POLYPHARMACY IS ASSOCIATED WITH HIGHER FRAILTY RISK IN OLDER PEOPLE: AN EIGHT YEAR LONGITUDINAL COHORT STUDY

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ABSTRACT

Background: It is unclear if polypharmacy is associated with incident frailty. Thus, we investigated whether polypharmacy is associated with a higher incidence of frailty in a large cohort of North Americans over eight years of follow-up.

Methods: Details regarding medication prescription were captured and categorized as: 0-3, 4-6, and ≥7. Frailty was defined using the Study of Osteoporotic Fracture (SOF) index as the presence of ≥2 out of: (i) weight loss ≥5% between baseline and the subsequent follow-up visit; (ii) inability to do five chair stands; (iii) low energy level according to the SOF definition. Cox's regression models calculating a hazard ratio (HR) with 95% confidence intervals (CIs), adjusted for potential confounders, were undertaken.

Results: During the 8-year follow-up, from 4,402 participants at baseline, 361 became frail. Compared to participants taking 0-3 medications, the incidence of frailty was approximately double in those taking 4-6 medications and six times higher in people taking ≥ 7 medications. After adjusting for 11 potential baseline confounders, participants using 4-6 medications had a higher risk of frailty of 55% (HR=1.55; 95%CI: 1.22-1.96; p<0.0001), whilst those using more than 7 drugs were at approximately 147% (HR=2.47; 95%CI: 1.78-3.43; p<0.0001). Each additional drug used at the baseline increased the risk of frailty at the follow-up of 11% (HR=1.11; 95%CI: 1.07-1.15; p<0.0001).

Conclusions: Polypharmacy is associated with a higher incidence of frailty over 8-year follow-up period. Our data suggest evidence of a dose response relationship. Future research is required to confirm our findings and explore underlying mechanisms.

Keywords: frailty; polypharmacy; frail, medication, older adult

INTRODUCTION

Frailty is usually defined as "a state of increased vulnerability to stressors resulting from a decrease in physiologic reserves in multiple organ systems causing limited capacity to maintain homeostasis".[1] Frailty has been associated with an increased risk of several deleterious outcomes in older people, including disability, falls, hospitalization, institutionalization and death. [1] Recent studies have however suggested that frailty could be considered an independent risk factor for cardiovascular[2] and metabolic[3] diseases that could further increase the transition from frailty to disability. Unsurprisingly, the prevention of frailty is an international priority, therefore the search for potential risk factors is of utmost importance.

To date, there has been a paucity of research considering the relationship between polypharmacy and frailty. Some recent cross-sectional studies found evidence of a strong association between polypharmacy and the prevalence of frailty. [4,5] Furthermore, several short-term follow up studies have suggested that polypharmacy is associated with a higher risk for incident frailty.[6-8] However, some limitations are evident with these studies, including the relatively short follow-up period (maximum five years) and the small sample sizes. The relationship between polypharmacy and frailty is complex, since, whilst several studies have suggested polypharmacy is associated with frailty [6-8], others have suggested that a higher adherence to medications could be associated with lower mortality rate in frail older subjects.[9-11] Given that frailty is a reversible condition if appropriately treated [12], understanding if polypharmacy is associated with incident frailty could be of public health importance.

The current study aimed to investigate whether polypharmacy is associated with a higher incidence of frailty in a large cohort of North Americans participating in the Osteoarthritis Initiative over eight years of follow-up. We hypothesized that higher number of medications is associated with a higher incidence of frailty.

MATERIALS AND METHODS

Data source and subjects

Data were obtained from the Osteoarthritis Initiative (OAI) database, which is available for public access at http://www.oai.ucsf.edu/. The specific datasets utilized were registered during the baseline and screening evaluations (V00) and each database reporting data on frailty until 96 months from baseline (V10). Patients at high risk of knee OA were recruited at four clinical centers in the USA (Baltimore, MD; Pittsburgh, PA; Pawtucket, RI; and Columbus, OH) between February 2004 and May 2006.

All the participants provided written informed consent. The OAI study protocol was approved by the institutional review board of the OAI Coordinating Center, University of California at San Francisco.

Number of medications (exposure)

A specific questionnaire investigating the name of the prescription medicine, duration of use, formulation code (oral, rectal, topical etc.) in the 30 days before the interview was used and the number of medications was recorded. Multivitamins' supplementations were not included. Trained interviewers checked the medications used by each participant in the last 30 days. Since there is no consistent definition of polypharmacy and the use of numeric threshold has been shown to be too simplistic and unhelpful [13], we used the categorization suggested in the development of multidimensional prognostic index [14], i.e. 0-3, 4-6 or $\geq$ 7 medications.

Outcome

The study's outcome of interest was incident frailty. In accordance with the Study of Osteoporotic Fracture (SOF) index [15,16] frailty was defined as the presence of $\geq$2 out of three of the following criteria: (i) weight loss $\geq$5% taking place between baseline and the follow-up examinations (at the baseline examination a body mass index, BMI, of less than 20 Kg/m^2 was used, since no

information regarding weight changes were recorded); (ii) the inability to rise from a chair five times without arm support (hereafter referred to as inability to carry out chair stands); and (iii) poor energy based on the SF12 questionnaire response of "little at a time" or "none at a time" to the question "in the past 4 weeks, did you have a lot of energy?"

Covariates

We identified 11 potential confounders including BMI; physical activity evaluated using the Physical Activity Scale for the Elderly (PASE) [17]; race; smoking habits; educational level and yearly income (< or ≥ $50,000 and missing data) to assess the relationship between number of medications at the baseline and incident frailty. Validated general health measures of self-reported comorbidities were assessed using the modified Charlson comorbidity score.[18]

Since nutritional parameters could be of importance to assess the association between number of medications and frailty[19], we included as covariates the daily calorie intake and the adherence to Mediterranean diet with a validated score.[20,21]

Statistical analyses

Normal distributions of continuous variables were tested using the Kolmogorov-Smirnov test. Data are shown as means±standard deviations (SD) for quantitative measures, and frequency and percentages for all discrete variables. P values for trends were calculated using the Jonckheere-Terpstra test for continuous variables and the Mantel-Haenszel Chi-square test for categorical ones.

Cox's regression analysis was used to assess the strength of the association between number of medications at baseline and incident frailty. Factors significantly different across number of medications categories (considering a p-value<0.10) or significantly associated with incident frailty at univariate analysis (p-value<0.05) were included. Multi-collinearity among covariates was

assessed using the variance inflation factor (VIF), with a score of 2 leading to the exclusion of a variable, but no parameter was excluded for this reason. Age (as continuous); sex; race (whites vs. others); body mass index (as continuous); education (degree vs. others); smoking habits (current and previous vs. others); yearly income (categorized as $\geq$ or < 50,000$ and missing data); Physical Activity Scale for Elderly score (as continuous); Charlson co-morbidity index (as continuous); daily energy intake (as continuous); adherence to Mediterranean diet (as continuous). The proportional hazard assumption was verified considering Schoenfeld's residuals of the covariates.[22] Cox's regression analysis data were reported as hazard ratios (HRs) with 95% confidence intervals (CIs). A similar analysis was run using the number of medications as continuous variable.

To test the robustness of our findings, sensitivity analyses were conducted evaluating the interaction between number of medications and selected factors (e.g. gender, median age, smoking status etc.) in predicting frailty onset at follow-up, but no one emerged as significant moderator of our findings.

All the analyses were performed using the SPSS 17.0 for Windows (SPSS Inc., Chicago, Illinois). All statistical tests were two-tailed and statistical significance was assumed for a p-value <0.05.

RESULTS

Sample selection

The OAI dataset initially includes a total of 4,796 North American participants. Twenty-one participants were excluded due to insufficient information regarding medications and 20 were already frail at the baseline. Another 353 were excluded since they do not have data regarding incident frailty. Thus, 4,402 participants were finally included in this study.

Descriptive characteristics

Of the 4,402 participants, 1,844 were males and 2,558 females. Mean age was 61.2 years (±9.2 years; range: 45-79). The number of medications used across the entire sample was in mean 3 (range: 0-27).

Table 1 shows the participants' characteristics classified by the number of medications used. Participants using 7 medications or more were significantly older, more likely to be females, smokers, poor and less physically active and white compared to those using less medications (p for trend<0.0001 for all comparisons). Moreover, those using 7 or more medications were more frequently obese and they had a significant higher presence of several co-morbidities (**Table 1**). Finally, they reported a significant higher calorie intake than those using less medications (**Table 1**). Regarding the frailty items at the baseline, the only statistically significant difference was for the presence of low energy (p for trend <0.0001) (**Table 1**).

Polypharmacy and incident frailty

During the 8-year follow-up, 361 subjects (=8.2% of the baseline population) developed frailty equating to a global incidence rate of 23 (95%CI: 14-32)/1,000 persons-year (**Figure 1**).

Table 2 illustrates the association between the use of medications and incident frailty at follow-up. Taking those using fewer medications as the reference group (0-3 medications), those using 4-6 medications had a doubled incidence of frailty, whilst participants using 7 medications or more had approximately a 6 times higher incidence of frailty. Using a Cox's regression analysis, adjusted for 11 potential confounders at baseline, participants using 4-6 medications had a higher risk of frailty of 55% (HR=1.55; 95%CI: 1.22-1.96; p<0.0001), whilst those using more than 7 drugs were almost at 150% increased risk of frailty (HR=2.47; 95%CI: 1.78-3.43; p<0.0001) (**Table 2**).

Modelling the number of medications as continuous, each drug used at the baseline increased the risk of frailty at the follow-up of 11% (HR=1.11; 95%CI: 1.07-1.15; p<0.0001).

DISCUSSION

In this study including more than 4,000 participants at baseline, we showed that polypharmacy was associated with higher risk of frailty over a follow-up of 8 years. After adjusting for 11 potential confounders (including the presence of co-morbidities) participants using 4-6 medications were at a 55% higher risk of frailty as well as those consuming more than 7 medications had approximately a 2.5-fold increased risk of developing frailty. Moreover, our analysis suggested a dose response relationship, with each additional medication being associated with an 11% increased risk of frailty. Altogether our findings suggest that polypharmacy is a common and potentially modifiable risk factor for frailty in the elderly.

Our results are in agreement with the findings of other studies regarding the same topic. [6-8] Across 1,662 men aged who were more than 70 years of age with a follow up period of two years, Gnjidic et al. found that the use of more than 5 medications is associated with incident frailty. [6] In a cohort with similar characteristics (n=1,705, follow up period =5 years), Jamsen et al. found that a higher number of medications was associated with greater risk of mortality in robust community-dwelling older men and with a higher risk of transitioning from the robust state to the prefrail state.[7] Even if these two studies were important to understand the role of polypharmacy in promoting frailty, they did not included any comprehensive multimorbidity score as Saum et al. proposed more recently.[8] However, whilst Saum et al. considered the type and number of medical conditions at baseline, the association between polypharmacy and incident frailty remained significant. Compared to all these studies, we included the largest population to date with the longest follow-up. Moreover, we included younger people than those considered in the previous studies suggesting that the association between polypharmacy and frailty is also of importance in a younger population. It is noteworthy that our sensitivity analysis did not suggest a potential role of age in moderating our results. Finally, we adjusted our analyses also for nutritional parameters important for the association between polypharmacy and frailty, such as adherence to Mediterranean diet.[23-25]

Several reasons could explain the association between polypharmacy and incident frailty. First, polypharmacy may contribute to the development of frailty through a negative influence on factors associated with frailty (such as comorbidities) or factors included in frailty definitions such as weight loss. [26,27] Further, polypharmacy has been linked to inappropriate prescribing [28], low adherence [29], preventable and unplanned hospitalization [30] and adverse drug events [31], all relevant to the development of frailty. This is particularly relevant to older individuals, who are more susceptible to adverse drug reactions (ADRs) [32], also caused by commonly used medications. [32] ADRs could further increase the risk of frailty as they might lead to a prescribing cascade, in which new medications are prescribed to counteract unwanted effects of the initial drug. (28)

Whether altering the number of medications could have a role in decreasing the incidence of frailty remains an important and unresolved question. Participants taking higher number of medications are, obviously, unhealthier than those taking less medications. In the current analysis, there was unsurprisingly a significant association between medical comorbidity and increased number of medications. However it is notable that when comorbidity was included as a confounding variable, each additional medication was associated with an 11% increased risk of frailty. Therefore, this provides compelling evidence to reduce polypharmacy, especially where older people may be taking non-essential medications. It has been estimated that about 50% of older adults take one or more medications that are not medically necessary.[33] Therefore, our findings, taken together with the wider established harms of polypharmacy, add to the growing need to evaluate the medication regimen for each individual treated with a high number of drugs. However, this should be done carefully since the beneficial effect of "deprescribing" has not been studied in randomized controlled trials, limiting our knowledge regarding this aspect.[8] A comprehensive geriatric assessment (that includes validated tools and reliable prognostic instruments) [14,34-36] could be important to better understand and monitor the role of deprescribing in the onset of frailty.

The study does have some limitations, the main one being that we used a slightly different definition of frailty at baseline with respect to the one used at the follow-up as far as weight loss was concerned. Using that definition, only 20 participants were considered frail at baseline. Unfortunately, no data regarding weight changes were available in the OAI at the baseline and this could limit our definition of frailty at baseline. Second, although we know the number of medications used by every participant, we could only ascertain osteoarthritis specific medications used in OAI, such as pain-killers. Thus, we don't know if there are some medications that could reduce the incidence of frailty. Finally, we were unable to assess the influence of bio-humoral markers (e.g. inflammation [37], insulin-resistance) on the association between polypharmacy and frailty.

In conclusion, our data provides robust longitudinal evidence that polypharmacy is associated with higher incidence of frailty, even after adjusting for several important confounders. Moreover, our analyses suggest a dose response relationship. Future interventional studies are warranted to see if decreasing the number of medications (particularly if not necessary) could be associated with a lower incidence of this condition.

Conflict of interest: none.

Founding source: The OAI is a public-private partnership comprised of five contracts (N01-AR-2-2258; N01-AR-2-2259; N01-AR-2-2260; N01-AR-2-2261; N01-AR-2-2262) funded by the National Institutes of Health, a branch of the Department of Health and Human Services, and conducted by the OAI Study Investigators. Private funding partners include Merck Research Laboratories; Novartis Pharmaceuticals Corporation, GlaxoSmithKline; and Pfizer, Inc. Private sector funding for the OAI is managed by the Foundation for the National Institutes of Health. This manuscript was prepared using an OAI public use data set and does not necessarily reflect the opinions or views of the OAI investigators, the NIH, or the private funding partners.

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Table 1. Characteristics of the participants classified according to number of medications.

	0-3 medications (n=2862)	4-6 medications (n=1236)	≥7 medications (n=304)	P value for trend[a]
Age (years)	60.0 (9.1)	63.7 (8.8)	63.7 (9.1)	<0.0001
Females (%)	54.3	64.3	68.4	<0.0001
PASE (points)	171.6 (83.7)	144.0 (73.7)	129.6 (78.1)	<0.0001
White race (%)	80.8	80.4	76.6	<0.0001
Smoking (previous/current) (%)	45.6	49.9	52.3	0.002
College/degree (%)	31.1	29.8	27.3	0.14
Yearly income (≥ $50,000) (%)	38.2	43.3	55.3	<0.0001
BMI (Kg/m^2)	28.2 (4.6)	29.3 (4.8)	30.5 (5.5)	<0.0001
Cardiovascular disease (%)	3.5	11.0	19.9	<0.0001
COPD (%)	1.5	2.4	8.9	<0.0001
Diabetes (%)	2.9	14.5	24.2	<0.0001
Cancer (%)	4.5	4.8	8.6	0.02
Charlson comorbidity index (points)	0.2 (0.7)	0.6 (1.0)	1.2 (1.4)	<0.0001
Energy intake (Kcal/day)	1417.6 (609.0)	1378.4 (543.7)	1429.1 (574.6)	0.03

	0-3 medications (n=2862)	4-6 medications (n=1236)	≥7 medications (n=304)	P value for trend[a]
aMED (points)	28.2 (5.1)	28.0 (4.9)	27.8 (5.1)	0.33
BMI≤ 18.5 Kg/m^2	2.4	1.9	2.3	0.57
Inability to do five chair stands	0.6	0.7	1.3	0.24
Low energy level	9.1	12.1	24.7	<0.0001

Notes: The data are presented as means (with standard deviations) for continuous variables and number (with percentage).

[a] P values for trends were calculated using the Jonckheere-Terpstra test for continuous variables and the Mantel-Haenszel Chi-square test for categorical ones.

Abbreviations: aMED: adherence to Mediterranean diet score; PASE: Physical Activity Scale for the Elderly; BMI: body mass index; COPD: chronic obstructive pulmonary disease.

Table 2. Association between number of medications and incident frailty.

	Cumulative incidence (%)	Incidence (95% CI)	Unadjusted HR (95%CI)	P value	Fully-adjusted[a] HR (95%CI)	P value
0-3 medications	164/2862 (=5.7)	8 (7-10)	1 [reference]		1 [reference]	
4-6 medications	137/1236 (=11.1)	15 (12-18)	2.00 (1.60-2.52)	<0.0001	1.55 (1.22-1.96)	<0.0001
≥ 7 medications	60/304 (=19.7)	46 (20-73)	3.92 (2.90-5.29)	<0.0001	2.47 (1.78-3.43)	<0.0001

Notes:

All the data are presented as hazard ratios (HRs) with their 95% confidence intervals.

[a]Fully-adjusted model included as covariates: age (as continuous); sex; race (whites vs. others); body mass index (as continuous); education (degree vs. others); smoking habits (current and previous vs. others); yearly income (categorized as ≥ or < 50,000$ and missing data); Physical Activity Scale for Elderly score (as continuous); Charlson co-morbidity index; daily energy intake; adherence to Mediterranean diet.

Abbreviations: CI: confidence intervals; HR: hazard ratio.

Figure 1. Risk of frailty by number of medications at the baseline.