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The Impact of Medications on Fall Risk: A Retrospective Observational Study Based on Medication Data from a Tertiary Hospital

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Abstract

Background: Patient falls are a critical issue that impacts patient safety and health outcomes while placing a significant burden on nursing staff. The medications administered to patients can strongly influence their risk of falling. Unfortunately, large-scale, multi-departmental studies investigating the relationship between various medications and fall risk are scarce. The PRISCUS list is a catalogue of medications derived by experts that are associated with adverse events, such as falls, in elderly patients. As such, it is a valuable reference for comparing results.

Objective: Conduct a large, multi-departmental pharmacoepidemiologic investigation into the association between various medications and fall risk. The results are then compared with those of PRISCUS 2.0, thus validating existing entries and identifying possible new candidates.

Methods: We conducted a retrospective cohort study using routine data from 20 departments at a German tertiary hospital (2016–2022; n=932,103 patients overall; analysis cohort n=8,470; 4,235 fallers and 4,235 random non-fallers). Exposure intervals were derived from medication administrations with a 7-day carryover. For each of 394 medications, exposed vs unexposed patients were matched 1:1 via propensity scores (age, sex, counts of prior diagnoses/procedures); balance was assessed by standardized mean differences (mSMD). We estimated odds ratios (ORs) with 95% CIs and P values (?² tests) and visualized results in a volcano plot. Pre-specified thresholds (log2(OR)=±0.3; P?.05) prioritized clinically relevant signals. Expert panels (clinical pharmacists; geriatricians) adjudicated plausibility and potential causality for selected drugs.

Results: Of the 394 medications examined, 217 exceeded the log?(OR) threshold. 39 of those showed statistically significant fall-risk-increasing associations (P<.05); 8 were already labeled as fall-risk increasing in PRISCUS 2.0. Clinical pharmacists adjudicated five non-PRISCUS medications (levetiracetam, melatonin, lacosamide, valproic acid, mycophenolic acid) as plausible and potentially causal; geriatricians concurred for three (levetiracetam, melatonin, lacosamide). Three PRISCUS medications without a fall indication (pantoprazole, domperidone, clonidine) were judged by pharmacists as plausible fall-risk-increasing. Geriatricians concurred for clonidine and domperidone. Six medications showed statistically significant fall-risk-decreasing associations.

Conclusions: Real-world, multi-department data support and refine the fall-risk entries in PRISCUS 2.0 and suggest additional candidate medications for consideration. Despite warranting consecutive subgroup validation analyses, our findings demonstrate how combining hospital EHR data with targeted clinician adjudication could improve geriatric medication safety. Clinical Trial: NCT07181993

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Abstract

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Patient falls are a critical issue that impacts patient safety and health outcomes while placing a significant burden on nursing staff. The medications administered to patients can strongly influence their risk of falling. Unfortunately, large-scale, multi-departmental studies investigating the relationship between various medications and fall risk are scarce. The PRISCUS list is a catalogue of medications derived by experts that are associated with adverse events, such as falls, in elderly patients. As such, it is a valuable reference for comparing results.

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standardized mean differences (mSMD). We estimated odds ratios (ORs) with 95% CIs and P values (χ^2 tests) and visualized results in a volcano plot. Pre-specified thresholds ($\log_2(OR)=\pm 0.3$; $P \leq .05$) prioritized clinically relevant signals. Expert panels (clinical pharmacists; geriatricians) adjudicated plausibility and potential causality for selected drugs.

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Of the 394 medications examined, 217 exceeded the $\log_2(OR)$ threshold. 39 of those showed statistically significant fall-risk-increasing associations ($P<.05$); 8 were already labeled as fall-risk increasing in PRISCUS 2.0. Clinical pharmacists adjudicated five non-PRISCUS medications (*levetiracetam*, *melatonin*, *lacosamide*, *valproic acid*, *mycophenolic acid*) as plausible and potentially causal; geriatricians concurred for three (*levetiracetam*, *melatonin*, *lacosamide*). Three PRISCUS medications without a fall indication (*pantoprazole*, *domperidone*, *clonidine*) were judged by pharmacists as plausible fall-risk-increasing. Geriatricians concurred for *clonidine* and *domperidone*. Six medications showed statistically significant fall-risk-decreasing associations.

Conclusions:
Real-world, multi-department data support and refine the fall-risk entries in PRISCUS 2.0 and suggest additional candidate medications for consideration. Despite warranting consecutive subgroup validation analyses, our findings demonstrate how combining hospital EHR data with targeted clinician adjudication could improve geriatric medication safety.

Trial Registration: NCT07181993

Keywords: Medication Systems, Accidental Falls, Pharmacoepidemiology, Electronic health records, Big Data, Retrospective Studies

Introduction

With an aging population [1] and a shortage of nursing staff [2], Germany's health care system is faced with a widespread and detrimental issue: patient falls. Patient falls worsen quality of care [3] increase costs [4,5], burden caregivers [6] and represent the most reported type of adverse event in hospitals [7,8]. At a large German university hospital, an average of over 2200 falls were recorded annually between 2016-2022.
Falls can cause serious clinical consequences, ranging from fractures [9] to life-threatening injuries [10]. Older patients are particularly affected by this, as any impairment of their mobility can have subsequent health implications. Prolonged periods of immobility frequently lead to muscle atrophy in old age, which increases the risk of subsequent falls [11].The correct treatment by caregivers is key to reducing fall risk, as some studies estimate up to 30% falls to be preventable [12]. One major factor influencing fall risk is the correct selection of administered medications [13,14].

Considering underlying causal mechanisms can help contextualize results when assessing the association between fall risk and medications. There are a variety of mechanistic pathways through which medications could affect a patient's fall risk. One category of medications acts on a patient's cognitive state, e.g. by reducing reaction speed. Sedatives [15] and anti-cholinergic drugs fall under this category. The latter group suppresses choline-based signal transmission [16], which could slow down reflexive stabilizing leg movement in response to a tripping or falling motion. Furthermore, medications influencing a patient's wake-sleep cycle, e.g. melatonin, could induce drowsiness, thus conceivably increasing fall risk [17]. Pharmacological agents increasing the function of the digestive/ excretory system such as laxatives may also impact fall risk [18] by increasing a patient's urge to use

the toilet, potentially lowering their attentiveness to the surroundings on the way there. Conversely, other medications may reduce fall risk by heightening a patient's cognitive state and focus, e.g. ephedrine.

This study focuses on medications that may reduce or increase a patient's risk of falling through direct and indirect mechanisms.

In general, when interpreting the statistical association between medications and fall risk, the existence of confounding factors, such as pre-existing conditions, must be considered. For example, the anti-seizure medication brivaracetam may appear to increase the risk of falls when investigated [19]. In this case, the underlying epilepsy, treated with brivaracetam, may be the more likely cause of an increased fall risk. To address this issue, clinical experts should evaluate the findings to identify possible confounding factors.

In Germany, guidance is provided by the PRISCUS list [20,21], comprising a set of medications potentially causing adverse events, such as falls, in elderly patients. Out of 233 medications in the current version PRISCUS 2.0 [21], 74 are indicated to increase fall risk. Therefore, three distinct groups can be compared: non-PRISCUS medications, PRISCUS medications with a fall indication and PRISCUS medications without a fall indication. PRISCUS was initially created based on expert interviews and literature reviews. However, little research has validated PRISCUS entries using large-scale, real-world patient data to assess fall risk. Additionally, as new medications are introduced into clinical practice, their impact on fall risk should be investigated, which may lead to their inclusion in the PRISCUS list. Addressing this gap is essential since some medication risks may go unnoticed based on clinical experience alone.

The aim of this study is to (1) identify medications that increase fall risk as well as (2) compare the findings with PRISCUS 2.0, both in terms of (2a) validating existing entries, as well as (2b) suggesting the inclusion of new ones.

Methods

Ethical considerations

The ethics committee of the Charité – Universitätsmedizin Berlin, Germany approved this data analysis (EA2/184/21). Due to the retrospective design of the study using data from standard care, the need for informed consent was waived.

Dataset

A dataset was extracted from the Health Data Platform at Charité - Universitätsmedizin Berlin containing data from 20 departments with the most recorded falls (incl. oncology, hematology, geriatrics and psychiatry) from 2016 to 2022. It encompassed over 932,103 patients, 11,469 of whom with at least one documented fall. The dataset covered medication intake, documentation on fall events as well as general patient history (diagnoses & procedures).

Medication records were encoded in an in-house catalog which was mapped to the ATC code system by a software-assisted [22] manual process. The software streamlined the matching by presenting possible matching candidates from the ATC code to a given in-house catalog entry using string-comparison metrics like Levenshtein distance [23].

Data Modelling

Longitudinal medication intervals were defined based on start and end of medication intake. A duration of seven days was appended to every interval to account for residual concentration of a medication after discontinuation of intake. The seven-day carryover window was selected in line with other studies' definition of current drug use as lasting through the end of the prescription's days of supply plus a grace period of seven days [24]. The interval is a pragmatic choice that ensures that residual pharmacologic effects are captured, rather than misclassifying a patient as unexposed immediately after they stop a medication. Information on dosage was unusable due to inconsistent documentation.

Data Processing & Sampling

Duplicate, incomplete, invalid (e.g., age>120) records as well as underaged patients (age<18) were excluded. Then the set of all patients with at least one documented fall that coincided with a medication interval was extracted (fallers) and joined with an equally large subset of patients without a documented fall event (non-fallers), constituting the final dataset for subsequent analysis. This final dataset contained 8,470 patients corresponding to 67,610 medication intervals (Figure 1).

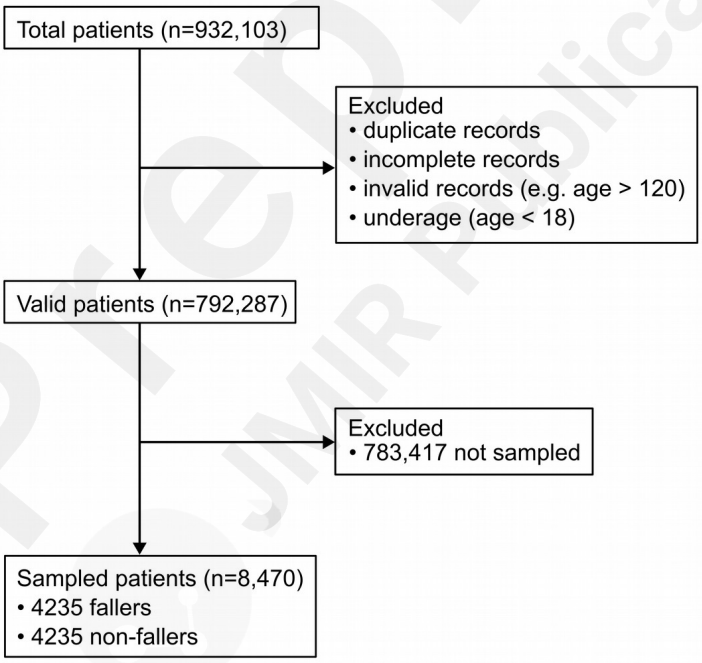


Figure 1. Consort diagram for this study. Note that the final dataset contains data from 8470 patients corresponding to 67610 medication intervals.

Statistical Analysis

For each of the 394 medications present in the data, we conducted propensity score matching (Model: logistic regression; Matching algorithm: 1:1 nearest neighbor without replacement) to balance the exposed and unexposed groups on age, sex, number of prior diagnoses, and number of prior procedures (proxies for baseline frailty and care intensity). Quality of balancing was checked

via computation of mean Standardized mean differences (mSMD) across all four covariates. For a covariate X, SMD is defined as:

(1) $$SMD = \frac{\bar{x}_T - \bar{x}_C}{s_T}$$ with:

$\bar{x}_T$ =mean of X in group that received medication (treated)

$\bar{x}_C$ =mean of X in group that did not receive medication (untreated)

s_T =standard deviation of X in treated group

For n covariates, mSMD is defined as:

(2) $$mSMD = \frac{\sum_{i=1}^{n} SMD_i}{n}$$

We then performed chi-squared tests of independence and estimated odds ratios (ORs) for the association between medication exposure and falls. Associations were summarized in a volcano plot using $\log_2(OR)$ on the x-axis and $-\log_{10}(P)$ on the y-axis. To prioritize clinically meaningful effects, we applied thresholds of $\log_2(OR)=\pm 0.3$ (≈OR 1.23 or 0.81) and $P=.05$. Results were categorized by statistical significance, effect direction (fall-risk-increasing vs fall-risk-decreasing[a]) and PRISCUS membership.

[a]Note that the wording “fall-risk-increasing” and “fall-risk-decreasing” is used here to describe the observed effect and shall not imply causality. However, it offers a clear and intuitive way to interpret the direction of the effect and was therefore chosen.

Expert Evaluation

To distinguish causal signals from likely confounding, two expert teams (clinical pharmacists; geriatricians) independently adjudicated a prioritized list of medications. For each medication, experts rated (1) plausibility of the association (Yes/No/NA) and (2) potential causality (Yes/No/NA), supported by summary side-effect information from specialist pharmacist records. Discrepancies were resolved qualitatively; we report convergent opinions and highlight medications flagged as probable confounding.

Results

Dataset Characteristics

Table 1 summarizes patient demographics and history for the analysis cohort. Mean age was 65.7 (SD 16.0) years; 54.4% were male.

Table 1. Patient demographics of the final dataset.

	All patients	Fallers	Non-fallers
	n=8470	n=4235	n=4235
Demographics			
Age in years [a]	65.3 (16.5)	69.6 (14.7)	62.9 (16.9)
Male sex (%)	54.9%	56.0%	54.3%
Patient history			
Number of medication intervals per patient [a]	7.6 (7.3)	8.1 (7.3)	7.3 (7.4)
Number of previous diagnoses per patient [a]	4.3 (6.0)	3.5 (5.5)	4.9 (6.3)

Number of previous procedures per patient [a]	2.5 (3.3)	2.3 (3.1)	2.7 (3.5)

[a]Mean value with standard deviation.

Propensity score matching

For all 394 medications, mSMD was below 0.25 after matching with 346 of those falling under an mSMD of 0.10. (Figure 2) shows mSMD distribution for all 394 before and after Propensity score matching.

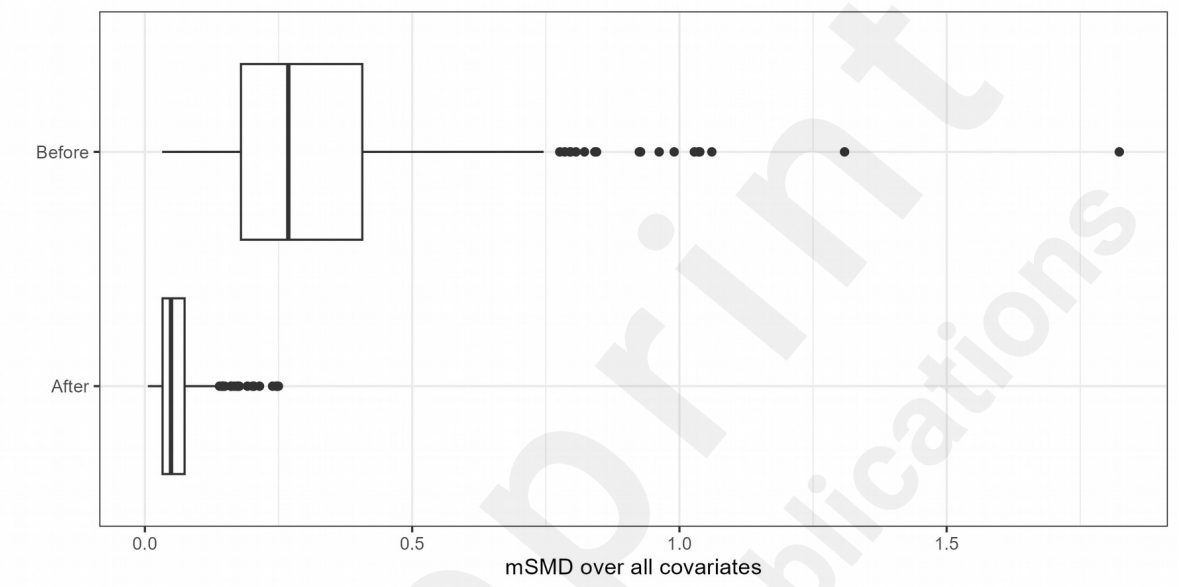


Figure 2. Propensity Score Matching effect. Shown is the distribution of mSMD before and after Propensity score matching.

After matching, all values fall below 0.25, with 346/394 values below 0.10. While there is no consensus on the exact SMD cutoffs, most guidelines converge on either 0.1 or 0.25 [25]. Hence, our conducted matching can be considered successful.

Medication–Fall Associations

Out of 394 tested medications, 217 displayed an LOR>0.3 or LOR<-0.3. From those 217, 39 exhibited statistically significant fall-risk-increasing associations (P<.05). Eight of these were already labeled as fall-risk increasing in PRISCUS 2.0; seven PRISCUS medications without a fall indication showed fall-risk-increasing associations, and 24 non-PRISCUS medications were fall-risk-increasing. A small subset demonstrated fall-risk-decreasing associations (n=6 overall; none were PRISCUS fall-risk entries). Table 2 shows the interesting medications grouped by PRISCUS membership, and effect direction.

Table 2. Statistically significant associations. Medications are grouped by PRISCUS membership

and effect direction.

PRISCUS membership	Effect	# Medications
No PRISCUS [a]	+ [d]	24
PRISCUS no fall indication [b]	+ [d]	7
PRISCUS fall indication [c]	+ [d]	8
No PRISCUS [a]	- [e]	3
PRISCUS no fall indication [b]	- [e]	3
PRISCUS fall indication [c]	- [e]	0

[a]Medication not on the PRISCUS list.
[b]Medication part of the PRISCUS list but not explicitly stated to increase fall risk.
[c]Medication part of the PRISCUS list and explicitly stated to increase fall risk.
[d]Increased odds of falling with medication present.
[e]Decreased odds of falling with medication present.

Aiming to identify medications with especially large effects for expert evaluation, the *P* values from the chi-squared tests were plotted against the log2 of the odds ratios (Figure 3). We have chosen $\log_2(OR)=\pm 0.3$ and $P=.05$ as cutoffs in the volcano plot (dashed lines). The $P<.05$ threshold is the conventional criterion for statistical significance in clinical research, and it is commonly applied in volcano plots [26]. Moreover, small odds ratios might reach statistical significance in large samples but have minimal clinical importance. Thus, in epidemiologic analyses, an odds ratio on the order of 1.2 (or its reciprocal 0.83) is often considered the lower bound of a meaningful association [27]. In the context of medication risk profiling, where effects tend to be modest, using a $\log_2(OR)$ threshold of ~0.3 is aligned with the idea of capturing only those drug–fall associations that exceed a minimal clinically relevant effect size.

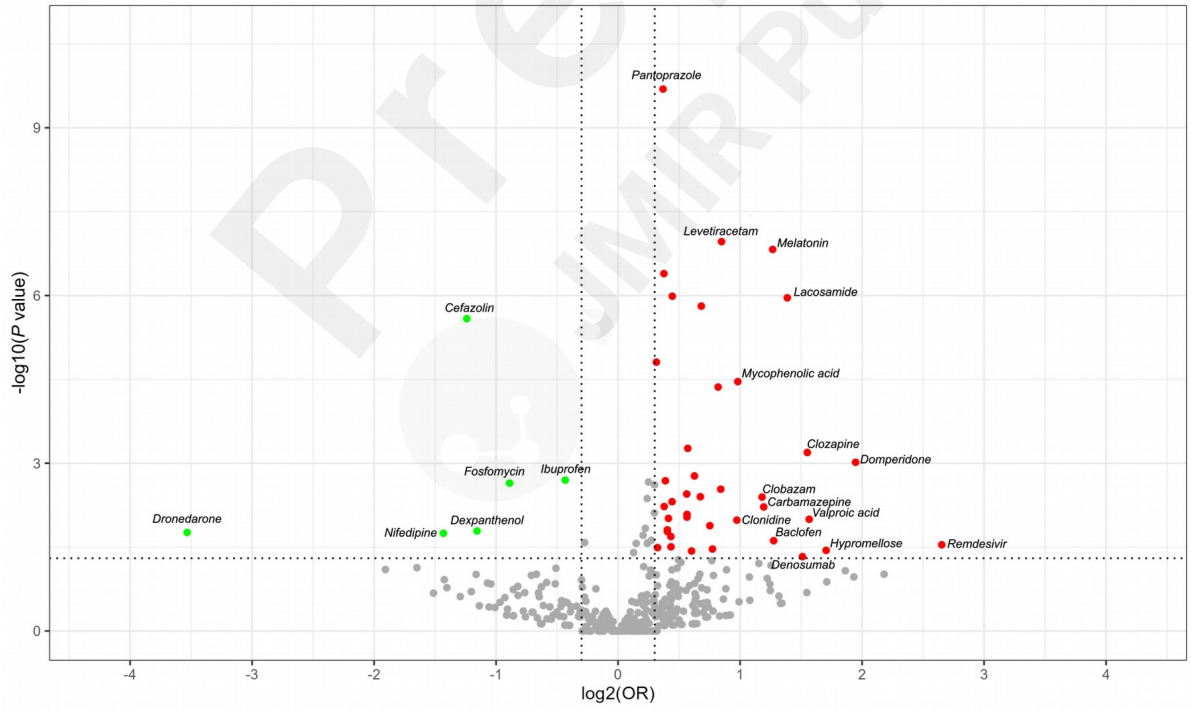


Figure 3. Chi-squared tests volcano plot. The x-axis shows log2(OR); the y-axis shows the negative decadic logarithm of the *P* value. Dotted vertical lines highlight cutoff of log2(OR) at -0.3 and 0.3. An alpha cutoff of -log10(0.05) is indicated by a dotted horizontal line. Medications are highlighted in green if their log2(OR)<-0.3 (fall-risk-decreasing) and their $P\leq.05$. Medications are highlighted in

red if their log2(OR)>0.3 (fall-risk-increasing) and their $P \leq .05$. Medications with especially strong association or statistical significance are annotated.

(Figure 4) shows ATC codes and corresponding ATC level 1 categories of the 21 annotated medications from (Figure 3).

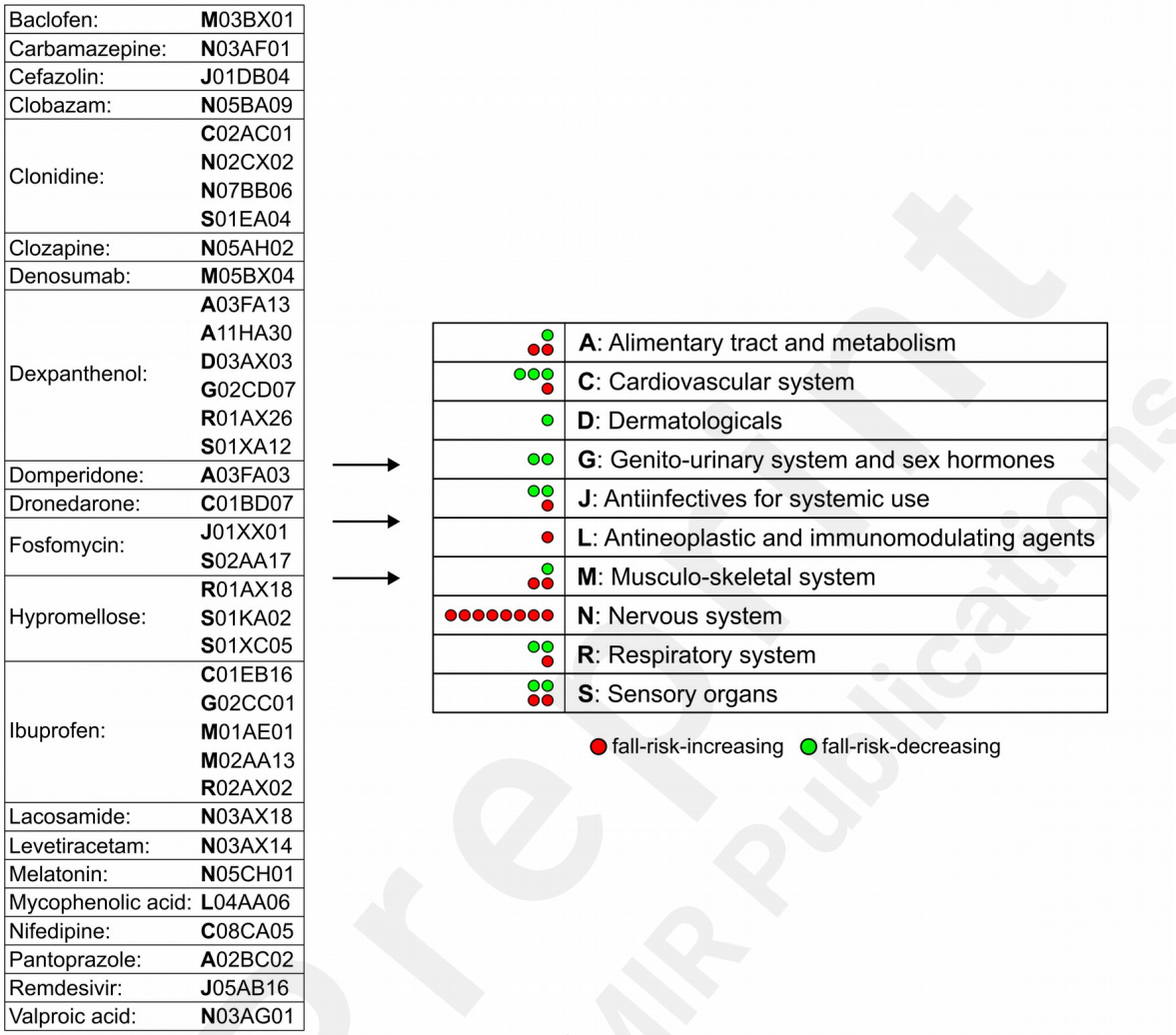


Figure 4. ATC categories of annotated medications. ATC codes (left) connect to their ATC level 1 categories (right). Each level 1 category membership is shown as a circle. Direction of fall risk association is color-coded as in (Figure 3): red for fall-risk-increasing and green for fall-risk-decreasing.

Expert Evaluation: Summary

The 21 annotated medications from (Figure 3) were provided to the two expert groups. Table 3 details the results of their evaluation on plausibility and possible causality of found associations.

Table 3. Expert evaluation results. P=”clinical pharmacists”; G=”Geriatricians”; Plaus=”Plausibility”; Cause=”Possible causality”.

Medication	N	*P* value	Odds ratio	PRISCUS[b]	P: Plaus	P: Cause	G: Plaus	G: Cause
Dronedarone	74	.02	0.09 (95% CI 0.01-0.72)	PnF	No	No	/	/
Nifedipine	548	.02	0.37 (95% CI 0.17-0.82)	PnF	No	No	No	/
Dexpanthenol	824	.02	0.45 (95% CI 0.24-0.84)	nP	No	No	No	No
Cefazolin	2340	<.001	0.42 (95% CI 0.30-0.61)	nP	No	No	Yes	Yes
Fosfomycin	1926	.002	0.54 (95% CI 0.37-0.80)	nP	No	No	Yes	Yes
Ibuprofen	7144	.002	0.74 (95% CI 0.61-0.89)	PnF	No	No	/	/
Pantoprazole	37024	<.001	1.29 (95% CI 1.19-1.40)	PnF	Yes	Yes	/	/
Levetiracetam	3862	<.001	1.80 (95% CI 1.45-2.24)	nP	Yes	Yes	Yes	Yes
Mycophenolic acid	2984	<.001	1.97 (95% CI 1.43-2.72)	nP	Yes	Yes	/	/
Lacosamide	1144	<.001	2.62 (95% CI 1.77-3.86)	nP	Yes	Yes	Yes	Yes
Melatonin	2330	<.001	2.41 (95% CI 1.73-3.35)	nP	Yes	Yes	Yes	Yes
Clonidine	1082	.01	1.96 (95% CI 1.19-3.24)	PnF	Yes	Yes	Yes	Yes
Clobazam	652	.004	2.27 (95% CI 1.31-3.91)	PF	Yes	Yes	Yes	Yes
Carbamazepine	830	.006	2.29 (95% CI 1.29-4.07)	PF	Yes	Yes	Yes	Yes
Baclofen	482	.02	2.42 (95% CI 1.16-5.04)	PF	Yes	Yes	Yes	Yes
Denosumab	322	.046	2.85 (95% CI 1.09-7.48)	nP	/	/	/	/
Valproic acid	318	.01	2.96 (95% CI 1.33-6.60)	nP	Yes	Yes	/	/
Hypromellose	260	.04	3.26 (95% CI 1.15-9.26)	nP	No	No	/	/
Clozapine	430	<.001	2.93 (95% CI 1.59-5.41)	PF	Yes	Yes	Yes	Yes
Domperidone	450	<.001	3.86 (95% CI 1.72-8.66)	PnF	Yes	Yes	Yes	Yes
Remdesivir	82	.03	6.29 (95% CI 1.28-30.84)	nP	/	/	/	/

[b]nP=”No Priscus”;PnF=”PRISCUS no fall indication”; PF=”PRISCUS fall indication”

Twenty-one prioritized medications were reviewed (Table 2). Clinical pharmacists adjudicated five non-PRISCUS medications with fall-risk-increasing associations –*levetiracetam*, *melatonin*, *lacosamide*, *valproic acid* and *mycophenolic acid* – as plausible and potentially causal. The geriatricians came to the same conclusion for three of those, excluding *mycophenolic acid* and *valproic acid* citing a lack of clinical evidence.

Three PRISCUS medications without a fall indication (*pantoprazole, domperidone, clonidine*) were judged by pharmacists as plausible fall-risk-increasing; geriatricians concurred for *clonidine* and *domperidone*. Both groups flagged remdesivir and denosumab as probable confounding.

Four PRISCUS members with fall indication and observed fall-risk-increasing effect were validated by both expert groups: *clobazam, carbamazepine, baclofen* and *clozapine*.
The clinical pharmacists identified no medications with fall-risk-decreasing effect as potential causes of reduced fall risk. They noted that evaluating fall-risk-decreasing effects was more challenging, primarily because their assessments relied on known side effects, which often underreport beneficial effects such as reduced fall risk.
On the other hand, the geriatricians identified two medications with fall-risk-decreasing effects as possible causes of a decreased fall risk: *cefazolin* and *fosfomycin*. They hypothesized that in both cases the intake effectively treats infection, lowering the patient's overall frailty and thus possibly decreasing the fall risk.

Further on, the geriatricians questioned the fall-risk-decreasing association of three medications: *dexpanthenol*, *dronedarone* and *ibuprofen*. The association of *dexpanthenol* and fall risk was considered to be far-fetched as it is used in dermatologic prescriptions, limiting its impact on the patient's internal system. For *dronedarone* and *ibuprofen*, the geriatricians could hypothesize mechanisms indirectly explaining a decreased fall risk (i.e. reduction of pain and reduction of arrhythmia). However, they cited studies describing a fall risk increasing association for both medications [13,14] questioning the validity of the found fall risk decreasing association.

Discussion

Principal Results

In a large, multi-department inpatient cohort, we found associations between various medications and fall risk. Our subsequent comparison with PRISCUS 2.0 validated a subset thereof and suggested new candidate medications. The triangulation of statistical associations with structured clinician adjudication strengthened interpretability, differentiating likely causal signals from confounding. To this end, the expert evaluation helped tremendously, refining our findings into a meaningful set of results to inform future research.

The investigation of the relationship between individual medications and fall produced a list of interesting candidates that were characterized by strong effect (large |LOR|), statistical significance (low *P* value) and PRISCUS membership. The fact that no PRISCUS fall indicated medications were found to be statistically significant and fall-risk-decreasing is an indication to the overall validity of the PRISCUS list. Just two PRISCUS fall indicated medications were found to have a non-significant fall-risk-decreasing effect, namely *methocarbamol* and *amisulpride*. In consequence, both medications' fall indication in PRISCUS may be re-evaluated.

ATC Level 1 group membership as shown in (Figure 4) provided a first indication to the validity of our study, as exemplified by the overrepresentation of category "N: Nervous system" within the subset of strongly fall associated medications as well as the unanimously fall promoting direction of associations within this category.

Both teams of clinical experts independently identified three fall-risk-increasing medications not currently included in PRISCUS: *levetiracetam, lacosamide* and *melatonin*. Despite being anti-

epileptic medications and therefore potential cases of confounding, the known side-effect spectrum of *levetiracetam* and *lacosamide* led the experts to evaluate them as plausible causes of an increased fall risk. This conclusion is supported by a 2018 meta-analysis, which found a significant fall risk increasing association of anti-epileptic medication with an OR of 1.95 [14]. In contrast, the literature on fall risk and *melatonin* appears to be less clear. One observational study concluded that melatonin was associated with a significant increase in risk of fall [28]. On the other hand, a different observational study with larger cohort size found an association between melatonin and increased risk of fall but attributed it to other factors [29]. Our study found melatonin to be strongly associated with fall risk identified by high significance as well as effect size (LOR) and provides an argument for labelling it as “fall risk increasing”. In the end, the decision on whether to include it in PRISCUS and other guidelines remains in the hands of clinical experts.

The clinical pharmacists additionally evaluated three fall-risk-increasing PRISCUS members without a current fall indication to be plausible causes of increased fall risk. The geriatricians concurred on two of those: *clonidine* and *domperidone*. For *clonidine*, previous research substantiates this result, as alpha-two receptor antagonists, like *clonidine*, have been found to be fall risk increasing with an OR of 1.20 [13]. In contrast, the association between *domperidone* and an increased fall risk has not been directly investigated. The experts argued that as a dopamine-receptor antagonist, *domperidone* intake could lead to extrapyramidal disorders [30] and thus increased fall risk. *Clonidine* and *domperidone* may be considered for fall indication in PRISCUS.

Both expert groups identified two probable cases of confounding: *remdesivir* and *denosumab*. In our study, *Remdesivir*, an anti-viral agent, showed the strongest fall-risk-increasing effect (Figure 3). In our dataset, *remdesivir* was predominantly administered in 2021 and 2022, coinciding with the Covid-19 pandemic. It is conceivable that *remdesivir* was primarily given severe Covid-19 cases, implying baseline higher frailty and therefore elevated fall risk. A 2023 review found no significant reduction of all-grade adverse events by *remdesivir* for mild to severe Covid-19 cases [31], going along with our hypothesis. If *remdesivir* strongly reduced adverse events such as falls, it may have shown a lower fall-risk-increasing effect in our study. Hence, the severity of an underlying Covid-19 infection appears to be the more likely cause for increased fall risk. A subgroup analysis focusing on the fall risk of Covid19 patients should be performed in future to investigate this hypothesis.

Denosumab is predominantly given to patients with osteoporosis. This condition has been linked to an increase in fall risk [32]. Interestingly, a 2024 review reported that *denosumab* may have a fall risk decreasing effect on patients with osteoporosis [33]. At first glance, it appears that this may contradict our study where *denosumab* was found with a fall risk increasing effect. However, our study compared absence with presence of medication in our entire analysis cohort, not accounting for specific preconditions. In contrast, Voltan et al. reported the finding for patients with osteoporosis only. If our analysis was limited to patients with osteoporosis, we may have found a fall risk decreasing effect for *denosumab*. A future subgroup analysis should test this hypothesis. Similarly, other medications may be followed-up on, e.g. subgroup-analysis for antidepressants only including patients with a pre-diagnosed depressive condition.

Limitations

This retrospective observational design cannot establish causality; residual confounding and exposure misclassification are possible. We analyzed data from a single tertiary center; external validation is warranted. Multiple testing increases the chance of false positives; our prioritization thresholds were chosen to balance statistical and clinical relevance, but sensitivity analyses (e.g.,

false discovery rate control) should be explored. Future work should include subgroup analyses (e.g., COVID-19 severity for *remdesivir*; *osteoporosis* for *denosumab*) and prospective validation.

Conclusions

This study identified medications that were observed to have a particularly strong association with fall risk. After expert evaluation, these findings may inform medication administration guidelines such as PRISCUS. We provided additional indications towards the validity of the PRISCUS list, although not all its fall-related entries were associated with fall risk in our study. Moreover, insights from the study demonstrated the usefulness of inter-disciplinary exchange, combining aspects from data science, statistics and clinical expertise. In summary, our study may help to inform medication administration guidelines with the potential to prevent falls thereby improving patient outcomes.

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Conflicts of Interest

Lukas Reinert is employed full-time by IQVIA Commercial GmbH & Co. OHG (formerly “Kairos GmbH - an IQVIA business”), which had no role in the study design, data collection, analysis, decision to publish, or preparation of this manuscript.
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Abbreviations

OR: odds ratio
LOR: log2(odds ratio)
nP: No Priscus
PnF: Priscus no fall indication
PF: Priscus fall indication
mSMD: mean Standardized Mean Difference

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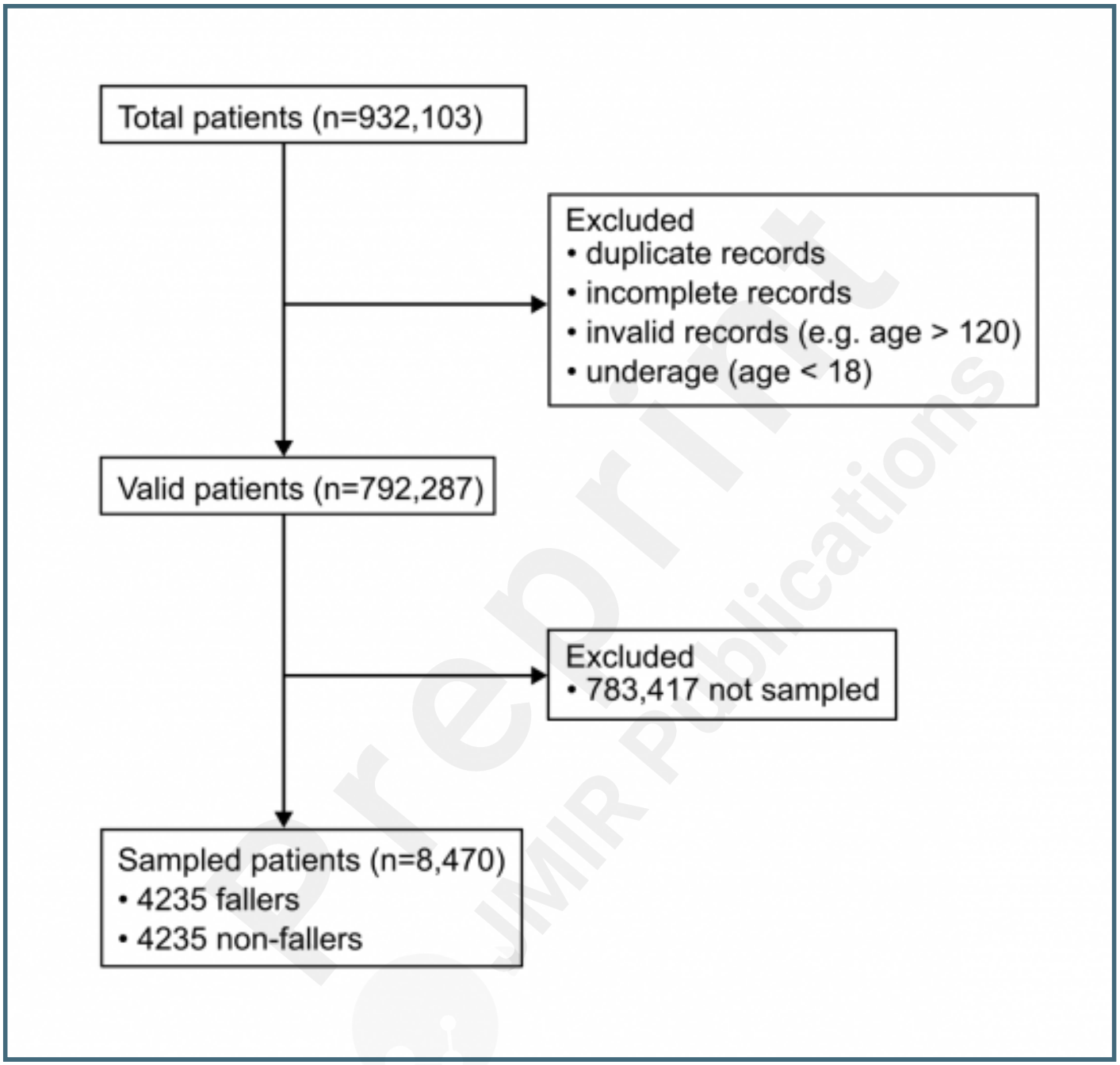
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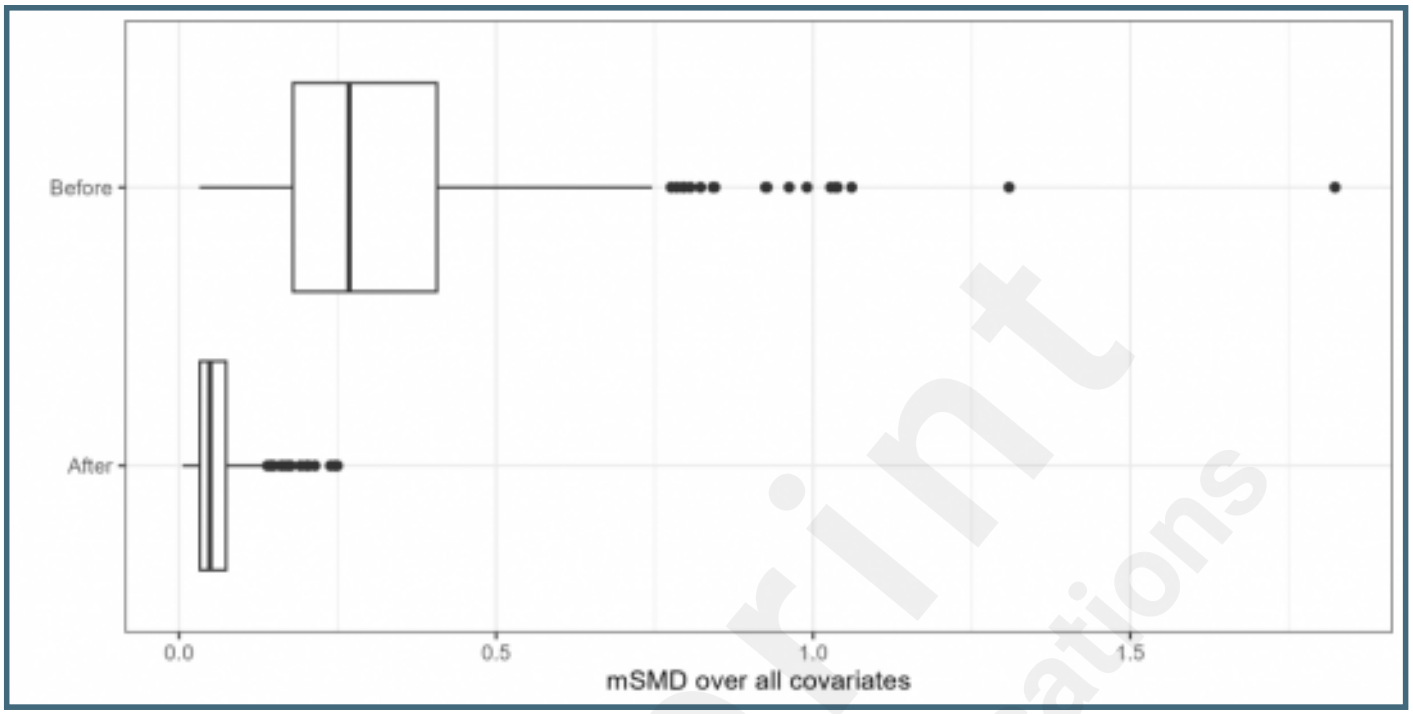
Figures

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Consort diagram for this study. Note that the final dataset contains data from 8470 patients corresponding to 67610 medication intervals.

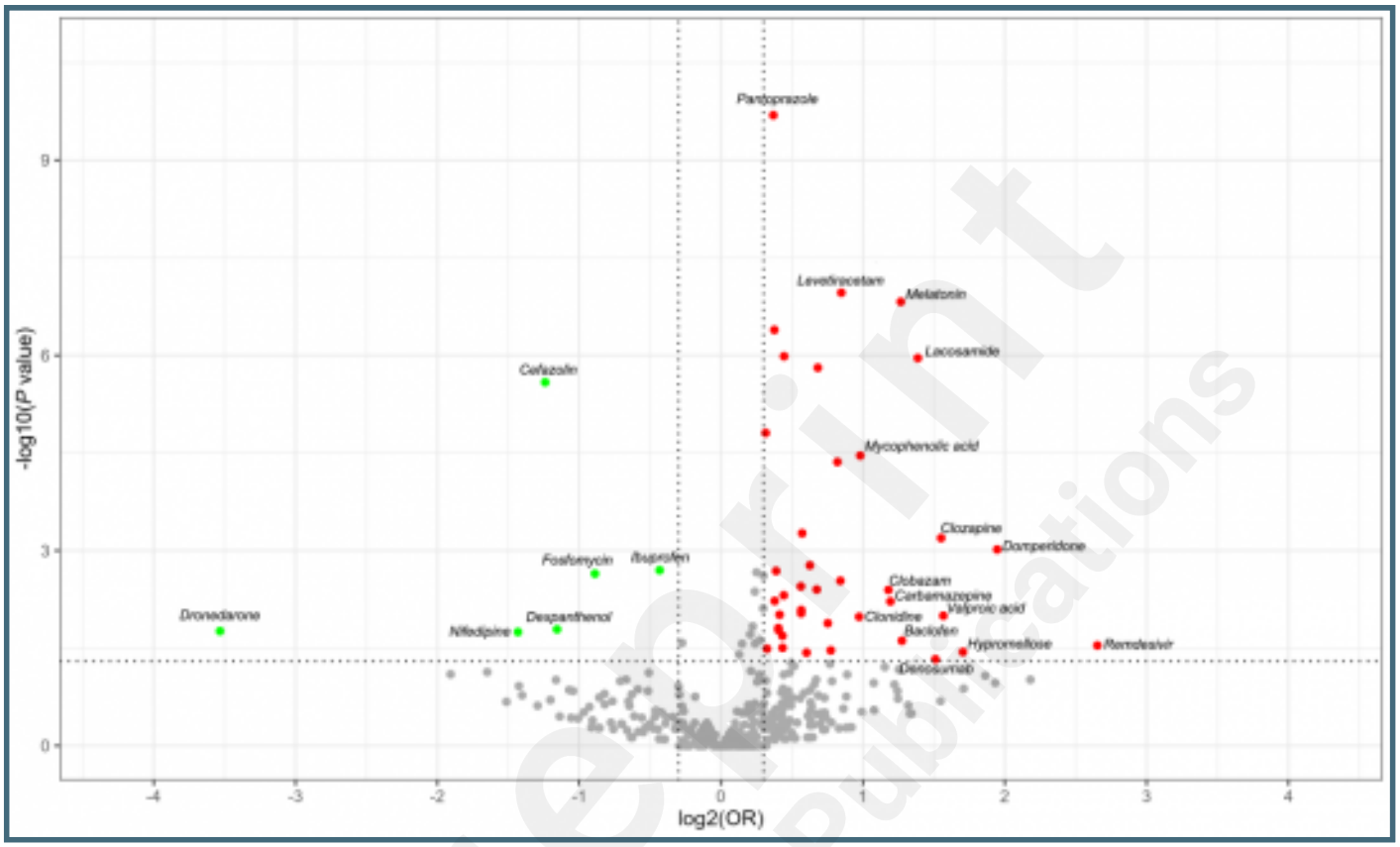


Propensity Score Matching effect. Shown is the distribution of mSMD before and after Propensity score matching.



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Chi-squared tests volcano plot. The x-axis shows log2(OR); the y-axis shows the negative decadic logarithm of the P value. Dotted vertical lines highlight cutoff of log2(OR) at -0.3 and 0.3. An alpha cutoff of -log10(0.05) is indicated by a dotted horizontal line. Medications are highlighted in green if their log2(OR)0.3 (fall-risk-increasing) and their P?.05. Medications with especially strong association or statistical significance are annotated.



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ATC categories of annotated medications. ATC codes (left) connect to their ATC level 1 categories (right). Each level 1 category membership is shown as a circle. Direction of fall risk association is color-coded as in (Figure 3): red for fall-risk-increasing and green for fall-risk-decreasing.

