The association between polypharmacy and falls and the role of fall-risk-increasing drugs.

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ABSTRACT

Background: Falling in older persons is a challenging health problem due to their common occurrence and the associated severity. Medication usage, particularly polypharmacy (using four or more medications simultaneously), is identified as a substantial contributor to falls. Importantly, the correlation between polypharmacy and falls may be more associated with the use of fall risk-increasing drugs (FRIDs) than with polypharmacy alone.

Aim: The main objective was to investigate the association between polypharmacy and falls and the impact of medications that increase the risk of falls (FRIDs).

Methods: To confirm the association between falls and polypharmacy, data from the AD*F*ICE_IT cohort were utilized. This extensive database comprises harmonized data from two Dutch databases and one German database. From this dataset, 5882 participants were eligible for this study. Polypharmacy was characterized by the consumption of four or more medications daily. We used Cox regression analysis to quantify the hazard ratios (HR) associated with the use of polypharmacy and the time until the first fall within a one-year follow-up period. The primary analysis aimed to investigate the association between polypharmacy and falls and the role of FRIDs.

Results: Patients using polypharmacy had an HR of 1.14 [1.03-1.26]. After correcting for probable various factors excluding the use of FRIDs, the association changed, and the HR became HR 1.39 [1.01-1.29]. Following correction for all probable various factors including FRIDs, the association was attenuated, and the HR became 1.03 [0.89-1.18].

Conclusion: We found that nearly a quarter of the total population used four or more medications. However, no significant association was found between the use of polypharmacy and falls over a one-year follow-up period. The correlation was influenced by different confounding factors and especially by the use of FRIDs. Further investigation with a vulnerable population and complete data on medication adherence is needed. If there is study involving an intervention design for medication review, it would be advisable to give more consideration to the role of FRIDs.

Keywords: polypharmacy, falls, older persons, cox-regression.

INTRODUCTION

Falls in older adults present a significant health challenge due to their widespread prevalence and the serious consequences associated with such incidents. The global number of individuals aged 60 and above is increasing. In the year 2019, the population within this age group was approximated to be one billion individuals, with projections indicating an increase to nearly 1.4

billion by 2030. Population aging is expected to continue growing, and it is estimated that the population of this age group will be about two billion by 2050 [1]. This demographic shift is closely associated with an uptick in fall incidents, particularly among those aged 80 and above, underscoring the critical challenge posed by the associated between population ageing and falls [2].

Accidental fatalities among individuals aged 65 years or older are predominantly attributed to falls [3]. Falling can lead to fractures. For example, 1% of falls lead to hip fractures and 90% of hip fractures are caused by falls. Moreover, instances of falls can result in hemorrhaging, diminished functional capacity, and an augmented utilization of healthcare [4], [5]. Falling is a difficult problem because the result of falling cannot only causing injury. Falls without injuries can lead to—heightened functional deterioration, social isolation, increased levels of anxiety and depression, and elevated healthcare utilization [6].

Falling is a multifactorial problem [7]. Many reasons for falling have been identified, including factors that come from within the person (intrinsic) and factors from the surroundings (extrinsic). Intrinsic factors such as advanced age, chronic diseases, muscle weakness, gait and balance issues. Extrinsic factors typically encompass potential environmental risks, activities with inherent dangers and the utilization of medications [8]. There are certain types of medications that increase the risk of falls. These medications are called fall risk increasing medications (FRIDs). A total of thirteen types have been defined according to the STOPPFall criteria, which were published in 2021 to support practitioners in selecting this type of medications [9].

Additionally, the concurrent and long-term usage of four or more medications (polypharmacy) was associated with an elevated risk of falls [10-11]. Seppala et al, found that polypharmacy was linked to an increased fall risk. It is not clear whether polypharmacy in itself leads to falls, for instance due to the presence of drug-drug interactions, or if individuals with polypharmacy use more FRIDs, resulting in a higher risk of falls [12]. In the systematic review, most of the existing studies failed to conduct a multivariate analysis and inadequately considered the impact of Fall-Risk-Increasing Drugs (FRIDs).

In a recent nationwide nested case-control study of Morin et al, a clear correlation was identified between the use of multiple medications and the likelihood of falls resulting in injury. This association significantly diminished when additional factors, such as medications that increase the risk of falls and the presence of multiple chronic health conditions, were considered [13]. Laflamme et al. conducted a study to determine whether the quantity or the specific types of medications play a crucial role in fall injuries leading to hospitalizations. They found that both a larger and smaller quantity of medications can influence the risk of falls even after adjustment for FRIDs [14].

Therefore, the main aim of this prospective cohort study is to assess how polypharmacy contributes to the occurrence of falls and to investigate whether the association is influenced by the utilization of FRIDs.

The current recommendation for polypharmacy in older individuals in the Netherlands is to conduct a medication review for patients at an increased risk for medication-related problems, such as those aged seventy-five and above who use ten medications or more. Perhaps, if an association between polypharmacy and falls is found, it might be beneficial to conduct medication review for patients with polypharmacy using four or more medications to reduce the increased risk of falls. If the heightened risk of falls is linked to the utilization of FRIDs, it is advisable to pay more attention to the specific use of FRID medications instead of focusing only on polypharmacy.

METHODS

Study population

Data was used from the harmonized AD*F*ICE_IT cohort [15]. The AD*F*ICE_IT cohort dataset is comprised of five cohort studies, three cohorts compiled prospective data on fall incidents and these three were included for the current study.

The LASA (Longitudinal Aging Study Amsterdam) wave C project was a continuous cohort study that investigated the factors and impacts of physical, cognitive, emotional, and social well-being in elderly individuals within the Netherlands. The data collection began 1992 and involved a randomly selected sample of individuals aged 55 years to 85 years. This sampling process employed a stratified approach based on age, gender, urbanization level, and predicted 5-year mortality rate. For analyses, data from wave C (1995/1996) was utilized [16].

The B-PROOF (B-vitamins for the Prevention Of Osteoporotic Fractures) study, conducted in the Netherlands, was a multicenter trial that employed a randomized, double-blind, placebo-controlled design. It focused on persons aged 65 and older with heightened homocysteine levels and included them between the period 2008 to 2011. The primary objective of this study was to investigate the effectiveness of vitamin B12 and folic acid in preventing osteoporotic fractures. In total, 2919 participants were included in this study [17].

The ActiFE Ulm (Activity and Function in the Elderly in Ulm) study, was conducted in Germany. The participants were form the larger areas of Ulm, Neu-Ulm, and an Alb-Donau-Kreis. It involved a random selection of 1500 individuals aged 65 years to 90 years. The recruitment phase spanned from March 2009 to April 2010. This study aims to examine physical activity and confirm the association between physical activity and cognitive function, medication, subjective health, and social context [18].

The inclusion criteria in our study were individuals who had medication information available. Exclusion criteria included individuals who had no information on the use of medication.

Ethics and informed consent

The three studies were conducted after receiving approval from their respective ethics committees, and participants from all cohort studies had provided informed consent [16-18].

Outcome

The primary outcome of the study was the time it took for participants to experience their first fall within a 12-month observation period. The characteristic of fall was a change in position resulting in lower level on the ground. The participants received a calendar and were asked to record any incidents of falls every week over a period of one year. The participants were required to submit their fall calendars to the study center every three months. In cases where the calendar was not returned or the data were incomplete, the participants were contacted by telephone [15-16]

Exposure

Drug exposure variables at the initial recruitment phase were categorized using Anatomical Therapeutic Classification (ATC) codes [19]. There was no standard definition for describing polypharmacy; therefore, we looked at the most studies that investigated the association between polypharmacy and falls. In most studies, the cutoff point for polypharmacy was the use of four or more different medication, thus this criterion was adopted. The use of FRIDs were also taken into account. To study the used of FRIDs medications, the types of FRIDs were examined based on the Screening Tool of Older Persons Prescriptions in Older Adults with High Fall Risk (STOPPFall). The following types of FRIDs were included in the

analysis: opioids, antipsychotics, antihistamine, antidepressant, vasodilators, various diuretics, alpha-blocker antagonists used in begin prostatic hypertrophy, medications with anticholinergic cognitive burden scale 3, benzodiazepines, antiepileptic, antiadrenergic antihypertension, medications for incontinence, medication for urinary frequency and benzodiazepine-related medications [9].

The collection of information regarding medication usage occurred in every study. In LASA- wave C, participants were asked to provide containers or packages of prescription medications that they had used in the fourteen days preceding their participation in the study. In the B-PROOF cohort, information about medication usage was collected through a survey. The patients recorded the information about medications themselves. For the ActiFE-Ulm study, barcodes were scanned from all pharmaceutical items found in participants home and consumed during the study. Articles without a barcode were registered manually. The barcode process minimized errors, providing accurate information.

Covariates

The main factors that played a role in the various cohort studies included gender, age, marital status, alcohol intake, tobacco usage, and body mass index. The presence of chronic conditions (cancer, diabetes, arthritis, cardiovascular diseases: arrhythmia, angina pectoris, myocardial infarction, heart failure) was determined through questionnaires. Additionally, depressive symptoms, blood pressure, and cognitive function were measured. The measurement of depression varied among different cohorts based on different methods. The LASA study evaluated depression by employing the Center for Epidemiologic Studies Depression Scale (CES-D). In the ActiFE-Ulm study, the Hospital Anxiety and Depression Scale HADS-Depression was utilized. In the B-PROOF study, the Geriatric Depression Scale (GDS-score) was employed. The education level was also measured in various studies based on the number of years participants dedicated to learning. Hypertension was also assessed in various studies. In LASA, participants themselves reported chronic conditions. If a patient indicated having higher blood pressure, further questions were asked about medications and whether they were being treated by a doctor. In Actif-Ulm, patients were asked about hypertension during baseline recording. In B-PROOF, participants were also asked if they had higher blood pressure, followed by inquiries about medication. If a systolic blood pressure of 140 mmHG and/or a diastolic blood pressure higher than 90 mmHg was observed, this was considered hypertension. The Mini-Mental-State Examination (MMSE) was used to assess cognitive function for participation [16-18].

Statistical analysis

Baseline characteristics (table 1) were assessed for the total group as well as for users of polypharmacy and those not using polypharmacy, separately.

Categorical variables were subjected to a Chi-square test to compare the groups, while continuous variables underwent a t-test. When a continuous variable displayed a non-normal distribution, an alternative statistical approach was employed, namely the Mann-Whitney U-test.

In this study, we conducted an analysis of the time until the first occurrence of falls using Cox regression. We used Cox regression analysis to quantify hazard ratios (HR) related to the use of polypharmacy and the time to the first fall within a one-year follow-up period, utilizing various model. In model zero, we examined the association between falls and the use of polypharmacy. Subsequently, in Model one (not corrected for the use of FRIDs), we corrected for age, gender, body mass index, education status, the use of alcohol, smoking, diabetes, and cardiovascular diseases: angina pectoris,

myocardial infarction, heart failure. In the second model (main model), all confounders were adjusted and the use of FRIDs. The three diseases: cancer, arthritis and arrhythmia contain a lot of missing data. Therefore, they were not included in the main analysis. To control for the influence of diseases with high missing data, we performed a sensitivity analysis to study the effects of the three diseases on the hazard ratio outcome. The Statistical Packages for Social Sciences (IBM-SPSS, version 28) was used for statistical analysis. The p-value was calculated, and if the value is less than 0.05, it indicated a statistically significant difference between the two groups.

RESULTS

Study population characteristics

From the cohort studies (LASA-wave C, B-PROOF, ActiFE-Ulm), a total of 7532 participants were initially identified (Figure 1). However, after applying the inclusion criteria, we included a total of 5882 individuals, details can be found in the flow chart. The characteristics of the patients are presented in table 1. The analysis indicated a statistically significant difference between the group using polypharmacy and the other group not using polypharmacy across various parameters, except for gender.

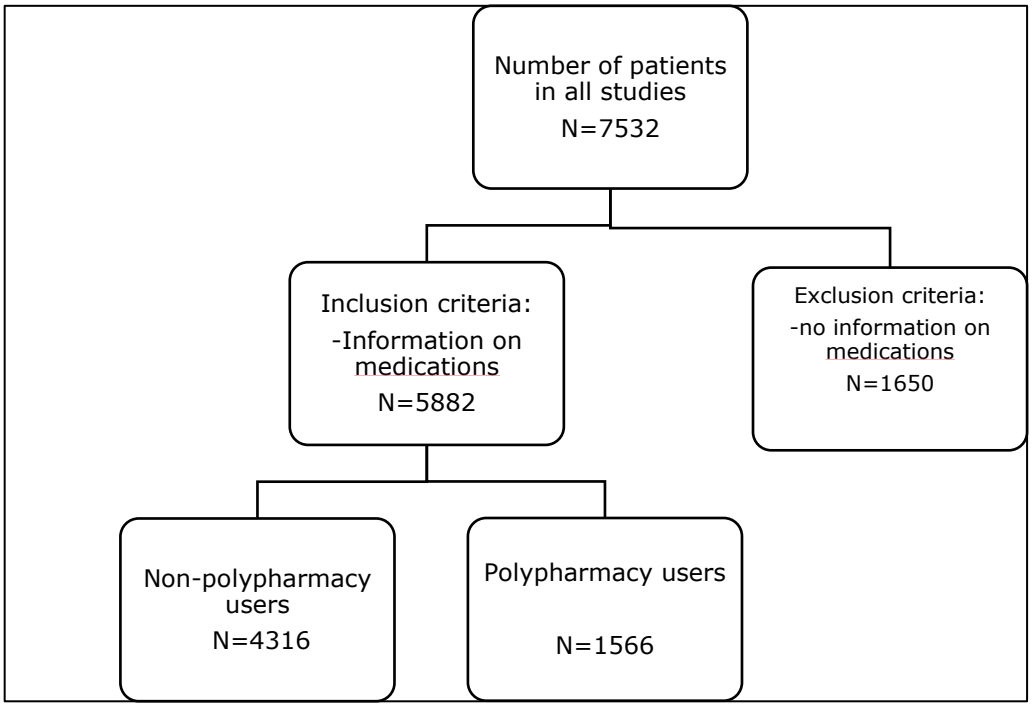

Figure 1 Flow chart: inclusion and exclusion criteria.

Table 1:baseline characteristic table.

Characteristics	Total	Participant with polypharmacy n=1566	Participant with non-polypharmacy users n=4316	P-value
Gender				0.456 *
Male	5882	789 (50.4)	2222 (51.5)	
Female		777 (49.6)	2094 (48.5)	
Age (years) †	5882	76 [71.0-82.0]	73 [69.0-79.0]	<0.001 #
BMI (kg/m^2) †	5822	27.92 [25.3-30.6]	26.4 [24.2-28.91]	<0.001 #
Education status	5829			0.001 *

Low		1174 (75.5)	3063 (71.2)	
Middle		110 (7.1)	417 (9.7)	
High		271 (17.4)	824 (19.1)	
Smoking	5877	130 (8.3)	538 (12.5)	<0.001 *
Alcohol use	5850	1284 (82.8)	3763 (87.5)	<0.001
Depressive Y/N (CES-D, HADS and GDS)	5719	203 (13.5)	312 (7.4)	<0.001 *
Hypertension**	5213	826 (60.1)	1167 (30.4)	<0.001 *
Arrhythmia	3713	151 (17.2)	215 (7.6)	<0.001 *
Heart failure	5191	221 (16.2)	161 (4.2)	<0.001 *
Stroke	5217	199 (14.5)	201 (5.2)	<0.001 *
Arthritis	2965	391 (54.2)	1077 (48.0)	0.004 *
Mental function † (MMSE)	5745	28 [27.0-29.0]	28 [27.0-29.0]	<0.001 #
Diabetes	5220	349 (25.4)	207 (5.4)	<0.001 *
Cancer	2964	157 (21.8)	304 (13.5)	<0.001 *
Opioids	5882	103 (6.6)	41 (0.9)	<0.001 *
Anticholinergics ACB3	5882	136 (8.7)	110 (2.5)	<0.001 *
Z drug	5882	34 (2.2)	28 (0.6)	<0.001 *
BZD	5882	182 (11.6)	199 (4.6)	<0.001 *
Antiadrenergic AH	5882	55 (3.5)	36 (0.8)	<0.001 *
Antidepressant	5882	144 (9.2)	116 (2.7)	<0.001 *
Antiepileptic	5882	73 (4.7)	39 (0.9)	<0.001 *
Antihistamines	5882	60 (3.8)	59 (1.4)	<0.001 *
Antipsychotics	5882	25 (1.6)	34 (0.8)	0.006 *
Alpha blockers BPH	5882	153 (9.8)	153 (3.5)	<0.001 *
Diuretics use	5882	762 (48.7)	591 (13.7)	<0.001 *
Vasodilators (nitrates)	5882	207 (13.2)	77 (1.8)	<0.001 *
Incontinence and urinary frequency	5882	52 (3.3)	29 (0.7)	<0.001*

† Mediaan, interquartile range
# Mann-Whitney U-test
* chi-square test
** self-reported Yes/no
BMI: body mass index. CES_D: Center for Epidemiologic Studies depression Scale. HADS: Hospital Anxiety and depression Scale. GDS-Score: Geriatric Depression Scale. MMSE: Mini Mental State examination. ACB 3: Anticholinergic Cognitive Burden scale 3, Z-drug: Benzodiazepine-related drugs, BZD: benzodiazepines. Alpha blocker BPH: alpha-adrenoreceptor antagonist used in begin prostatic hypertrophy.

Polypharmacy and fall risk

Model 0 exhibited the Hazard Ratio (HR 1.14[1.03-1.26]), indicating an increased risk of falls associated with polypharmacy. Model 1 exhibited the highest hazard ratio (HR 1.39[1.01-1.29]). Conversely, Model 2 showed the lowest estimate (HR 1.03[0.89-1.18]).

Table 2: COX-regression models

	Model 0 (n=5722)	Model 1 (n=4708)	Model 2 (n=4708)
Association between polypharmacy and falls	1.14 [1.03-1.26]	1.39 [1.01-1.29]	1.03 [0.89-1.18]

Data is displayed as Hazard Ratio (95% Confidence interval)

Model 0: basic model.
Model 1 (not corrected for FRIDs): modified for age, sex, BMI, diabetes, hypertension, depression, heart failure, stroke, alcohol intake, smoking, education level)
Model 2 (main model, corrected for FRIDs): modified for age, sex, BMI, diabetes, hypertension, depression, heart failure, stroke, alcohol intake, smoking, education level) and FRIDs (anticholinergics-ACB3, alpha blocker-BPH, antiadrenergic AH, antidepressant, antihistamines, antiepileptics, antipsychotic, vasodilators (nitrates use), BZD, incontinence and urinary frequency drug, diuretics, opioids, and Z drugs.

Sensitivity model: In the sensitivity model, all confounders were adjusted with substantial missing data: cancer, arrhythmia, and arthritis. The number of participants in this model was 1324, there was a slightly broader range of confidence interval, HR 1.13[0.81-1.58] compared to the other models.

DISCUSSION

In our study, we explored the association between polypharmacy and the risk of falls in older persons. Based on the results, it became clear that the use of polypharmacy was not associated with an increased risk of falls after correction for different confounding factors. Chronic diseases and especially FRIDs emerged as important confounders. The changes in the effect size after correcting for FRIDs can explain part of the effect between polypharmacy and falls.

Numerous investigations have been carried out to explore the connection between the use of multiple medications and the occurrence of falls. Morin et al. identified a linear increase in fall incidents among older patients, but this association became invisible after adjusting for other confounding factors, such as the use of medications increasing the risk of falls and chronic conditions [13]. Dhalwani et al. found that the use of polypharmacy results in a 21% higher risk of falls in older patients over a period of two years [20]. Our results were consistent with the observations reported by Morin et al.

It could be that the differences in results between different studies is related to the following aspects. The difference in the study population. For example, in my study, a quarter of the population consisted of polypharmacy users, whereas in study of Dhalwani et al, a third of the total population were polypharmacy users. This probably indicates that the population in my study was healthier compared to the others. The definition of polypharmacy was not the same across different studies. Laflamme et al used a cut-off point five or more medications, while in all other studies the cut-off point was the used of four or more medications. Perhaps if the same number and type of medications had been included in the different studies, a different result might have been obtained. Also, FRIDs were assessed differently in each study. Laflamme et al the Swedish National Board of Health and Welfare classification was used, while in our study we used the STOPPFall criteria. It could be that by using the STOPPFall-criteria, we corrected for more complications, thereby leading to a reduction in the association between polypharmacy and falls.

Clinical implication

Based on the findings of our study, older persons using polypharmacy (four medications or more) shows no association between falls and polypharmacy. The association between falls and polypharmacy was influenced by different confounding factors and especially the utilization of medications that increase the risk of falls. My research provides additional evidence that attention should be given to the use of FRIDs by older persons.

In the interdisciplinary guideline for polypharmacy in older persons in Netherlands, it is recommended that physicians and pharmacists conduct a medication review for patients at an increased risk for medication-related problems, such as those aged seventy-five and above who use ten medications or more, or those who are considered vulnerable patients. Considering the time-intensive nature of medication reviews and the logistical challenges faced by general practitioners and pharmacists [21]. The guidelines for preventing falls in older persons have been established in 2017. This protocol included recommendation to conduct a medication review as part of a multifactorial assessment of fall risk. The emphasis should be placed on medications that increased the risk of falls, rather than exclusively focusing on the quantity of medications[22].

As suggested based on my study for practice, it is relevant to focus on the use of FRIDs in older persons. This is intended to reduce problems associated with medication use, such as falls and injuries.

STRENGTHS AND LIMITATIONS

This study exhibits both strengths and limitations. Employing the falls calendar enables precise measurement of falls incidents on a weekly basis throughout the one-year follow-up period. A large population was included in the analysis plan, providing more power to this study. This power increased the reliability of the study results. Falls were the endpoint of the research, and the fact that this was a subjective endpoint adds more certainty to the interpreting the results. Nevertheless, a pharmacy dataset was not accessible as this information was unavailable in the harmonized AD*F*ICE_IT cohort. Participants self-reported information regarding medication usage, yet no consideration was given to medication adherence or the duration of treatment with various medications. The fact that no pharmacy information was available could potentially lead to misclassification of the information. Furthermore, the analysis was conducted based on the time to the first falls, without consideration for the severity of the falls.

CONCLUSION

We found that nearly a quarter of the total population used four or more medications. However, no significant association was found between the use of polypharmacy and fall incidents over a one-year follow-up period. The correlation was influenced by different confounding factors and especially by the use of FRIDs. My research provides additional evidence that attention should be given to the use of FRIDs.

Recommendation for future study; A study could be conducted among a vulnerable population with complete data on medication adherence. In this study, a quarter of the population used polypharmacy, and it is possible that a different association could be found in a vulnerable population. If there is research involving an intervention design for medication review, it would be advisable to give more attention to the role of FRIDs. This is intended to mitigate problems associated with medication usage as falls.

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