Polypharmacy is associated with multiple health-related outcomes in Mexican community-dwelling older adults

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Abstract

Objective. To determine the association between polypharmacy and multiple health-related outcomes in older adults. **Materials and methods.** We carried out a cross-sectional analysis with 274 community-dwelling older adults aged ≥60 years in Mexico City. We used the following health-related outcomes: frailty, dementia, functional capacity, falls, disability, and quality of life. The main exposure was polypharmacy (chronic use of six or more drugs). Ordinal logistic regression, binary logistic regression, Poisson regression, and linear regression models were used to estimate the association between polypharmacy and the outcomes analyzed. **Results.** Polypharmacy was present in 45% of the sample. Polypharmacy was significantly associated with frailty status, and marginally, with dementia. We also observed significant associations for instrumental activities of daily living, falls, disability, and quality of life. **Conclusions.** Given that polypharmacy has reached levels of a global epidemic, it is necessary to take radical actions to reduce the concomitant problems of the use of multiple drugs.

Keywords: health-related outcomes; older adults; polypharmacy

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Resumen

Objetivo. Determinar la asociación entre la polifarmacia y múltiples resultados relacionados con la salud de los adultos mayores. **Material y métodos.** Se llevó a cabo un análisis transversal con 274 adultos mayores que residen en comunidad, edad ≥60 años, en la Ciudad de México. Se utilizaron los siguientes resultados relacionados con la salud: fragilidad, demencia, capacidad funcional, caídas, discapacidad y calidad de vida. La exposición principal fue la polifarmacia (uso crónico de seis o más fármacos). Se utilizaron modelos de regresión logística ordinal, regresión logística binaria, regresión de Poisson y regresión lineal para estimar la asociación entre la polifarmacia y los resultados analizados. **Resultados.** La polifarmacia estuvo presente en 45% de la muestra. La polifarmacia se asoció significativamente con el estado de fragilidad y marginalmente con la demencia. También se observaron asociaciones significativas para actividades instrumentales de la vida diaria, caídas, discapacidad y calidad de vida. **Conclusiones.** Dado que la polifarmacia ha alcanzado niveles de epidemia global, es necesario tomar medidas radicales para reducir los problemas concomitantes del uso de múltiples medicamentos.

Palabras clave: resultados relacionados con la salud; adultos mayores; polifarmacia

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Polypharmacy is an old concern among geriatricians because it is associated with multiple adverse health outcomes among the older adult population, and it is also a common clinical practice, due to the need to treat chronic diseases that arise as individuals age.[1] Polypharmacy has been reported to be a major risk factor for falls,[2] functional capacity,[3] frailty,[4] disability,[5] quality of life,[6] increased number of hospital admissions,[7] and mortality.[8]

Polypharmacy is also one of the main concerns for the older adult population; partly because this population is the largest consumer of drugs. Furthermore, its prevalence has increased globally due to the presence of multimorbidity and geriatric syndromes.[9] Although data on its prevalence depend on the operationalization (number of drugs used in its definition), a recent systematic review reported numbers ranging from 27% to 50% in community-dwelling older adults,[10] while the prevalence in institutionalized individuals was higher (38% to 91%).[11] In Mexico, studies on this issue have been scarce and with limited sample sizes, with a reported prevalence of 18% for older adults living in the community,[12] and 84% among institutionalized subjects.[13]

Although polypharmacy is a broad concept, there is not a single and precise definition, and different characterizations have been used in the literature.[14] While the most commonly operationalization is the use of five or more medicines,[2] definitions are variable, ranging from two or more drugs[15] to over 20 (excessive polypharmacy).[16] Despite this diversity, studies have shown that, regardless of the cut-off used, polypharmacy is associated with several health-related outcomes.[17]

Even though the adverse effects of polypharmacy among older adults have been documented, most of the evidence has been obtained in populations residing in high-income countries;[17] and few studies have analyzed several outcomes simultaneously.[2,3] For this reason, the objective of this study was to determine the association between polypharmacy and multiple health-related outcomes (frailty, dementia, functional capacity, falls, disability, and quality of life) in a sample of community-dwelling older Mexican adults.

Materials and methods

Sample and procedures

We used data from the Study of Costs Associated with Frailty in Older Mexican Adults; a prospective study aimed to estimate the economic impact of frailty in a sample of older adult residents of Mexico City between 2014 and 2016.[18] This study had a baseline measurement in 2014, and three semiannual follow-up measurements from 2015 to 2016. The baseline measurement included a non-probabilistic sample of 274 older adults who were users of the Geriatric Unit of the National Institute of Medical Sciences and Nutrition, a highly specialized national public hospital within the National Institutes of Health of Mexico. Of these 274 older adults, eight died during follow-up, and one was lost to follow-up.

For the present study, we only used the baseline information, because longitudinal data were mainly collected for the healthcare costs of frailty. We obtained information on outcomes, exposure, and covariates using an individual questionnaire and conducting an exhaustive review of the clinical records of each older adult.

Measures

Outcomes

Frailty. The phenotype of frailty was determined according to the criteria proposed by the Cardiovascular Health Study[19] as follows: a) slowness: determined by the time taken to perform a 4-meter walk test. The cut-off point was adjusted by sex and height, and those in the lowest quintile were identified as having a slow gait speed; b) handgrip strength: measured using a hand dynamometer (Baseline Electronic Smedley Hand Dynamometer, Fabrication Enterprises, White Plains, NY, USA). Three measurements were made in both hands, and the highest one was retained. The cut-off point was adjusted by body mass index (kg/m^2) and sex, and those in the lowest quintile were determined to have the poorest handgrip strength; c) physical activity: defined using the Physical Activity Scale for the Elderly (PASE).[20] PASE is an instrument that measures the level of physical activity for older adults. It is comprised of self-reported occupational, household, and leisure activities over a one-week period to assign a score, ranging from 0 to 793, with higher scores indicating greater physical activity. The criteria for low physical activity was defined as the lowest quintile of this score, adjusted by sex; d) exhaustion: participants with a negative response to the following two questions from the Geriatric Depression Scale were considered exhausted: "Do you feel full of energy?" and "Do you have enough energy for your everyday life?", and e) weight loss: defined based on the self-report of unintentional weight loss (≥5 kg) in the past six months. Those meeting three or more of the criteria were considered frail; those meeting one or two criteria were considered pre-frail, and those who met none of the above conditions were considered non-frail.

Dementia. The clinical diagnosis of dementia (major neurocognitive disorder) was determined through the review of the clinical records of each older adult. The procedure for obtaining the diagnosis is briefly described here. The older adults who attend the Geriatric Unit of the National Institute of Medical Sciences and Nutrition undergo a comprehensive geriatric assessment that includes tools for the global evaluation of the cognitive function using the DSM-V criteria. Those with suspected deterioration are referred to the Cognition Clinic of the Institute, where a detailed clinical and neuropsychological assessment is made to establish the definitive diagnosis of dementia. In some cases, and for the purpose of obtaining a differential diagnosis, biochemical and brain imaging tests are performed.

Falls. Information regarding falls was obtained by asking the older adults: how many falls have you had in the last twelve months? With this data, we generate a count variable that expresses the number of falls in the last twelve months.

Functional capacity. We used Katz scale[21] to assess difficulties in basic activities of daily living (ADL), which include bathing, dressing, toileting, transferring, continence, and feeding. We also used Lawton scale[22] to assess difficulties in instrumental ADL (IADL): using the telephone, going shopping, managing drugs and money, and using public or private transportation. Both scales assess these difficulties for a period of three months. Participants who reported requiring help or being unable to carry out at least one of the above activities were considered as having impaired functional capacity.

Disability. We measured this variable according to the World Health Organization Disability Assessment Schedule (WHODAS 2.0). The WHODAS 2.0 scale is widely used to measure last-month limitations in activity and daily-life participation. It covers six domains explored through a total of 12 items (two per domain): a) cognition and communication, b) self-care, c) mobility, d) interpersonal relationships, e) life activities, and f) participation. The results of the 12 items are added up to obtain a global score expressed on a continuous scale from 0 (no disability) to 100 (full disability).[23]

Health-related quality of life. It was measured with the SF-36,[24] a validated instrument with 36 items for appraising the activities of the previous month, considering eight outcome domains: physical functioning, social functioning, role limitations due to physical functioning, role limitations due to emotional problems, general mental health, vitality, bodily pain, and general health self-perception. The SF-36 domains are grouped into two categories: a) Physical Component Summary (PCS), and b) Mental Component Summary (MCS), with values ranging from 0 to 100 each (100 reflecting a better health-related quality of life).

Main exposure

Polypharmacy. Data on usual home medication regimen were recorded based on clinical records and personal interview. The number of drugs usually consumed in the last 30 days was determined from the prescriptions that the participants took home. Drug use refers to the regular consumption of drugs, excluding vitamins and mineral supplements. In line with previous studies, polypharmacy was defined as the use of more than six drugs.[25,26]

Covariates

Using the literature on factors associated with the multiple health-related outcomes (frailty, dementia, functional capacity, falls, disability, and quality of life) and polypharmacy as guides, risk factors were selected as potential covariates and then identified in our dataset. Covariates were categorized as follows:

Sociodemographic characteristics. Sex (female=1); age; health insurance (yes=1); retirement pension (yes=1); schooling (years of formal instruction); having a paid job (yes=1), and living arrangements (older adult living alone=1).

Health. We included indicator variables for each of the following 19 conditions that were obtained by reviewing the participants' clinical records of the two immediate previous years to this study: hypertension, diabetes, hypercholesterolemia, heart disease (angina pectoris, heart failure), embolism, stroke or cerebral thrombosis, arthritis or rheumatism, bronchitis or pulmonary emphysema, osteoporosis, kidney chronic disease, tuberculosis, cataracts (one or both eyes), urinary incontinence, prostate disease (men only), cancer (skin/melanoma, cervix, breast, prostate, stomach, leukemia / blood). With this list, a count variable was generated to express the total number of chronic conditions of each participant.

Lifestyle-related behaviors. We used tobacco and alcohol consumption as indicators. We defined the smoking habit as the smoking of at least 100 cigarettes in the person's lifetime or current smoking. We categorized

alcohol consumption according to the frequency of excessive use, defined as the ingestion of five standard drinks or more (any alcoholic beverage containing the equivalent of 10 grams of pure alcohol) on occasion for men and four standard drinks or more on occasion for women. When alcohol consumption occurred for three days or more per week, the subject was defined as a frequent heavy drinker. Both definitions have been used among older Mexican adults.[27]

Socioeconomic status (SES). For SES measurement, an asset index was created using a total of nine dichotomous (yes/no) variables that evaluate the possession of assets in the household (car, movie player, stereo recorder, computer, stove, blender, microwave, washing machine, and boiler). The asset index was created using a polychoric correlation matrix through the application of a principal component analysis. The first component accounted for 44% of the variation in the data. This index is continuous, and higher values imply a higher household socioeconomic level.

Statistical analysis

Variables were described using means (SD) or proportions, as appropriate. In bivariate analysis, the following statistical procedures were used according to the characteristics of each variable: Chi-squared test for categorical data and Mann-Whitney test for continuous data. The association between polypharmacy and multiple health-related outcomes was estimated using different regression models as described below.

Ordinal logistic regression. We used this model to analyze the probability of being pre-frail or frail according to the ordinal variable generated by the procedure proposed by Fried and colleagues.

Binary logistic regression. This model was used to analyze the following dichotomous variables: dementia and functional capacity (ADL & IADL).

Poisson regression. Falls were analyzed using this model to estimate the conditional mean of these count variable.

Linear regression. The WHODAS score (disability), the Physical Component Summary, and the Mental Component Summary scores of the SF-36 (quality of life) were analyzed as continuous variables, using linear regression models.

The final models were evaluated in terms of collinearity, goodness of fit, and residuals. Differences were considered statistically significant if $p<0.05$, and marginally significant if $0.05<p<0.10$. All analyses were performed using Stata 15.1.

Ethical review

The study was approved by the Ethics Boards of the National Institute of Public Health (*Instituto Nacional de Salud Pública*, INSP) and the Salvador Zubirán National Institute of Medical Sciences and Nutrition (*Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán*, INCMNSZ). Written informed consent was obtained from all subjects.

Results

Table I shows the sociodemographic and health characteristics of participants by polypharmacy status. Polypharmacy was present in 45% of participants. In comparison with individuals without polypharmacy, those with polypharmacy proved more proportion of pre-frail or frail older adults ($p<0.01$), had a higher proportion of dementia ($p=0.04$) and functional impairment (ADL $p=0.02$; IADL $p<0.01$); had a larger number of falls ($p= 0.03$), higher scores on WHODAS ($p<0.01$), and a lower score on the Physical Component Summary of the SF-36 scale ($p<0.01$). They also displayed a significantly higher number of chronic conditions ($p<0.01$).

The results of the regression models for the different health-related outcomes analyzed are displayed in tables II, III, and IV. Table II shows the results for frailty status and dementia. Polypharmacy was significantly associated with an increase in the likelihood of being pre-frail or frail (OR=1.92, $p=0.04$) and, marginally, with the probability of having dementia (OR=2.06, $p=0.07$). Regarding functional capacity, we did not observe a significant association for ADL (OR=1.66, $p=0.15$), although we did for IADL (OR=3.43, $p<0.01$). The association with falls was also statistically significant ($e^{\beta}=1.93$, $p<0.01$) (table III). Finally, table IV shows the results for disability and quality of life. Polypharmacy was associated with higher WHODAS scores ($\beta=9.54$, $p=0.02$) and lower scores in the PCS of the SF-36 ($\beta=-12.42$, $p<0.01$). Association with the MCS was not significant ($\beta=-0.56$, $p=0.88$).

Discussion

In this study, we have proved that the presence of polypharmacy in older Mexican adults affects multiple health-related outcomes. These results contribute to the current body of evidence in at least two ways. First, a couple of studies have analyzed the effect of polyphar-

Table I
Sociodemographic and health characteristics of the study sample by polypharmacy status. Mexico City, 2014-2016*

	Polypharmacy (>6 drugs)		
	No n=151 (55%)	*Yes* n=123 (45%)	$p^{\ddagger}$
Outcomes			
Frailty			
Non-frail	38	21	
Pre-frail	48	55	
Frail	14	24	<0.01
Dementia	20	31	0.04
Functional capacity			
Difficulties in ADL	35	52	0.02
Difficulties in IADL	40	72	<0.01
Falls	0.81 ± 1.47	1.37 ± 2.17	0.03
Disability (WHODAS score)	32.55 ± 29.35	44.97 ± 27.05	<0.01
Quality of life (SF-36 score)			
SF-36 PCS	54.78 ± 27.09	38.43 ± 24.08	<0.01
SF-36 MCS	66.25 ± 25.88	62.33 ± 24.36	0.26
Covariates			
Sex (female=1)	74	78	0.53
Age	80.24 ± 8.28	80.82 ± 8.30	0.61
Number of chronic conditions	3.49 ± 1.77	4.77 ± 2.07	<0.01
Tobacco (one hundred cigarettes smoked and/or current smoker)	26	25	0.93
Alcohol (frequent heavy drinker)	18	11	0.10
Health insurance (yes=1)	45	46	0.89
Retirement pension (yes=1)	75	71	0.61
Schooling (years of formal instruction)	7.81 ± 5.02	7.38 ± 5.15	0.55
Paid job (yes=1)	11	8	0.55
Older adult lives alone	12	7	0.20
Socioeconomic status (household asset index)	0.01 ± 0.99	0.09 ± 1.06	0.16

*The figures in the cells are means ± SD or percentages
‡ Mann-Whitney or Chi-squared tests
ADL: activities of daily living
IADL: instrumental activities of daily living
WHODAS: World Health Organization Disability Assessment Schedule
PCS: Physical Component Summary
MCS: Mental Component Summary

macy on multiple health-related outcomes, but only in older adults residing in high-income countries;[2,3] our study shows that the same association is also observed in a middle-income country. Second, studies on polypharmacy in older adults have analyzed health outcomes in isolation, or in a reduced set of outcomes;[17] in our study, we analyzed the association of polypharmacy with eight different outcomes, evidencing significant associations.

Our results with respect to the relationship between polypharmacy and various health outcomes are consistent with what has been reported in the gerontological literature. Regarding frailty and polypharmacy, a systematic review reported that the probability of being frail increases in the presence of polypharmacy (OR between 1.13 and 5.8),[4] a range in which our observed association is situated (OR = 1.92). As for dementia and

Table II

ADJUSTED ASSOCIATIONS OF POLYPHARMACY WITH FRAILTY STATUS AND DEMENTIA. MEXICO CITY, 2014-2016

	*Frailty status**				*Dementia‡*			
	OR	*95%CI*		*p*	*OR*	*95%CI*		*p*
Polypharmacy	1.92	1.05	3.53	0.04	2.06	0.95	4.48	0.07
Sex (female=1)	1.49	0.72	3.07	0.28	1.51	0.59	3.89	0.39
Age	1.07	1.03	1.11	<0.01	1.08	1.03	1.14	<0.01
Number of chronic conditions	1.21	1.03	1.41	0.02	0.91	0.74	1.11	0.35
Tobacco (one hundred cigarettes smoked and/or current smoker)	1.38	0.68	2.80	0.37	2.99	1.28	6.99	0.01
Alcohol (frequent heavy drinker)	0.52	0.23	1.15	0.11	0.36	0.11	1.18	0.09
Health insurance (yes=1)	1.43	0.79	2.58	0.24	0.80	0.38	1.71	0.57
Retirement pension (yes=1)	0.93	0.46	1.87	0.84	0.88	0.35	2.20	0.78
Schooling (years of formal instruction)	1.02	0.96	1.08	0.52	1.01	0.94	1.09	0.78
Paid job (yes=1)	0.52	0.18	1.51	0.23	0.27	0.03	2.37	0.24
Older adult lives alone	0.71	0.26	1.98	0.52	0.88	0.22	3.52	0.86
Socioeconomic status (household asset index)	0.95	0.69	1.30	0.73	1.12	0.74	1.69	0.59

* Ordinal logistic regression model using as response variable the frailty phenotype (non-frail, pre-frail and frail categories)
‡ Logistic regression model using as response variable the diagnosis of dementia

Table III

ADJUSTED ASSOCIATIONS OF POLYPHARMACY WITH FUNCTIONAL CAPACITY AND FALLS. MEXICO CITY, 2014-2016

	Functional capacity								*Falls§*			
	*ADL**				*IADL‡*							
	OR	*95%CI*		*p*	*OR*	*95%CI*		*P*	eβ	*95%CI*		*p*
Polypharmacy	1.66	0.84	3.28	0.15	3.43	1.69	6.94	<0.01	1.93	1.40	2.66	<0.01
Sex (female=1)	3.11	1.24	7.75	0.02	1.48	0.64	3.43	0.37	1.41	0.93	2.12	0.11
Age	1.08	1.03	1.13	<0.01	1.12	1.06	1.18	<0.01	0.99	0.97	1.01	0.33
Number of chronic conditions	1.15	0.96	1.37	0.13	1.20	1.00	1.45	0.06	1.03	0.95	1.11	0.46
Tobacco (one hundred cigarettes smoked and/or current smoker)	1.96	0.86	4.46	0.11	0.84	0.37	1.91	0.68	0.86	0.58	1.27	0.44
Alcohol (frequent heavy drinker)	0.54	0.21	1.40	0.20	0.39	0.15	0.98	0.05	0.93	0.60	1.45	0.75
Health insurance (yes=1)	1.10	0.56	2.16	0.79	1.13	0.56	2.28	0.74	1.09	0.80	1.48	0.60
Retirement pension (yes=1)	0.41	0.18	0.94	0.03	0.26	0.11	0.63	<0.01	1.10	0.77	1.56	0.60
Schooling (years of formal instruction)	0.97	0.91	1.04	0.43	1.01	0.94	1.08	0.88	1.00	0.97	1.03	0.77
Paid job (yes=1)	0.39	0.09	1.67	0.21	0.62	0.18	2.11	0.44	1.04	0.61	1.76	0.89
Older adult lives alone	0.76	0.23	2.50	0.65	0.40	0.12	1.39	0.15	0.85	0.48	1.51	0.58
Socioeconomic status (household asset index)	0.99	0.69	1.41	0.95	0.85	0.58	1.23	0.39	0.99	0.85	1.17	0.94

* Logistic regression model using as response variable the activities of daily living (ADL)
‡ Logistic regression model using as response variable the instrumental activities of daily living (IADL)
§ Poisson regression model using as response variable the number of falls in the last 12 months

Table IV
Adjusted associations of polypharmacy with disability and quality of life. Mexico City, 2014-2016

	Disability				*Quality of life*							
	*WHODAS Score**				*SF-36 PCS‡*				*SF-36 MCS§*			
	β	*95%CI*		*p*	β	*95%CI*		*p*	β	*95%CI*		*p*
Polypharmacy	9.54	1.47	17.62	0.02	-12.42	-19.59	-5.24	<0.01	-0.56	-8.02	6.91	0.88
Sex (female=1)	7.41	-2.21	17.03	0.13	-6.42	-14.97	2.13	0.14	-9.78	-18.67	-0.88	0.03
Age	1.07	0.57	1.57	<0.01	-0.93	-1.38	-0.49	<0.01	-0.16	-0.62	0.31	0.51
Number of chronic conditions	1.26	-0.81	3.32	0.23	-2.48	-4.31	-0.64	0.01	-2.15	-4.06	-0.24	0.03
Tobacco (one hundred cigarettes smoked and/ or current smoker)	1.71	-7.69	11.12	0.72	0.85	-7.50	9.21	0.84	-0.59	-9.29	8.11	0.89
Alcohol (frequent heavy drinker)	-3.36	-13.91	7.19	0.53	2.16	-7.22	11.54	0.65	3.64	-6.12	13.40	0.46
Health insurance (yes=1)	-0.01	-8.00	7.99	1.00	0.34	-6.76	7.45	0.92	-1.53	-8.93	5.86	0.68
Retirement pension (yes=1)	-8.01	-17.25	1.23	0.09	13.89	5.69	22.10	<0.01	8.18	-0.36	16.72	0.06
Schooling (years of formal instruction)	-0.24	-1.03	0.56	0.56	0.26	-0.45	0.96	0.48	0.02	-0.71	0.76	0.95
Paid job (yes=1)	-6.76	-20.12	6.59	0.32	4.91	-6.96	16.78	0.42	9.21	-3.14	21.56	0.14
Older adult lives alone	-3.76	-17.12	9.61	0.58	1.18	-10.69	13.06	0.85	-2.53	-14.89	9.83	0.69
Socioeconomic status (household asset index)	0.20	-3.88	4.28	0.92	1.02	-2.60	4.65	0.58	0.21	-3.57	3.98	0.91

* Linear regression model using as response variable the World Health Organization Disability Assessment Schedule (WHODAS) score
‡ Linear regression model using as response variable the Physical Component Summary (PCS) of the SF-36
§ Linear regression model using as response variable the Mental Component Summary (MCS) of the SF-36

polypharmacy, a case-control study with Taiwanese older adults reported a significant association (OR = 1.34; 95% CI 1.23-1.46) using as exposure variable the consumption of 5-9 drugs.[28] This result is similar to ours, although in our case the association was marginally significant. In our study, we also observed a significant association of polypharmacy with IADL but not with ADL, which confirms what has been reported in the literature.[3] Our results also confirm what multiple studies have shown with regard to the relationship between polypharmacy and falls in older adults.[17] Finally, a previous study analyzed the relationship between polypharmacy and quality of life, using a reduced version of SF-36 (SF-12) in a sample of American adults with arthritis, and reported a significant decrease in PCS (β = −1.68), but not in the MCS; this finding agrees with what we observed in our study.[29]

An interesting finding in our study was the existence of a significant association between polypharmacy and IADL, but not with ADL. This association has been little analyzed in the literature. In fact, most of the studies on the effects of polypharmacy have focused only on difficulties in ADL.[30] In this sense, a strength of our study is that we have included both dimensions of functional capacity: ADL and IADL. Difficulties in ADL refer to the private sphere of individuals, assessing the difficulties that subjects experience in relation to self-care and autonomy; while IADLs refer to the way in which the subjects interact with their environment and with those around them. It could be hypothesized that polypharmacy (as an indicator of a poor health status) primarily affects IADLs, given that older adults with functional disabilities abandon those activities that relate to their environment and their peers, and then, perhaps, their capacity for self-care is affected. However, it should be noted that it is intrinsically difficult to establish a causal relationship between the two factors, since the general state of health is associated with both polypharmacy and physical function (a confounding factor).

Although several studies have reported that polypharmacy is associated with various adverse health outcomes, it is important to note that whether polypharmacy in itself is a risk factor or whether it is rather an indicator of poor health status remains controversial.[31] The evidence suggests that both explanations are plausible. On the one hand, some studies have shown that consumption of a large number of drugs is associated,

per se, with a larger number of falls,[32] the presence of cognitive impairment,[3] and functional capacity;[3] but on the other hand, it has been shown that, beyond the number of drugs, inappropriate prescription is what might have adverse effects on the health of older adults.[33] Future studies, with more robust designs, should help clarify this issue.

Polypharmacy occurs in older adults, among other reasons, due to the changes that occur in the body over time. Given the pharmacokinetic and pharmacodynamic changes related to age, there is an increased risk of adverse reactions to drugs. In fact, each component of pharmacokinetics (such as absorption, distribution, metabolism, and elimination) slows down as individuals age.[34]

Our results have several implications. First, given that polypharmacy is now a globally urgent issue,[9] immediate actions must be taken to reduce or control the use of drugs, and to obtain better prescriptions based on a comprehensive assessment of the older adults. In that vein, certain screening tools have been identified (STOPP/START,[35] ARMOR[36]) which could be useful for evaluating polypharmacy in older adults and for offering specific actions to improve drug prescription among this population. Second, given that multimorbidity usually accompanies polypharmacy, the approach to pharmacological treatment must differ from the single disease model. As has been pointed out "A single disease-by-disease approach obscures the multimorbid patients' individual pattern of symptoms and overrides their preferences for care.";[9] therefore, some efforts are necessary to reframe the clinical treatment of older adults with multimorbidity. Third, in many low- and middle-income countries (like Mexico), medical care of older adults is not routinely provided by a specialist (geriatrician or gerontologist) but by a general practitioner. Health policy actions must be taken to integrate qualified personnel into the care of the older adult population, specifically in the pharmacological treatment for the health needs of this age group.

Our study has some limitations. First, our sample of older adults is restricted to the metropolitan area of Mexico City, and therefore our observed associations could be overestimated, as this population has more resources and greater access to health services. Populations with less income and more limited access may report lower levels of polypharmacy. Additionally, and as a result of the sample size, we were unable to disaggregate the information related to health insurance. This would be important because older adults affiliated to *Seguro Popular*, for example, might have less access to drugs and therefore report a lower prevalence of polypharmacy. Second, although this is a prospective study, we were able to use baseline data only because follow-up information was collected for the healthcare costs associated with frailty, and therefore we have the known limitations of cross-sectional studies, mainly, the possibility of reverse causality. Third, given that multiple comparisons were made, an adequation of the significance level may have been carried out. Even so, and with the aim of not missing any real associations, alpha levels of 5% and 10% were used.

In conclusion, our study shows that polypharmacy is associated with multiple health-related outcomes (frailty, dementia, functional capacity, falls, disability, and quality of life). This finding confirms what gerontological literature has identified in regard to polypharmacy as a major risk factor for several health outcomes among the older adult population. Given that polypharmacy has reached the levels of a global epidemic, today, more than ever, it is necessary to take radical actions to reduce the concomitant problems of the use of multiple drugs, including a paradigm shift in the medical and pharmacological care of the older adults.

Declaration of conflict of interests. The authors declare that they have no conflict of interests.

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