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Survival of the elderly and exposition to polypharmacy in the city of São Paulo, Brazil: SABE Study

Sobrevida de idosos e exposição à polifarmácia no município de São Paulo: Estudo SABE

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ABSTRACT: ***Introduction:*** The use of polypharmacy may be due to the concomitant presence of chronic conditions, medical care by several doctors simultaneously and self-medication. Combined with the vulnerability of the elderly to the effects of drugs due to pharmacokinetic and pharmacodynamic changes, polypharmacy makes this population more susceptible to adverse outcomes. In Brazil, studies show that polypharmacy is a common problem among elderly people. However, few information is available on the association between polypharmacy and mortality. ***Objective:*** It was assessed the survival of the elderly from São Paulo city exposed to the use of polypharmacy (five or more medications). ***Methods:*** That was a population-based cohort, the Health, Well-Being and Aging Study (SABE Study), conducted from 2006 to 2010. The sample was composed of 1,258 individuals aged 60 years or more. The Kaplan-Meier method and Cox proportional risks model were used to examine the association between polypharmacy and mortality. ***Results:*** The probability of survival after five years of the users of polypharmacy at baseline was 77.2%, while among the non-users was 85.5%. Polypharmacy remained as a risk factor for death even after adjustment in other conditions associated with mortality, such as age, gender, income, chronic diseases and hospitalization. ***Conclusion:*** The results point polypharmacy as an indicator of mortality in elderly people. The use of multiple medications by the elderly should be carefully assessed to avoid or minimize the damage to this population.

Keywords: Polypharmacy. Aged. Pharmacoepidemiology. Cohort studies. Mortality.

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RESUMO: ***Introdução:*** O uso de polifarmácia pode ser resultante da presença concomitante de condições crônicas, atendimento por diversos médicos e automedicação. Combinada com a vulnerabilidade de idosos aos efeitos dos medicamentos devido a alterações farmacocinéticas e farmacodinâmicas, a polifarmácia torna essa população mais suscetível a desfechos adversos. No Brasil, estudos mostram que a polifarmácia é um problema frequente entre idosos, mas faltam informações sobre sua associação com mortalidade. ***Objetivo:*** Avaliar a sobrevida de idosos do município de São Paulo expostos ao uso de polifarmácia (cinco ou mais medicamentos). ***Métodos:*** Trata-se de uma coorte de base populacional, o Estudo Saúde, Bem-Estar e Envelhecimento (Sabe), da qual se pesquisou o seguimento de 2006 a 2010. A amostra foi composta por 1.258 indivíduos com 60 anos ou mais. O método de Kaplan-Meier e o modelo de riscos proporcionais de Cox foram usados para examinar a associação entre mortalidade e polifarmácia. ***Resultados:*** A probabilidade de sobrevida após cinco anos dos indivíduos usuários de polifarmácia na linha de base foi de 77,2%, enquanto nos não usuários foi de 85,5%. A polifarmácia permaneceu como fator de risco para óbito mesmo após ajuste de demais condições associadas à mortalidade, como idade, sexo, renda, doenças crônicas e internação hospitalar. ***Conclusão:*** Os resultados apontam para a polifarmácia como um preditor de mortalidade para pessoas idosas. O uso de múltiplos medicamentos por idosos deve ser cuidadosamente avaliado para evitar ou minimizar danos a essa população.

Palavras-chave: Polimedicação. Idoso. Farmacoepidemiologia. Estudo de coortes. Mortalidade.

INTRODUCTION

The improper use of pharmacotherapy in the elderly has been the subject of several studies in which various types of problems are addressed, such as the ingestion of potentially inappropriate medications (PIM), the non-use of specified drugs, the use of excessive doses, or treatments lasting longer than necessary, as well as polypharmacy[1,2].

Several factors contribute to the occurrence of polypharmacy in the elderly, such as the concomitant presence of chronic conditions, medical care by several doctors simultaneously, and self-medication[3]. Combined with the increased vulnerability of the elderly to the effects of the drugs due to pharmacokinetic and pharmacodynamic changes caused by aging, polypharmacy makes this population more susceptible to adverse outcomes. Studies have shown the association between polypharmacy and the occurrence of adverse drug reactions, drug interactions, intoxication, use of PIM, and lack of adherence to treatment, resulting in increased health-care costs due to the need for hospitalization or emergency or outpatient care services[3-6].

Additionally, polypharmacy has been a significant predictor, in statistical terms, to other outcomes of large magnitude such as hospitalizations, admissions to long-term institutions, hypoglycemia, fractures, reduced mobility, pneumonia, and poor nutrition[5]. Particularly in relation to elderly living in communities and institutionalized, polypharmacy is associated with higher mortality risk[1,2,7-10].

In Brazil, although previous studies have shown that polypharmacy is a common problem among the elderly[11-15], there is not much information about its association with mortality. This population-based study aimed at analyzing the survival of elderly people previously exposed to polypharmacy.

METHODS

SAMPLE AND STUDY DESIGN

This study is part of the Health, Well-Being and Aging Study (SABE Study). The complete methodology is available in the first article of this supplement.

This study used as baseline the second follow-up visit of the cohort, i.e., 1,413 elderly aged 60 or over in 2006. Because it is an investigation on the consumption of medication, all the elderly included used some kind of drug on a regular basis in 2006. Thus, after the exclusion of 155 participants who did not use drugs regularly that year, the final sample of this analysis was of 1,258 elderly people. Figure 1 summarizes the composition of the study population.

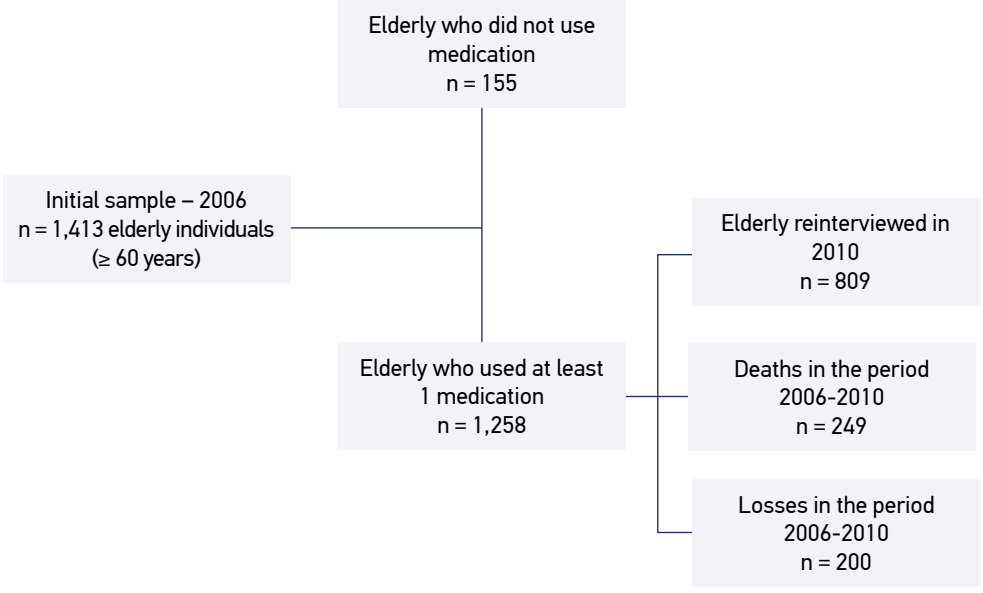


Figure 1. Composition of the sample in the follow-up period of the SABE Study (2006–2010).

Data were obtained through home interviews conducted by trained interviewers. The questionnaire used consisted of sections relating to living conditions and health status of the elderly. Physical data and anthropometric variables were collected by trained nutritionists, using duly calibrated equipment[16].

The SABE Study was approved by the Research Ethics Committee of the School of Public Health of Universidade de São Paulo. All participants signed an Informed Consent (IC). There are no conflicts of interest.

MEASUREMENTS

The use of drugs was determined by the following questions: "Can you show me the medicines that are currently using or taking" and "Can you tell me the name of the medicines that are using or taking?". The respondents were asked to show the packaging of medicines and their prescriptions, if any. The independent variable of interest was polypharmacy, defined as the use of five or more drugs.

The analyses were conducted using the independent sociodemographic and health variables. Demographic variables included were gender, age, education (years of schooling completed), per capita income (categorized into distribution thirds), and living arrangement (living alone or living with someone). Health variables that are part of the issue were primary health services provider (public or private), self-rated health (categorized as very good/good, regular, and bad/very bad), and the presence of self-reported chronic diseases (hypertension, diabetes, cardiovascular disease, cerebrovascular disease, osteoporosis and osteoarticular disease, and the total number of self-reported chronic diseases). The occurrence of hospital admissions in the last year and the score on the modified version of the Mini Mental State Examination (MMSE), validated for the SABE Study, were also included. This scale has 13 items (maximum score of 19 points) that are less dependent on education, and the cutoff point used for positive screening is 12 or less.

STATISTICAL ANALYSIS

For descriptive analysis, mean values and standard error were calculated for continuous variables, and the proportions for categorical variables were also calculated. Differences between groups were estimated by the Wald test for average equality and the Rao–Scott test, considering sample weights to the population estimates with population weights.

For survival analysis, all deaths in the period were seen as failure. The observation time used to estimate survival functions was the time interval between the 2006 interview and the 2010/2011 interviews for those who were monitored until the end of the period. In case

of death, the observation time was the time interval between the 2006 interview and the date of death. For those lost during follow-up (refusals, institutionalized, and not found), the observation time was half the time between the 2006 interview and the average period of the 2010/2011 interviews.

The survival functions were calculated using the Kaplan–Meier method, in which curves were estimated by grouping the elderly according to the variables selected for the study. The Log-rank test was used to compare the survival functions for each variable.

In order to assess the risk factors associated with death, the hazard ratios (HR) were calculated with 95% confidence intervals, according to the Cox proportional hazards model, including the independent variable of interest — polypharmacy (group reference: elderly who consumed one to four drugs) — and other sociodemographic and health variables mentioned above. The proportionality of the Cox model was verified based on the Schoenfeld residuals diagnostic test and through visual inspection of the curves $\ln(-\ln(S(t))) \times$ follow-up time.

The variables with $p < 0.20$ in the univariate Cox analysis for association with mortality were included in the multiple Cox model as covariates. After the estimation of the final model, the adjusted survival function was drawn according to the occurrence of polypharmacy.

The analyses were performed using the Stata® software, version 11 (ST module), taking into account the sample weights and inferences considering the effect of the design.

RESULTS

In 2006, in the baseline study, polypharmacy was found in 33% of the elderly, being more frequent among women than among men: 36.6 and 26.9%, respectively ($p = 0.010$). Polypharmacy was also more common in elderly aged over 75 years (41.3%) than in elderly aged 60–74 years (30.1%, $p = 0.002$) and in subjects with chronic diseases such as hypertension, diabetes, cardiovascular disease, cerebrovascular disease, and articular disease ($p < 0.001$). The average number of prevalent chronic diseases in the elderly who had polypharmacy at baseline was 2.4, while in the elderly who consumed between one and four drugs, the average was 1.4 ($p < 0.001$).

Table 1 shows the characteristics of the elderly according to their follow-up status at the end of the period between 2010 and 2011. The elderly who died in the meantime showed higher frequency of polypharmacy than the elderly group that was monitored up to the end the study ($p < 0.001$). Deaths were also more common in elderly men, older and presenting the chronic diseases mentioned. The occurrence of hospitalization in the year prior to the baseline interview was also higher in the group of patients who died.

The probability of survival after 5 years for patients with polypharmacy at baseline was 77.2%, while in individuals taking up to four medications, it was 85.5%. The survival curves during follow-up showed a significant difference ($p < 0.001$ in the Log-rank test).

Table 1. Distribution of the elderly according to sociodemographic and health variables at baseline and status at follow-up. SABE Study, São Paulo (2006–2010).

Variables	Elderly individuals in follow-up (%)	Death (%)	p-value
Number of medications used			< 0.001
1 – 4	68.0	53.1	
5 and more	32.0	46.9	
Sex			< 0.001
Male	33.9	48.1	
Female	66.1	51.9	
Age in years			< 0.001
60 – 74	80.4	39.3	
75 or more	19.6	60.7	
Education (years of study)			0.003
8 and over	15.3	25.0	
4 – 7	27.1	19.5	
1 – 3	38.2	41.4	
None	19.4	14.1	
Per capita income			0.079
1.º Tertile	30.2	37.7	
2.º Tertile	33.2	35.0	
3.º Tertile	36.6	27.3	
Living arrangements			
Lives alone	12.6	14.3	0.591
Lives with company	87.4	85.7	
Primary health services provider			0.499
Public	53.5	50.7	
Private	46.5	49.3	
Self-rated health			< 0.001
Very good/good	43.1	25.9	
Regular	48.3	54.5	
Bad/very bad	8.7	19.7	
Hypertension	69.5	64.9	0.333
Diabetes	22.5	30.6	0.04
Cardiovascular disease	24.1	36.2	0.003
Cerebrovascular disease	7.1	16.4	< 0.001
Osteoarticular disease	37.9	29.9	0.090
Number of chronic diseases – mean (SE)	1.7 (0.05)	2.0 (0.09)	0.018
Hospitalization in the last year			< 0.001
None	91.3	74.9	
One or more	8.7	25.1	
Score on the adapted MMSE* – mean (SE)	16.4 (0.15)	12.4 (0.53)	< 0.001

SE: mean, standard error; MMSE: Mini Mental State Examination.

The crude and adjusted Cox proportional hazards regression models are shown in Table 2. Polypharmacy remained a risk factor for death even after adjusting for other conditions associated with mortality, such as age, gender, income, chronic diseases, and hospitalization, with a 57% higher HR in comparison to those who consumed up to four drugs. The survival curve, adjusted after the final model (Figure 2), shows that the probability of death is greater (and proportional) in elderly patients with polypharmacy throughout the follow-up period, more markedly from the second year on.

DISCUSSION

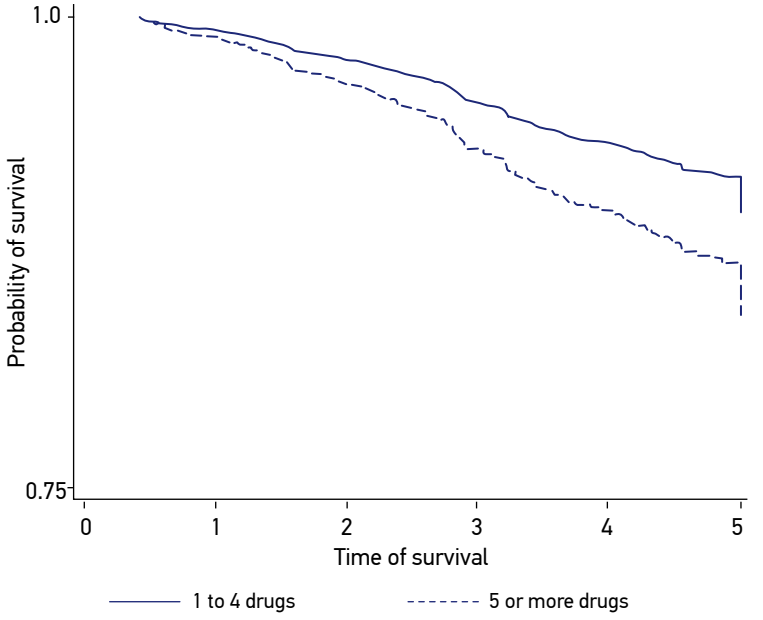
Polypharmacy proved to be an important risk factor for deaths in the 4-year follow-up period in elderly people, regardless of other factors associated with mortality such as age, gender, income, chronic diseases, and hospitalization. The HR was 57% higher compared to those who took up to four drugs.

Population-based studies conducted previously also found association between polypharmacy and mortality, although the comparison of the findings is hampered by methodological aspects. The definitions of polypharmacy, the ages of the elderly at baseline, the follow-up time, and the adjustments vary widely.

Table 2. Cox proportional hazards models for mortality in the period. SABE Study, São Paulo (2006–2010).

Variables	Crude analysis		Adjusted analysis	
	HR (95%CI)**	p-value	HR (95%CI)**	p-value
Polypharmacy*	1.84 (1.33–2.54)	< 0.001	1.57 (1.05–2.34)	0.026
Female	0.60 (0.43–0.83)	0.002	0.47 (0.33–0.66)	< 0.001
Age (years)	1.11 (1.09–1.13)	< 0.001	1.09 (1.06–1.11)	< 0.001
Per capita income				
1.º Tertile	1.00		1.00	
2.º Tertile	0.85 (0.58–1.25)	0.416	0.86 (0.57–1.28)	0.449
3.º Tertile	0.62 (0.41–0.96)	0.031	0.72 (0.45–1.67)	0.186
Diabetes	1.48 (1.03–2.11)	0.034	1.58 (0.95–2.63)	0.077
Cardiovascular disease	1.71 (1.22–2.39)	0.002	1.25 (0.80–1.94)	0.326
Cerebrovascular disease	2.19 (1.42–3.34)	< 0.001	1.01 (0.63–1.62)	0.966
Number of chronic diseases	1.22 (1.04–1.43)	0.014	0.87 (0.68–1.11)	0.259
Hospitalization in the last year	3.21 (2.2–4.70)	< 0.001	1.68 (1.10–2.57)	0.015
Score on the adapted MMSE	0.86 (0.84–0.89)	<0.001	0.92 (0.90–0.95)	<0.001

*Five drugs or more; **hazard ratio (95% confidence interval); Schoenfeld residuals diagnostic test: p = 0.117.



*Adjusted for sex, age, per capita income, presence of diabetes, cardiovascular disease, cerebrovascular disease, number of chronic diseases, hospitalization in the last year, and score on the adapted MMSE.

Figure 2. Adjusted survival* in the period according to the number of drugs used. SABE Study, São Paulo (2006–2010).

A cohort study in Finland assessed the association between polypharmacy and mortality among the elderly aged over 75 years, in a follow-up period divided into two 5-year phases, the first with an average follow-up of 3.62 years, and the second, 3.79 years. The authors considered polypharmacy as using six to nine drugs and excessive polypharmacy as ten or more drugs. The members of the group not exposed to polypharmacy, i.e., using five or less drugs, showed a higher survival rate. The mortality rate in the group with excessive polypharmacy was higher (55% in the first phase and 61% in the second phase) than in the group with polypharmacy (33 and 40%, respectively), while the group without polypharmacy has 27 and 23%, respectively. In the second phase of the study, there was an association between excessive polypharmacy and mortality (HR = 2.23) in the multivariate model, after adjusting for demographic variables and functional and cognitive status. However, there was no adjustment for comorbidity[8].

A study with Mexican-American elderly individuals aged 65–99 years, being monitored for 8 years, considered polypharmacy as the use of more than 4 drugs and found an association with mortality after adjustments, including comorbidities. The risk of mortality associated with polypharmacy was 27% higher among individuals exposed to polypharmacy[2].

In Australia, a cohort of about 4,000 men aged between 65 and 83 years was monitored for 4½ years. Polypharmacy, understood as the intake of five or more drugs, was used as an indicator of suboptimal drug use. Research has shown that the number of drugs used was independently associated with mortality (HR = 1.04), after the adjustment of comorbidities[1].

An 18-year cohort held with individuals aged over 65 years living in the UK demonstrated association between polypharmacy (consumption of five or more medications) and short-term mortality (the first 2 years) for female and male elderly individuals. This association remained, although attenuated, in the medium and long term for women, but became insignificant for men in the long term. The HR of the total period was 1.42 for men and 1.30 for women, after adjustments, including comorbidities[7].

Also in the UK, a follow-up period of 1 year with individuals aged 65 years or older living in the community or institutionalized observed positive association of mortality with the use of three drugs or more—the association increased with the number of drugs used. In comparison with the use of 0–2 drugs by the elderly in the community and the institutionalized elderly, respectively, the HR was 1.12 and 1.16 for the use of 3–5 drugs; HR = 1.48 and 1.34, respectively, for the use of 6–10 drugs; and HR = 2.32 and 1.59, respectively, for the use of 11 or more medications, after adjustments, including comorbidity[9].

An investigation carried out in eight European countries has shown that polypharmacy, considered as the use of ten drugs or more, is associated with increased mortality in institutionalized patients with cognitive impairment at the end of life, after a follow-up period of 1 year[10].

Polypharmacy has been linked to several negative consequences, particularly high costs with health, increased risk of adverse drug events, drug interactions, non-adherence to drug treatment, reduced functional capacity, and multiple geriatric syndromes[17]. In this sense, polypharmacy (six or more drugs) proved to be an important predictor of mortality in elderly Japanese patients (aged over 85 years) monitored for 1 year after discharge, even after adjusting for comorbidities. It has been argued that, since it is well established that polypharmacy increases the possibility of adverse drug events, such events might be involved in the mortality of the elderly subjects, since the risk and severity of events are directly proportional to the amount of drugs used and age[18].

In addition, studies show that elderly individuals who receive five or more drugs are three times more likely to get a PIM than those who use fewer drugs[19]. Also, adverse drug events resulting from inappropriate drug prescriptions can lead to increased hospitalizations and mortality[20].

Polypharmacy could also have a direct effect on mortality through the cumulative effect of multiple drugs in the elderly's kidney and liver systems, initiating a cascade of interactions in these individuals, who already suffer from multimorbidity[2].

This study's main limitation is the large number of losses in the follow-up period. Polypharmacy was less frequent in this group (26.9%), and, if the losses were considered,

estimates exposed here could be changed. However, cohort studies show this intrinsic limitation, especially those made with individuals living in communities, who often move or refuse to continue the follow-up. In the case of the elderly, there is a portion that is institutionalized or dies without the knowledge of researchers.

On the other hand, the strength of this study was that it contains a large representative sample of the population studied and is the only Brazilian study to evaluate the survival of elderly with polypharmacy. Still, as already mentioned, it was possible to adjust the analyses for several of the most prevalent diseases among the elderly, as well as the average number of chronic diseases, eliminating them as confounding factors and emphasizing the independent effect of polypharmacy as a risk factor.

CONCLUSION

In this study, polypharmacy was independently associated with mortality. Thus, the use of multiple medications should be carefully monitored, and especially in the older, male population, with lower scores on the adapted MMSE and with a history of hospitalization.

Seeking a balance between the benefits and risks of drug therapy is a challenge. Polypharmacy can be considered as iatrogenic when adverse events caused by drugs are not recognized as such, resulting in new prescriptions. Polypharmacy can also result from the unnecessary use through repeated prescriptions and lack of monitoring[8]. Reducing the number of prescription drugs, therefore, requires a multidisciplinary approach[21].

Thus, the results of this study reinforce the need to develop strategies to avoid or minimize negative outcomes related to polypharmacy, contributing to the security of the elderly in medication use.

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