since 2017 the reduction of potential risks related to the use of medicines has been listed as a priority by the World Health Organization [24].

The prevalence of PIM use in the two stages of this cohort was above 40%, a high result, however, consistent with estimates that used versions of the AGS Beers criteria prior to 2019 [5–10, 25]. Nevertheless, it is important to highlight that the inclusion of new drugs in the Beers 2019 list, and the form of classification of the PIM used in this study may have contributed to the high frequency observed [3]. Various studies have been developed since the publication of the AGS Beers criteria 2019. In the

United States, the prevalence of PIM prescription in a 5-year retrospective sample was 34.4% and there was a significant decrease in prevalence from 35.3% in 2011 to 32.5% in 2015 [4]. Another study performed in the United States analyzing new PIM prescriptions showed that in a 90-day follow-up period, 2.5% received new PIM prescriptions [14]. Roux et al. (2020) applied the Beers 2015 criteria in a 1-year follow-up study, and showed that 25.1% of the use of PIM initially prescribed at baseline persisted after one year [2].

Although the health conditions of older adults influence the increase in PIM consumption, specifically in Brazil, other factors such as the absence of a surveillance system and information on the use of PIM in older adults, communication failures between different prescribers, the lack of training for people on the subject of aging with a focus on pharmacovigilance contribute to persistent PIM use. Consequently, it is important that measures for deprescribing are implemented in order to confront this problem. Deprescribing refers to the review and evaluation of the long-term therapeutic plan, which allows suspending, replacing or modifying the dose of drugs that were properly prescribed, however, which, given certain clinical conditions, may be considered to have an unfavorable risk-benefit ratio [26]. Therefore, in the context of the aging process and use of medications, deprescribing is related to polypharmacy and PIM, and its applicability is favorable for pharmacological treatment in older adults. Some initiatives, such as the International Group for Reducing Inappropriate Medication Use & Polypharmacy (IGRIMUP), which brings together 26 countries, propose recommendations to reduce PIM use among older adults [27], however, in Brazil, the recommendations for deprescribing are still incipient.

It is known that multimorbidities are risk factors for polypharmacy [28] which could explain the increase in the rate of PIM use throughout the follow-up in this study. National [6, 29–31] and international [32–35] studies have shown that a higher number of diseases was associated with PIM use. The use of PIM results from a cascade of events: changes in health conditions, need for treatment and disease control, access to professionals from different specialties, and the use of many medications. In general, the treatment for most geriatric diseases is with the use of drugs, which are not always the most appropriate due to their potential to cause harm to the patient. For each new drug introduced into adult therapy, there is a corresponding increased risk of up to 10% for an adverse event [36]. The World Health Organization has included polypharmacy as one of the three priority categories of the 3rd Global Patient Safety Challenge [24], which requires attention in populations similar to the one in this study with a high prevalence of polymedication and PIM use.

Being diagnosed with Diabetes Mellitus (DM) increased the rate of PIM use in the cohort period. Some studies have shown that older adults with DM consume multiple medications in greater proportions [37–42], which in consequence may increase the risk of using some type of PIM. A recent study in Quebec showed that more than half of the people with DM used at least one PIM in a year [43]. Furthermore, people with DM have more comorbidities than the general population. In Brazil, a representative study with 70 municipalities showed that although DM was not the disease in the highest proportion, it was the one with the highest number of associated comorbidities [44]. Added to this, the symptoms or systemic manifestations of the different types of complications can lead to the use of health services and the

consequent prescribing of other medications, which may include PIM. Considering the growing number of people with DM and the proportion that use PIM, the impacts on people's health and in terms of public health are significant [37].

Over the 10 years, there was an increase in the rate of PIM use in the older adults who were hospitalized. Hospitalization was a risk factor reported for PIM use in previous studies [45–47]. Hospitalized older adults are more frequently submitted to drug therapy, due to their preexisting clinical conditions and those acquired during the hospitalization process [41]. Therefore, changes in prescriptions can increase the risk of using a PIM. A study carried out in the city of São Paulo showed that PIM use increased the frequency of unscheduled hospitalization in older adults by 64% [48]. Considering this, it is relevant to highlight the importance of specific care for the older adult population during hospitalization that considers their needs, and functionality, in addition to an appropriate therapeutic regimen. The use of PIM can either be a risk factor for hospitalization or a consequence of it, however, the presence of professionals with specific training and education can prove effective in preventing unnecessary PIM use. Increased awareness and specific training is necessary for the multidisciplinary team regarding the risks of using PIM in this population that is highly susceptible to harm, this action is in accordance with the global health agenda [24].

Despite the potential, in this study it was not possible to identify the interruption of PIM use over the period of 10 years, or to verify at what moment other PIM were included in the treatment of the participants, thereby constituting a limitation of the study. Nevertheless, this study is a population cohort of older adults from a capital city of the Central-West region of Brazil, which used the updated Beers criterion, allowing for more accurate estimates of PIM use.

The use of PIM was high at the two moments analyzed, reaching more than 50% of the participants. Risk factors for PIM use among older adults in the community were related to their health conditions, such as the presence of three or more diseases, polypharmacy, diabetes and hospitalization. Interventions are needed to improve the process of drug prescriptions in order to prevent unnecessary and inappropriate medications for older adults from being continuously prescribed. Future studies are needed to implement actions to reduce inappropriate prescriptions.

Declarations

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Author Contributions

All authors contributed to the study concept and design. Material preparation, data collection and analysis were performed by [Natacha Christina de Araújo], [Brenda Godoi Mota], [Valéria Pagotto] and [Rafael Alves Guimarães]. The first draft of the manuscript was written by [Natacha Christina de Araújo] and [Valéria Pagotto] and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Data availability. The datasets generated and/or analyzed in the current study are available from the corresponding author upon reasonable request.

Conflict of interest

The authors declare that they have no conflict of interest

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Figures

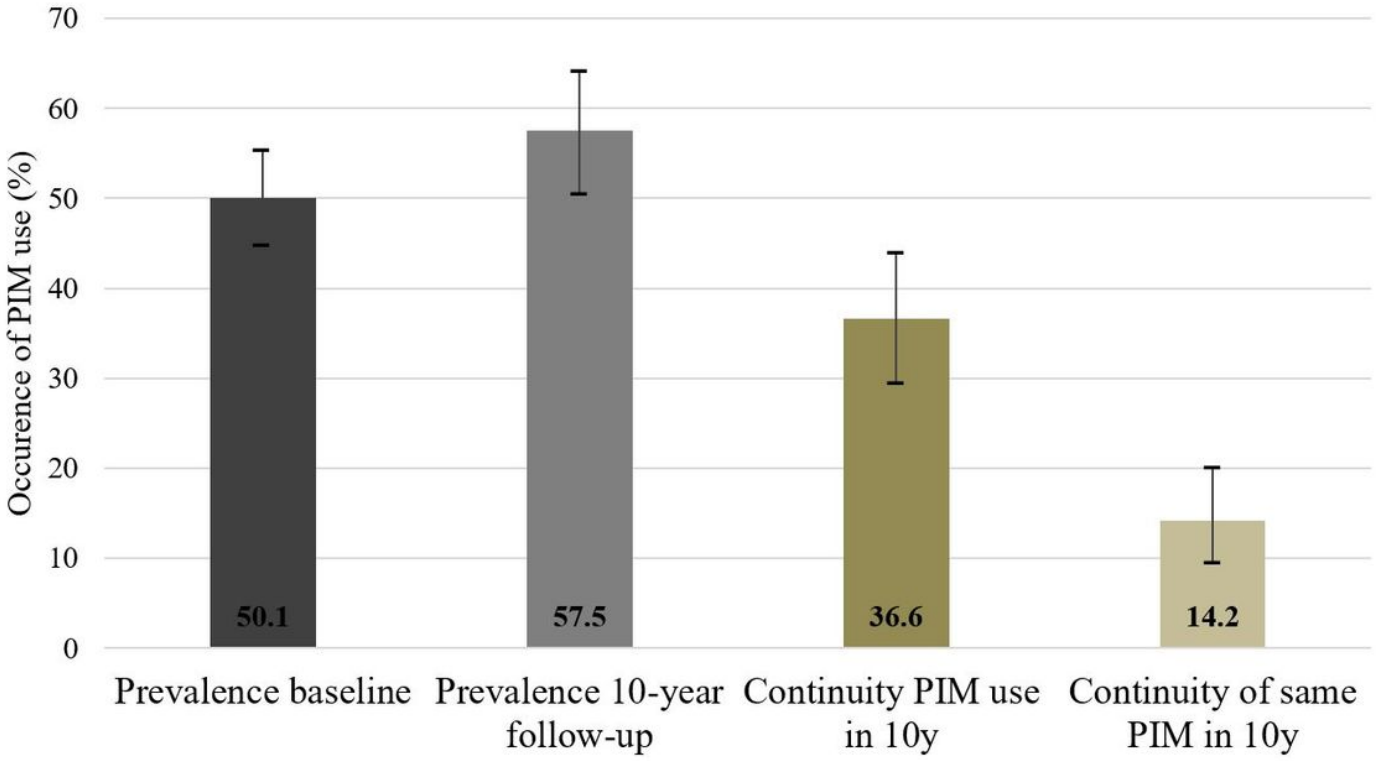

Figure 1

Prevalence of PIM use and continuity of use among the older adults, at baseline and ten-year follow-up