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Polypharmacy Is Associated With Higher Frailty Risk in Older People: An 8-Year Longitudinal Cohort Study

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Abstract

Objective—To investigate whether polypharmacy is associated with a higher incidence of frailty in a large cohort of North Americans during 8 years of follow-up.

Design—Longitudinal study, follow-up of 8 years.

Participants—A total of 4402 individuals at high risk or having knee osteoarthritis free from frailty at baseline.

Measurements—Details regarding medication prescription were captured and categorized as 0–3, 4–6, and 7. Frailty was defined using the Study of Osteoporotic Fracture index as the presence of 2 out of (1) weight loss ≥5% between baseline and the subsequent follow-up visit; (2) inability to do 5 chair stands; and (3) low energy level according to the Study of Osteoporotic Fracture definition. Cox's regression models calculating a hazard ratio (HR) with 95% confidence intervals (CIs), adjusted for potential confounders, were undertaken.

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The authors declare no conflicts of interest.

Results—During the 8-year follow-up, from 4402 participants at baseline, 361 became frail. Compared with participants taking 0–3 medications, the incidence of frailty was approximately double in those taking 4–6 medications and 6 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; $P < .0001$), whereas those using more than 7 drugs were at approximately 147% (HR = 2.47; 95% CI 1.78–3.43; $P < .0001$). 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; $P < .0001$).

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

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 cardiovascular² and metabolic³ 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 5 years) and the small sample sizes. The relationship between polypharmacy and frailty is complex; several studies have suggested polypharmacy is associated with frailty,^{6–8} whilst 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 (OAI) during 8 years of follow-up. We hypothesized that higher number of medications is associated with a higher incidence of frailty.

Methods

Data Source and Participants

Data were obtained from the OAI database, which is available for public access at <http://www.oai.ucsf.edu/>. The specific datasets used 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 osteoarthritis were recruited at 4 clinical centers in the United States (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. Multivitamin supplementations were not included. Trained interviewers checked the medications used by each participant in the last 30 days. Because 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 index¹⁴ (ie, 0–3, 4–6, or 7 medications).

Outcomes

The outcome of interest of the study was incident frailty. In accordance with the Study of Osteoporotic Fracture index^{15,16} frailty was defined as the presence of 2 out of 3 of the following criteria: (1) weight loss ≥5% taking place between baseline and the follow-up examinations [at the baseline examination a body mass index (BMI), of less than 20 kg/m² was used because no information regarding weight changes were recorded]; (2) the inability to rise from a chair 5 times without arm support (hereafter referred to as inability to carry out chair stands); and (3) 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 Elderly¹⁷; 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

Because 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 $\pm$ standard deviations 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 χ^2 test for categorical ones.

Cox 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 of $<.10$) or significantly associated with incident frailty at univariate analysis (*P* value of $<.05$) were included. Multicollinearity among covariates was assessed using the variance inflation factor, 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); BMI (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 comorbidity index (as continuous); daily energy intake (as continuous); adherence to Mediterranean diet (as continuous). The proportional hazard assumption was verified considering Schoenfeld residuals of the covariates.²² Cox 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 (eg, sex, 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 v 17.0 for Windows (SPSS Inc, Chicago, IL). All statistical tests were 2-tailed, and statistical significance was assumed for a *P* value of $<.05$.

Results

Sample Selection

The OAI dataset initially includes a total of 4796 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 because they do not have data regarding incident frailty. Thus, 4402 participants were finally included in this study.

Descriptive Characteristics

Of the 4402 participants, 1844 were male and 2558 female. Mean age was 61.2 years (± 9.2 years; range: 45–9). The number of medications used across the entire sample was in mean 3 (range: 0–27).

Table 1 shows the participant 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 with those using less medications (P for trend $<.0001$ for all comparisons). Moreover, those using 7 or more medications were more frequently obese, and they had a significant higher presence of several comorbidities (Table 1). Finally, they reported a significant higher calorie intake than those using fewer 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 $<.0001$) (Table 1).

Polypharmacy and Incident Frailty

During the 8-year follow-up, 361 participants (8.2% of the baseline population) developed frailty equating to a global incidence rate of 23 (95% CI 14–32)/1000 person-years (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, whereas participants using 7 medications or more had approximately a 6 times higher incidence of frailty. Using a Cox 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; $P < .0001$), whereas those using more than 7 drugs were almost at 150% increased risk of frailty (HR = 2.47; 95% CI 1.78–3.43; $P < .0001$) (Table 2).

Modeling 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; $P < .0001$).

Discussion

In this study including more than 4000 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 comorbidities), 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 1662 men aged who were more than 70 years of age with a follow-up period of 2 years, Gnjjidic et al⁶ found that the use of more than 5 medications is associated with incident frailty. In a cohort with similar characteristics ($n = 1705$, follow-up period = 5 years), Jansen et al⁷ 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. Even if these 2 studies were important to understand the role of polypharmacy in promoting frailty, they did not include any

comprehensive multimorbidity score as Saum et al⁸ proposed more recently. However, although Saum et al⁸ considered the type and number of medical conditions at baseline, the association between polypharmacy and incident frailty remained significant. Compared with 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,³² also caused by commonly used medications.³² Adverse drug reactions 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 nonessential medications. It has been estimated that about 50% of older adults take 1 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 because 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 painkillers. Thus, we do not know if there are some medications that could reduce the incidence of frailty. Finally, we were unable to assess the influence of biohumoral markers (eg, inflammation,³⁷ insulin-resistance) on the association between polypharmacy and frailty.

Conclusions

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.

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

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*
Age (years)	60.0 (9.1)	63.7 (8.8)	63.7 (9.1)	<.0001
Females (%)	54.3	64.3	68.4	<.0001
PASE (points)	171.6 (83.7)	144.0 (73.7)	129.6 (78.1)	<.0001
White race (%)	80.8	80.4	76.6	<.0001
Smoking (previous/current) (%)	45.6	49.9	52.3	.002
College/degree (%)	31.1	29.8	27.3	.14
Yearly income (< \$50,000) (%)	38.2	43.3	55.3	<.0001
BMI (Kg/m ²)	28.2 (4.6)	29.3 (4.8)	30.5 (5.5)	<.0001
Cardiovascular disease (%)	3.5	11.0	19.9	<.0001
COPD (%)	1.5	2.4	8.9	<.0001
Diabetes (%)	2.9	14.5	24.2	<.0001
Cancer (%)	4.5	4.8	8.6	.02
Charlson comorbidity index (points)	0.2 (0.7)	0.6 (1.0)	1.2 (1.4)	<.0001
Energy intake (Kcal/day)	1417.6 (609.0)	1378.4 (543.7)	1429.1 (574.6)	.03
aMED (points)	28.2 (5.1)	28.0 (4.9)	27.8 (5.1)	.33
BMI 18.5 Kg/m ²	2.4	1.9	2.3	.57
Inability to do 5 chair stands	0.6	0.7	1.3	.24
Low energy level	9.1	12.1	24.7	<.0001

aMED, adherence to Mediterranean diet score; COPD, chronic obstructive pulmonary disease; PASE, Physical Activity Scale for the Elderly. The data are presented as means (with standard deviations) for continuous variables and percentages.

* P values for trends were calculated using the Jonckheere-Terpstra test for continuous variables and the Mantel-Haenszel χ^2 test for categorical ones.

Table 2**Association Between Number of Medications and Incident Frailty**

	Cumulative Incidence (%)	Incidence (95% CI)	Unadjusted HR (95% CI)	P Value	Fully Adjusted* 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)	<.0001	1.55 (1.22–1.96)	<.0001
7 medications	60/304 (=19.7)	46 (20–73)	3.92 (2.90–5.29)	<.0001	2.47 (1.78–3.43)	<.0001

All the data are presented as HRs with their 95% CIs.

* Fully adjusted model included as covariates: age (as continuous); sex; race (whites vs others); BMI (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 comorbidity index; daily energy intake; adherence to Mediterranean diet.