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Artigo Original

Idosos frágeis não institucionalizados: há medicamentos associados a quedas? Um estudo caso-controle.

Non-institutionalized frail elderly: are there any medications associated with falls? A case-control study.

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RESUMO

Objetivo: Analisar a associação entre queda e o uso de medicamentos em idosos frágeis não institucionalizados. **Materiais e M**étodos: Trata-se de um estudo caso-controle realizado com usuários da Atenção Básica do Sistema Único de Saúde (SUS) na cidade de Divinópolis, interior de Minas Gerais, Brasil. Os casos eram idosos frágeis com queda autorreferida no último ano e os controles eram idosos frágeis sem relato de queda, pareados por sexo, idade e centro de saúde. A variável de desfecho foi a ocorrência de queda no último ano. As variáveis de exposição foram o uso de medicamentos por classe de medicamentos, o uso de terapia medicamentosa combinada, início e interrupção e ajuste de dose nos últimos 12 meses. A magnitude das associações foi estimada por Odds Ratio (OR). **Resultados:** Na análise univariada, o uso de medicamentos antianêmicos, antiinflamatórios, antiepilépticos e a suspensão e iniciação da medicação estiveram associados à queda. Após ajuste

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pelas demais variáveis de exposição e covariáveis, houve associação significativa entre quedas e uso de medicação antianêmica (OR = 6,10; IC95% 1,72 - 21,58). **Conclusão:** A queda de idosos frágeis não institucionalizados esteve associada ao uso de medicamentos antianêmicos, associação não descrita em outros estudos.

Palavras-Chave: Queda; Fragilidade; Idosos Frágeis; Medicações.

ABSTRACT

Objective: To analyze the association between falls and medication use in non-institutionalized frail elderly. **Method:** This is a case-control study that was conducted with users of Primary Care of the Unified (Public) Health System (SUS) in the city of Divinópolis, in the state of Minas Gerais, Brazil. The cases were frail elderly individuals with a self-reported fall in the last year, and the controls were frail elderly individuals with no report of falling, matched for gender, age and health centers. The outcome variable was fall occurrence in the last year. Exposure variables were medication use by medication class, use of combination medication therapy, initiation and cessation, and dose adjustment over the past 12 months. The magnitude of the associations was estimated by Odds Ratio (OR). **Results:** In the univariate analysis, the use of anti-anemic medication, anti-inflammatory medication, antiepileptics and medication cessation and initiation were associated with falling. After adjusting for the other exposure and covariate variables, there was a significant association between falls and use of anti-anemic medication (OR=6,10; 95% CI 1,72 – 21,58). **Conclusion:** A fall in non-institutionalized frail elderly individuals were associated with the use of anti-anemic medication, an association that has not been described in other studies.

Keywords: Fall; Frailty; Frail Elderly; Medications.

INTRODUCTION

Changes in the age profile of the world population with a decrease in birth and mortality rates have resulted in an aging population internationally. Estimates published by the United Nations indicate that the number of older people worldwide will grow significantly, from 901 million in 2015 to 1.4 billion in 2030 to over two billion in 2050[1]. The elderly population has an important characteristic that is its heterogeneity, which justifies the adoption of measures that support the identification of those considered fragile. The concept of frailty is related to older people at higher risk of developing negative outcomes, including falls and increased need for institutionalization[2,3,4].

The fall is a multifactorial event that represents the second leading cause of accidental death in the world, accounting for 646,000 deaths a year5. The World Health Organization (WHO) defines a fall as an event that causes a person to fall inadvertently to the ground, floor, or other lower level[6]. The frequency of its occurrence increases with age and the degree of frailty, in addition to the presence of other risk factors, such as medication use[7,8]. Several classes of medications are associated with increased risk of falls[9,10], including cardiovascular medication, benzodiazepines, antidepressants, antiepileptics, antipsychotics, antiparkinsons, opioids, and urological spasmolytics. These classes make up a specific list of medication associated with hip fractures in the elderly (FRIDs - fall-risk-increasing drugs)[9,11].

The relationship between falls and medication use in the elderly has been described in primary studies and systematic reviews[12,13,14,15]. These studies analyzed this association in different contexts, including older people living in the community setting[16,17], in long-term care facilities[18,19] and also in hospital settings[20,21]. Given this diversity of settings, the European Society of Geriatric Medicine (EuGMS) with the collaboration of its Special Interest Group on Pharmacology and the European Union of Medical Specialists (UEMS) stressed the importance of identifying the main confounders involved in studies and the precise definition of the study population with respect to the population's characteristics such as frailty[22].

In view of the scarcity of studies conducted with Brazilian and non-institutionalized frail elderly individuals, and investigating the association of medication use with the occurrence of falls, it is essential to conduct studies that assess the magnitude of this association, especially in view of clinical conditions that are common to this heterogeneous population. Given the above, the objective of this study was to analyze the association between falls and the use of medications in non-institutionalized frail elderly individuals.

MATERIAL AND METHODS

Study design

A paired case-control study was performed following the instructions established in the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) initiative[23].

Study location and information source

The study was conducted in the municipality of Divinópolis – Minas Gerais state, Brazil, which, according to the Brazilian Institute of Geography and Statistics (IBGE), has an estimated population of 238,230 inhabitants[24]. During the study period the municipality had 33 primary health care units.

The variables and covariates used to conduct the study were extracted from a secondary data source, the Computerized Health System (CHS) of the Unified (Public) Health System (SUS) of the municipality of Divinópolis. The data were extracted from the system and transferred to an Excel spreadsheet between the months of April 2016 to September 2017. All information contained in this data source was collected by primary care health professionals of the municipality during medical and/ or nursing routine consultation.

Study Population

Eligible to participate in the study were the elderly who are under the care of primary health care professionals, and who have systemic arterial hypertension (SAH) and/or diabetes mellitus (DM), classified as fragile, registered in the CHS from January 2011 to July 2015. Patients aged 60 years and over were considered elderly (following the definition of the United Nations (UN) 1982, and the National Policy of the Elderly 1994)[25, 26], and fragile being those who presented one or more situations according to the criteria used by the municipality, which are:

- Be over 80 years old.
- Being over 60 years with one of the following conditions: Polypathologies (≥ 5 diagnoses); Polypharmacy (≥ 5 medications/day; Partial or total immobility; Fecal or urinary incontinence; Postural instability (recurrent falls); Cognitive impairment (cognitive decline, dementia syndrome, depression, and delirium); Elderly with a history of frequent hospitalization and/or post discharge hospitalization; Elderly dependent in basic activities of daily living (BADL); and Family insufficiency: Elderly in socially vulnerable situations, both in families and institutionalized (aged care facilities - Instituição de Longa Permanência para Idosos – ILPI)[27].

Criteria for case definition and control selection

The cases were considered frail elderly individuals who self-reported, at the time of the medical or nursing routine consultation, falling in the last year. Controls were selected from the frail elderly who reported no fall in the previous year, matched for gender, age (range of about five years) and health centers Pairing was performed using the ratio 1 case: 1 control[6,7].

Outcome and exposure variables

The variable outcome was the self-reported occurrence of a fall within the preceding 12 months. Exposure variables were: I - Medication use (for identification of medication use by the frail elderly individuals, the medication dispensed to the participants before the fall reporting year was considered. These medications were classified up to the fifth level of the Anatomical Therapeutic Chemical classification (ATC)[28]. No prescription medication taken from private or non-primary pharmacies were evaluated). II - Initiation of medications (medications that were first prescribed and dispensed within the 12-month period preceding the fall outcome). III - Cessation of medication (medications whose use was discontinued within 12 months prior to the fall outcome. To be considered a cessation, the suspension of dispensation of this medication must have occurred for at least three consecutive months). IV - Dose adjustment (dose adjustment was considered to be the increase or decrease of the daily dose of medications). V - Combined medication therapy, which are combinations of medication classes in the study population described and recommended to patients with SAH and/or DM by clinical guidelines[29,30,31,32].

1ª – Medication used in diabetes (A10) + medication acting on the renin-angiotensin system (C09)

2ª – Medications used in diabetes (A10) + renin-angiotensin system medication (C09) + calcium channel blockers (CCB) (C08)

3ª – Medication used in diabetes (A10) + renin-angiotensin system medication (C09) + CCB (C08) + diuretics (C03)

4ª – Medication used in diabetes (A10) + lipid modifying agents (C10) + antithrombotic agents (B01) + renin-angiotensin system medication (C09).

Covariates

The covariates were categorized into sociodemographic (living alone and skin color) and clinical (presence of chronic conditions and diseases such as SAH and DM, cardiovascular risk classification, number of cardiovascular risk factors, physical inactivity, stress, urinary incontinence, fecal incontinence, alcoholism, and smoking), referring to the WHO model of risk factors for falling in the elderly[6].

Data analysis

A descriptive analysis of categorical variables and a measure of central tendency of continuous variables was performed. Conditional logistic regression was performed by analyzing the sociodemographic and clinical characteristics in order to compare the two groups and show the quality of matching. All analyses were performed considering a significance level of 95%. Data normality was assessed by the Kolmogorov Smirnov test. To analyze the magnitude of the association between the variable outcome and the exposure variables, the paired Odds Ratio (OR) was estimated using univariate conditional logistic regression[33].

Univariate analysis included pharmacological classes that presented a frequency of use of more than 5 % in the case group and/or presented biological and clinical plausibility of the association with the outcome[7,9,10].

In order to eliminate the influence of some confounders on the magnitude of the association, two multivariate analysis models were performed using multivariate conditional logistic regression. First, Model 1 was performed, which included all variables that obtained p value ≤ 0.20 in the univariate analysis. Model 2 was then performed, where all Model 1 variables were adjusted by sociodemographic and clinical covariates. To perform the analyses, EpiInfo version 7.2.2.2 software was used.

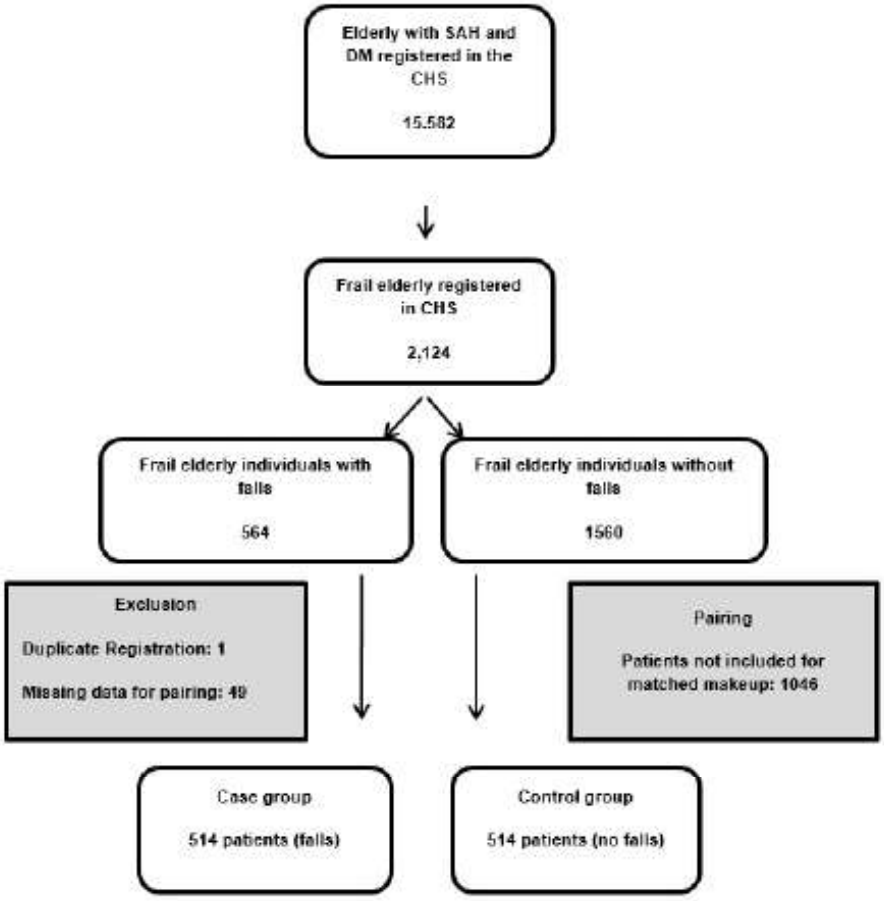
Ethical aspects

This study was approved by the Ethics Committee in research involving human beings of the Federal University of São João del Rei (UFSJ) (number CAAE 53104416.9.0000.5545, opinion number 1.464.908) and by the Divinópolis Municipal Health Secretariat.

RESULTS

A total of 15,582 elderly people with SAH and/or DM were identified, of which 2,124 (13.6%) were considered frail. From this total, 564 cases that fell in the last year were selected. Fifty (8.9%) individuals were excluded (49 for lack of available control and one for duplicate registration), resulting in a final sample of 514 elderly in each group (Figure 1)[34].

Figure 1. Diagram of selection and matching of frail elderly participants in the case-control study (n = 1,028) (34).



The median age of the study participants was 71 years (interquartile range 66 – 76.5 years). Regarding the clinical characteristics of the participants, SAH was the most common clinical condition. Additionally, more than half had five or more risk factors for cardiovascular disease and were classified as patients with high cardiovascular risk, according to the criteria adopted by the municipality (Table 1).

Table 1. Descriptive analysis of sociodemographic and clinical characteristics of the case (fall) group and the control (no fall) group of frail elderly individuals.

Sociodemographic characteristics		No fall n (%) n=514	Fall n (%) n= 514	Total (%) n=1,028	p-value*
Gender	Female	381 (74.1)	381 (74.1)	762 (74.1)	1.0000
	Male	133 (25.9)	133 (25.9)	266 (25.9)	
Age (years)	60 to 64	94(18.3)	97 (18.9)	191 (18.6)	0.5906
	65 to 69	123 (23.9)	125 (24.3)	248 (24.1)	0.2855
	70 to 74	121 (23.5)	121 (23.5)	242 (23.5)	0.1568
	75 to 79	101 (19.6)	88 (17.1)	189 (18.4)	0.6760
	≥ 80	75 (14.6)	83 (16.1)	158 (15.4)	
Skin color	White	292 (56.8)	295 (57.4)	587 (57.1)	0.8429
	Not white	222 (43.2)	219 (42.6)	441 (42.9)	
Lives alone	No	431 (83.9)	422 (82.1)	853 (83.0)	0.4587
	Yes	83 (16.1)	92 (14.9)	175 (17.0)	
Clinical characteristics					
Arterial hypertension		491 (95,5)	491 (95,5)	982 (95,5)	1,0000
Diabetes Mellitus		255 (49,6)	260 (50,6)	515 (50,1)	0,7474
Cardiovascular risk classification	Low/Moderate	202 (39,4)	184 (35,9)	386 (37,6)	0,2387
	High	311 (60,6)	329 (64,1)	640 (62,3)	
Alcoholism		17 (3,3)	19 (3,7)	36 (3,5)	0,7393
Smoker		59 (11,5)	46 (8,9)	105 (10,2)	0,1837
Sedentary		323 (62,8)	334 (64,9)	657 (63,9)	0,4754
Stress		146 (28,4)	166 (32,3)	312 (30,4)	0,1475
Urinary incontinence		99 (19,3)	151 (29,4)	250 (24,3)	0,0002
Clinical characteristics		No fall n (%) n=514	Fall n (%) n= 514	Total (%) n=1,028	p-value*
Fecal incontinence		44 (8,6)	38 (7,4)	82 (7,9)	0,4810
Number of cardiovascular risk factors	0-4	228 (44,4)	195 (37,9)	423 (41,2)	0,0230
	≥5	286 (55,6)	319 (62,1)	605 (58,9)	

*: Conditional Logistic Regression

The medications working in the cardiovascular system were those with the highest frequency of use among the study participants, of which medications acting on the renin-angiotensin system were the most used (Table 2).

Table 2. Univariate analysis of medication use by the Anatomical Therapeutic Chemical (ATC) classification between the case (fall) group and the control (no fall) group to estimate odds ratio (OR) among frail elderly individuals.

ATC classification medication	No fall n (%) n=514	Fall n (%) n=514	OR (IC 95%)	p-value
Stomatological preparations(A01)	5 (1,0)	8 (1,6)		
Medication for acidity-related disorders (A02)	126 (24,5)	135 (26,3)	1,09 (0,83-1,44)	0,5280
Medicines for disorders of gastrointestinal function (A03)	1 (0,2)	2 (4,0)	2,00 (0,18-22,05)	0,5715
Antidiarrheals, Intestinal Anti-Inflammatory Agents, Anti-Infective Agents (A07)	5 (1,0)	13 (2,5)		
Medication Used In Diabetes (A10)	190 (37,0)	220 (42,8)	1,28 (0,99-1,64)	0,0564
Mineral Supplement (A12)	3 (0,6)	2 (0,4)		
Antithrombotic Agents (B01)	190 (37,0)	211 (41,1)	1,19 (0,92-1,53)	0,1813
Anti-anemics (B03)	3 (0,6)	19 (3,7)	6,33 (1,87-21,38)	0,0030
Cardiac therapy (C01)	50 (9,7)	60 (11,7)	1,26 (0,83-1,93)	0,2820
Antihypertensives (C02)	63 (22,3)	74 (14,4)	1,20 (0,84-1,70)	0,3232
Diuretics (C03)	292 (56,8)	318 (61,9)	1,23 (0,96-1,57)	0,1048
Beta blockers (C07)	152 (29,6)	178 (34,6)	1,28 (0,97-1,67)	0,0762
Calcium channel blockers (C08)	126 (24,5)	139 (27,0)	1,13 (0,86-1,48)	0,3740
Renin-angiotensin System Medication (C09)	312 (60,7)	334 (65,0)	1,21 (0,94-1,58)	0,1457
Lipid Modifying Agents (C10)	222 (43,2)	235 (45,7)	1,10 (0,87-1,40)	0,4251
Antihistamines (D04)	1 (0,2)	2 (0,4)		
Dermatological corticosteroids (D07)	8 (1,6)	9 (1,8)		
Antibiotic/gynecological antifungal (G01)	3 (0,6)	4 (0,8)		
Corticosteroids for systemic use (H02)	10 (1,9)	8 (1,6)		
Thyroid Therapy (H03)	86 (16,7)	80 (15,6)	0,91 (0,65-1,28)	0,6046
Antibiotic for systemic use (J01)	27 (5,3)	34 (6,6)	1,28 (0,76-2,16)	0,3551
Antifungal for systemic use (J02)	4 (0,8)	7 (1,4)		
Anti-inflammatories (M01)	36 (7,0)	55 (10,7)	1,76 (1,07-2,88)	0,0240
Medication for treatment of bone diseases (M05)	21 (4,1)	28 (5,4)	1,33 (0,76-2,35)	0,3190
Analgesics (N02)	56 (10,9)	49 (9,5)	0,86 (0,58-1,29)	0,4738
Antiepileptics (N03)	61 (11,9)	84 (16,3)	1,51 (1,04-2,20)	0,0317
Antiparkinsons (N04)	1 (0,2)	3 (0,6)	2,99 (0,31-28,74)	0,3421
Antipsychotic/Anxiolytics (N05)	65 (12,6)	67 (13,0)	1,04 (0,72-1,49)	0,8527
Antidepressants (N06)	55 (10,7)	69 (13,4)	1,30 (0,89-1,90)	0,1792
Anthelmintics (P02)	8 (1,6)	13 (2,5)		
Medication for obstructive airway diseases (R03)	23 (4,5)	20 (3,9)	0,86 (0,47-1,60)	0,6403
Antihistamines for systemic use (R06)	13 (2,5)	19 (3,7)		

OR (95% CI): Odds Ratio paired with 95% confidence interval

In univariate conditional logistic regression, anti-anemic medication (B03) (OR = 6.33; 95 % CI = 1.87-21.38), anti-inflammatory medication (M01) (OR = 1.76; 95 % CI = 1.07 -2.88) and antiepileptics (NO3) (OR = 1.51; 95 % CI = 1.04-2.20) had a significant association (Table 2). Among the evaluated medication combinations, there was a significant association with the fall with concomitant use of medication used in DM and medication acting on the renin-angiotensin system (A10 + C09) and also the combined use of medication used in DM, medication acting on the renin-angiotensin system, calcium channel blockers and diuretics (A10 + C09 + C08 + C03) (Table 3). Additionally, there was an association between falls and the initiation or cessation of medications (Table 3).

Table 3. Univariate analysis of the use of Combined Medication Therapy, of Dose Adjustment, Cessation of Medication and Initiation of Medication to estimate odds ratios (OR) among frail elderly.

Combined Medication Therapy	**n=1028 (%)**	**OR(IC 95%)**	**p-value**
1ª Diabetes Medication (A10) + renin-angiotensin system medication (C09)	262 (25,5)	1,35 (1,02-1,79)	0,0346
2ª Diabetes Medication (A10) + renin-angiotensin system medication (C09) + CCB (C08)	96 (9,3)	1,41 (0,94-2,13)	0,1006
3ª Diabetes Medication (A10) + renin-angiotensin system medication (C09) + CCB (C08) + Diuretics (C03)	66 (6,4)	1,67 (1,00-2,76)	0,0479
4ª Diabetes Medication (A10) + Lipid Modifying Agents (C10) + Antithrombotic Agents (B01) + Renin-Angiotensin System Medication (C09)	75 (7,3)	1,38 (0,86-2,22)	0,1873
Dose adjustment, Cessation of Medication and Initiation of Medication			
Dose adjustment	148 (14,4)	1,23 (0,85-1,76)	0,2718
Initiation of medication	840 (81,7)	1,49 (1,06-2,09)	0,0196
Cessation of medication	582 (56,6)	1,68 (1,30-2,17)	0,0001

CCB: Calcium channel blockers.

After performing Model 1 of the multivariate analysis, where all variables with p-value ≤ 0.20 were inserted, the following variables maintained their association with the variable outcome: the medications used in anemia (B03) (OR = 5.42; 95 % CI 1.57-18.76 and p-value = 0.0076), and medication exclusion (OR = 1.40; 95 % CI 1.04-1.89 and p-value equal to 0.0248). In Model 2, where all Model 1 variables were adjusted for sociodemographic and clinical covariates, only the class of medication used in anemia (B03) maintained a significant association with the outcome (OR = 6.10; 95 % CI 1.72 -21.58 and p-value equal to 0.0051) (Table 4).

Table 4. Multivariate analysis considering medication use by Anatomical Therapeutic Chemical (ATC) classification, use of combined medication therapy, medication exclusion, medication inclusion, and clinical and sociodemographic covariates to estimate odds ratios (OR) among the frail elderly.

	Model 1	p-value	Model 2	p-value
Medication used in Diabetes (A10)	1,13 (0,73-1,75)	0,5861	1,14 (0,72-1,81)	0,5644
Antithrombotic Agents (B01)	1,07 (080-1,43)	0,6442	1,03 (0,77-1,39)	0,8380
Anti-anemics (B03)	5,42 (1,57-18,76)	0,0076	6,10 (1,72-21,58)	0,0051
Diuretics (C03)	1,09 (0,83-1,45)	0,5201	1,11 (0,83-1,49)	0,4801
Beta blockers (C07)	1,18 (0,87-1,59)	0,2808	1,18 (0,86-1,61)	0,3004
Medication acting on the renin-angiotensin system (C09)	0,92 (0,64-1,31)	0,6394	0,99 (0,68-1,46)	0,9748
Anti-Inflammatories (M01)	1,50 (0,90-2,53)	0,1224	1,46 (0,86-2,48)	0,1654
Antiepileptics (N03)	1,36 (0,91-2,04)	0,1363	1,41 (0,92-2,16)	0,1138
Antidepressants (N06)	1,07 (0,72-1,62)	0,7233	1,11 (0,73-1,68)	0,6356
Initiation of medication	1,05 (0,72-1,56)	0,7867	1,07 (0,72-1,60)	0,7385
Cessation of medication	1,40 (1,04-1,89)	0,0248	1,29 (0,94-1,78)	0,1093
1ª A10 + C09	1,14 (0,64-205)	0,6540	1,18 (0,64-2,17)	0,6036
2ª A10 + C09 + C08	1,03 (0,46-2,32)	0,9441	1,05 (0,44-2,51)	0,9094
3ª A10 + C09 + C08 + C03	1,35 (0,52-3,50)	0,5358	1,26 (0,46-3,45)	0,6555
4ª A10 + C10 + B01 + C09	0,93 (0,51-1,71)	0,8150	0,89 (0,47-1,67)	0,7168

Model 1: OR adjusted for all variables with p≤ 0.20

Model 2: Model 1 adjusted for sociodemographic (skin color and living alone) and clinical covariates (Systemic Arterial Hypertension (SAH), Diabetes Mellitus (DM), cardiovascular risk classification, Alcoholism, Smoking, Sedentary lifestyle, Stress, Urinary incontinence, Fecal incontinence, Amount of cardiovascular risk factors).

DISCUSSION

Anti-anemic (B03) were the only drugs presenting a significant independent association with fall, even after being adjusted for sociodemographic and clinical conditions in the multivariate analysis. Reardon et al (2012)[35] also investigated B03 class (such as folic acid and iron) in elderly residents in a rest home and showed a positive association of fall and lower levels of hemoglobin. However they did not found association of anti-anemic drugs with the risk of fall. In this sense, knowing that a) medication is an pointer (proxy) of the disease itself, b) anemia is a common medical condition in the elderly, being associated with several negative health outcomes (fragility, disability, muscle weakness and falls); therefore, the association found may reflect the presence of the disease itself, and not a medicine adverse event[36,37]. It is also worth noting the low frequency of drug use by participants, and the wide confidence interval presented[33].

Menawhile, in the univariate analysis, the association anti-inflammatory and antiepileptic drugs with a fall, corroborated the results of the meta-analysis conducted by Bloch et al. (2013)[38]. That observed a significant estimate of OR with these classes of drugs, among others. However, these estimates were grouped only in unadjusted results and, therefore, vulnerable to bias. In the meta-analysis carried out by Seppala et al. (2019)[39], the association of antiepileptics with fall was present even after adjusted. In the present study, the adjustment influenced the strength of these two classes of drugs association, probably due to the strength of the association of the other variables[39].

When testing the combinations of classes, it was shown that the joint use of drugs used to treat DM and drugs used to control blood pressure was associated with a drop in two of the analyzed combinations, but this association was not maintained in any of the models multivariate analysis, which may have happened due to the strength of the association of other factors, such as the clinical conditions presented by the study participants. Approaching the association of the use of classes of drugs related to falls independently, without approaching therapeutic combinations was the objective of studies such as Huang and collaborators (2012)[7], however few studies have focused on drug combination therapy, where the greater the number of classes of drugs in use, the greater the incidence and the association with falls[40,41,42].

In the present study, the association of fall with drug therapy initiation or cessation was not maintained after the final adjustment. Gillespie et al (2009), Poliender et al (2016) and Hamza et al (2019)[43,44,45] showed benefits of FRIDs withdrawal in the pharmacotherapy of elderly patients and the risk of falling, with a decrease in its incidence and possible consequences. Regarding the initiation of new drugs, a study conducted by Kahlaee et al (2018)[12] showed that the initiation of treatment with antihypertensive drugs may contribute to a fall in susceptible elderly people, quite possibly due to substantial drops in blood pressure common at the beginning of treatment. The lack of association between falls and initiation / cessation of medication in the therapeutic plan, in the multivariate analysis models, is probably explained by the fact that it was not possible to independently assess who had an initiation or cessation, and the same participant may have had both[34].

Among the limitations of the study, it is important to highlight: a) - the fall record was self-reported by the elderly, and there may be a memory bias; b) - the failure to address self-medication and the use of drugs obtained outside SUS public primary care services; c) - do not consider the presence of some clinical conditions, this is due to the lack of this information in the patient's records or due to the lack of completion by primary care health professionals. In this sense, prospective studies aiming to assess the influence of all possible risk factors for falls in frail elderly people is necessary in order to try to elucidate the effect of the use of medications and the presence of clinical conditions on the risk of falls in this population.

Considering the potential of this study, some observations should be analyzed when studies are carried out with the objective of investigating the association of falls with the use of medications, such as the study design and the inherent biases, the studied population and other confounding factors that can contribute to overestimate or underestimate the association[21]. For example, the homogeneity of the population is an important factor in obtaining accurate estimates. In this sense, the population of our study was composed only of elderly people with comorbidities, classified as fragile and living in community, which brought more robustness and quality to our analyzes. To date, no other study investigated the association of the use of medications with the occurrence of falls in frail elderly non-institutionalized people. Finally, methodological robustness stands out, which manages to eliminate some confounders common to the outcome, in addition to the pairing used.

CONCLUSION

The use of anti-anemic by frail non-institutionalized elderly is associated with falls. On the other hand, the other pharmacological classes and the use of drug combinations, the inclusion, exclusion of drugs and dose adjustment did not present a significant association with the outcome after a final analysis adjusted by sociodemographic and clinical covariates.

The results show that there is a need for further longitudinal investigations, using primary sources of information to investigate the influence of other risk factors for falls, including the presence of other clinical conditions presented by the elderly, as the medication is an indicator (proxy) of the presence of the disease, so it is important to investigate the influence of both factors on the fall outcome.

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Contributions

FRB: Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; Drafting the work or revising it critically for important intellectual content; Final approval of the version to be published; Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

TBE: Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; Final approval of the version to be published; Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

CS: Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; Drafting the work or revising it critically for important intellectual content; Final approval of the version to be published; Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

GMR: Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; Final approval of the version to be published; Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

CS2: Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; Final approval of the version to be published; Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

YCM: Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; Final approval of the version to be published; Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

LRA: Drafting the work or revising it critically for important intellectual content; Final approval of the version to be published; Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

TMR: Drafting the work or revising it critically for important intellectual content; Final approval of the version to be published; Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved AOB: Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; Drafting the work or revising it critically for important intellectual content; Final approval of the version to be published; Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declaration of Interest

No conflict of interest.

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