scientific reports

Check for updates

OPEN

Sex differences of fall-risk-increasing drugs in the middle-aged and elderly: a descriptive, cross-sectional study of FDA adverse event reporting system

Ying Zhao[1], Yuke Zhong[1], Liuqing Wu[1], Jiao Yan[2] & Weitao Lu[3]✉

It's well known that sex is a risk factor for the occurrence of adverse events (AEs), most of which have found sex differences. Real-world data studies on the sex differences of fall-risk-increasing drugs (FRIDs) are few and far between, with most small-scale retrospective studies based on FRID classes. To establish a list of FRIDs and describe their sex differences, we used preferred terms from the Medical Dictionary for Regulatory Activities to search for AEs in the FDA Adverse Event Reporting System (FAERS), and then perform disproportionality analyses and female/male ratio analyses. During January 2004 to March 2023, 101,746 fall-related AEs were reported in FAERS from patients aged 50 to 100, with 68,492 (67.3%) females and 32,547 (32.0%) males. We found 261 signals for females while 284 for males. For females, the top 3 signals with the highest reporting odds ratio (ROR) were anethole trithione, clopenthixol, nikethamide (ROR: 388.88, 212.10, 113.94), while the top 3 signals with the highest lower limit of information component (IC_{025}) were nikethamide, anethole trithione, benzbromarone (IC_{025}: 3.91, 3.15, 2.49). For males, the top 3 signals with the highest ROR were fluprednidene acetate, potassium hydroxide, ketazolam (ROR: 216.86, 108.43, 108.43), while the top 3 signals with the highest IC_{025} were clomethiazole, piribedil, melperone (IC_{025}: 3.31, 3.24, 2.99). Moreover, among the 119 shared signals found between males and females, 33 were positively correlated with falls in females and 38 with falls in males. Signals showing significant sex differences were mainly concentrated on agents of the immune, nervous, musculo-skeletal, and cardiovascular systems. We offered a series of FRIDs and suggested their sex differences in falls through the FAERS. In the future, it is essential to balance the inclusion of women and men, and analyse sex-stratified for FRIDs.

Keywords Fall-risk-increasing drugs, Sex differences, Pharmacovigilance, Middle-aged and elderly, Reporting odds ratio, Bayesian confidence propagation neural network

As one of the top global causes of injury-related deaths and disabilities in middle-aged and elderly people, falls have become a major public health concern worldwide. During 2019 in mainland China, the incidence rate of falls among individuals aged 60 and above was 3799.4 per 100,000. Falls led to 39.2 deaths and 1238.9 disability-adjusted life years per 100,000 people[1]. Wang et al.[2] found that the frequency of falls, including recurrent and injurious falls, was more common in those aged 50–55 and over 55 than in those under 50, which suggests that preventing falls in middle age could be effective in mitigating fall risks in older age as well.

In the management of many chronic diseases, polypharmacy (use of multiple medications) is often unavoidable in older people[3]. However, taking multiple medications is considered a risk factor for falls due to the adverse effects of drug-drug or drug-disease interactions. Studies have determined that taking ≥ 4 drugs is associated with an increased incidence of falls, recurrent falls, and injurious falls[4]. Therefore, it is critical to

[1]Shenzhen Longgang Central Hospital, Shenzhen 518116, China. [2]Department of Respiratory Medicine, Traditional Chinese Medicine Innovation Research Center, Shenzhen Hospital of Integrated Traditional Chinese and Western Medicine, Shenzhen, China. [3]Department of Pharmacy, Jiangmen Central Hospital, Affiliated Jiangmen Hospital of Sun Yat-sen University, Jiangmen, Guangdong, China. ✉email: luweitao012345@163.com

reduce fall-risk-increasing drugs (FRIDs) as far as possible for those who are middle-age and elderly taking multiple medications.

According to previous studies, it has been consistently observed that certain medications, including hypnotics, cardiovascular drugs, and psychotropics are implicated in a concomitant rise in the risk of falls among the elderly[5–9]. For example, drugs with sedative properties are linked to a decrement in gait velocity among older individuals[10]. Furthermore, loop diuretics were significantly associated with an augmented fall risk, while digitalis and digoxin may similarly elevate this risk[5]. In genetics, antidepressant-related fall risk may be associated with certain genetic variants modify[11].

Pharmacological response is woven with the biologic sex, which serves as a genetic determinant in the variance of drug effects. The combination of all sex-specific genetic, epigenetic, and hormonal influences on cellular systems produces different in vivo male and female biologic systems, which results in sex differences in the pharmacokinetics and pharmacodynamics of multiple drugs[12]. In a telling statistic, a significant proportion—76 out of 86 (88%)—of FDA-approved drugs exhibit elevated pharmacokinetic parameters in women relative to men. Elevated blood concentrations and longer elimination times were often manifested by women, which was inextricably linked to sex differences in adverse drug reactions[13].

An abundance of research has suggested a disquieting trend: women bear a higher risk in response to most of medications that exhibit sex-specific effects[14]. Five or more concurrent medications emerge as a notable independent correlate of falls, which is observed exclusively in the female population[15]. Women were taking more sedatives among patients aged 60 years or older who were admitted to two referral hospitals due to falls leading to fracture[16]. Moreover, over 40% of older adults seeking emergency care after a fall had previously been prescribed benzodiazepines and hypnotic drugs, in which some notable sex differences were seen, particularly prescriptions above the recommended dosage and of drugs with an extended half-life[17]. Unfortunately, although a series of drugs have been identified that could induce falling for the middle-aged and elderly, few studies have specified fall-related adverse drug effects according to sex, which hampers other studies like meta-analysis that might lead to new insights.

The US Food and Drug Administration Adverse Event Reporting System (FAERS), which has been widely used to analyze the safety profiles of various drugs, is a vast repository that contains post-marketing surveillance data on adverse event (AE) and medication error reports submitted worldwide to the FDA[18]. In light of this, we purposed to list the drugs related to falls (i.e., signals), and describe their sex differences for the middle-aged and elderly in the FAERS database.

Results

Overview across AE reports

101,746 AE reports were extracted in which fall related drugs were reported as suspect, interacting or concomitant drug, after raw FAERS reports had been executed the inclusion and exclusion criteria. The data processing and study scheme were shown in Fig. 1. Simultaneously, there are 261 fall-related drugs for female involved in subsequent signal analysis while 284 for male.

We summarized the basic clinical characteristics of AE reports in Table 1. Among 101,746 AE reports, 68,492 (67.3%) for female and 32,547 (32.0%) for male were enrolled in following analysis, while 707 (0.7%) were excluded with unknown sex. The average age and its standard deviation of females and males were 69.8 ± 11.5 and 71.5 ± 11.2 years old respectively. During the 20-year period, the number of reports showed fluctuating growth since 2004, with notable peaks in 2010 to 2012 and the highest peak in 2018 to 2019. Overall, a large porpotion of AE reports were from America (females: 62.3%, males: 55.4%) and the AE outcomes were mainly hospitalization (females: 51.3%, males: 51.2%). Except for Other and unknown indications, AEs with multiple sclerosis reported the most (females: 14.2%, males: 6.2%).

Overview across signals

The details of detected signals, which are satisfied both of Reporting Odds Ratio (ROR) and Bayesian Confidence Propagation Neural Network (BCPNN) algorithms, were presented in Fig. 2 and Supplementary Table S4. For females, the top 3 signals with the highest ROR were anethole trithione (ROR: 388.88, 95% CI: 50.20-3012.23; IC_{025}: 3.15), clopenthixol (ROR: 212.10, 95% CI: 25.53-1761.84; IC_{025}: 2.24) and nikethamide (ROR: 113.94, 95% CI: 53.94-240.72; IC_{025}: 3.91), while the top 3 signals with the highest IC_{025} were nikethamide (ROR: 113.94, 95% CI: 53.94-240.72; IC_{025}: 3.91), anethole trithione (ROR: 388.88, 95% CI: 50.20-3012.23; IC_{025}: 3.15) and benzbromarone (ROR: 13.44, 95% CI: 7.92–22.79; IC_{025}: 2.49). For males, the top 3 signals with the highest ROR were fluprednidene acetate (ROR: 216.86, 95% CI: 24.24-1940.33; IC_{025}: 1.59), potassium hydroxide (ROR: 108.43, 95% CI: 19.86-592.02; IC_{025}: 1.55) and ketazolam (ROR: 108.43, 95% CI: 19.86-592.02; IC_{025}: 1.54), while the top 3 signals with the highest IC_{025} were clomethiazole (ROR: 24.50, 95% CI: 15.68–38.29; IC_{025}: 3.31), piribedil (ROR: 25.99, 95% CI: 15.81–42.73; IC_{025}: 3.24) and melperone (ROR: 13.98, 95% CI: 9.99–19.54; IC_{025}: 2.99).

Sex differences for the number of signals

If the absolute difference in the number of signals was ≥ 2 in anyone 2nd-level ATC class, we considered that there were sex differences in the number of signals for this 2nd-level ATC class. The total number of signals for different 2nd-level ATC classes by sex was displayed in Supplementary Table S3. Furthermore, sex differences of the Top 6 2nd-level ATC classes with the highest total number of signals were presented in Fig. 3. Among the top 6 2nd-level ATC classes with more signals detected for female, the total number of signals was 38 for females versus 20 for males. Among the top 6 ATC classes with more signals detected for male, the total number of signals was 83 for females versus 112 for males. Among the top 6 ATC classes almost without sex differences, the total number of signals was 44 for females versus 42 for males.

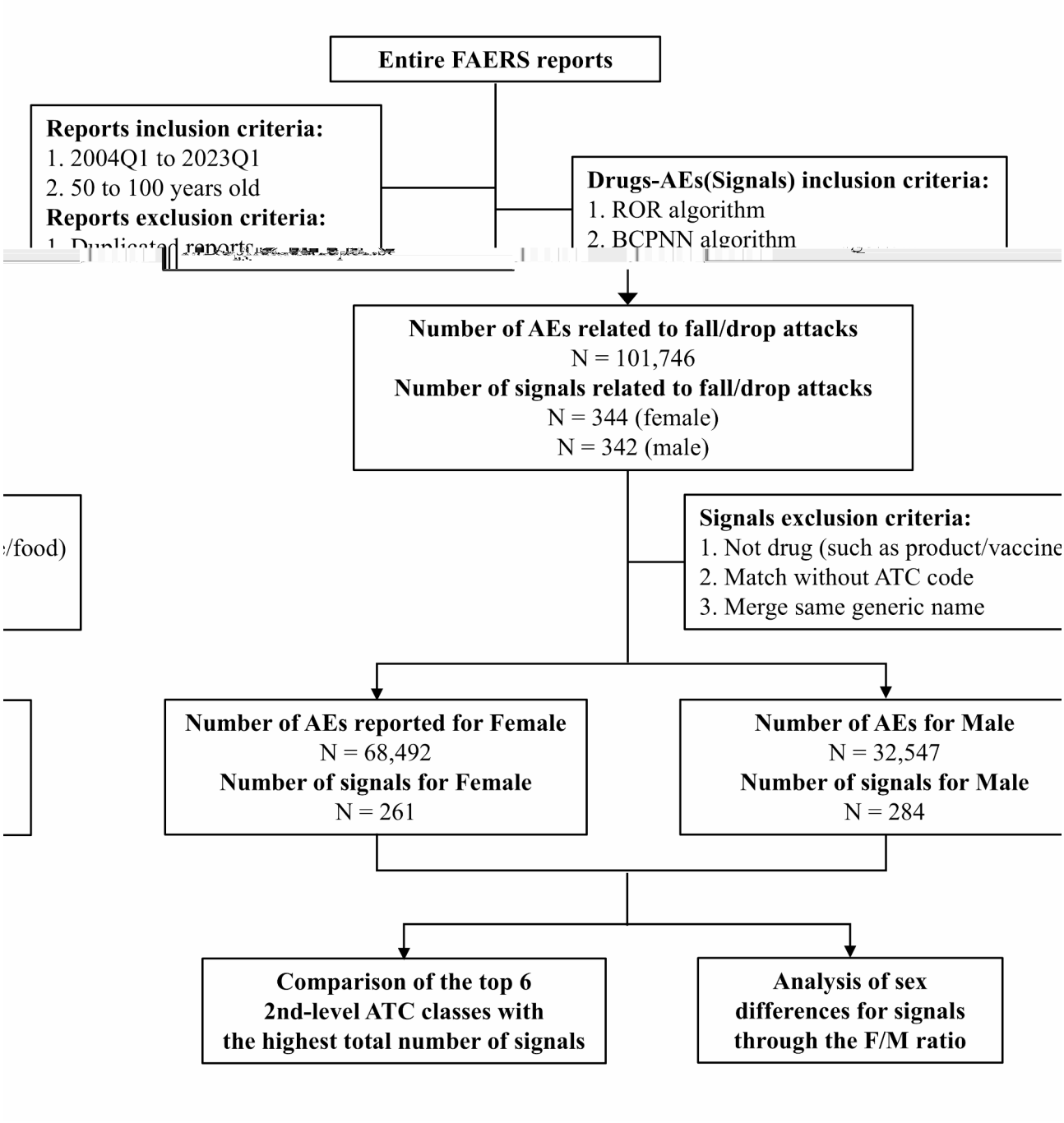

Fig. 1. Scheme of this study. FAERS, FDA Adverse Event Reporting System; AEs, Adverse Events; N, number of reports or signals; ATC, Anatomical Therapeutic Chemical; F/M ratio, ratio of fall related adverse events concerning women versus men.

According to sex differences of the top 6 ATC classes with the highest total number of signals, more signals were mainly detected in the nervous system for male than female, which is coded as N in the 1st-level code. On the contrary, more signals were mainly detected in the cardiovascular system for female than male, which is coded as C in the 1st-level code. In 2nd-level ATC classes detected more signals for male than female, psycholeptics (N05) was the most followed by Psychoanaleptics (N06) and Anti-parkinson drugs (N04). Besides, in 2nd-level ATC classes detected more signals for female than male, there were successively Cardiac therapy (C01), Drugs for treatment of bone diseases (M05), and Drugs for functional gastrointestinal disorders (A03).

Sex differences for signals

To clarify the association between FRIDs and sex, we performed F/M ratio analysis on the 119 shared signals we found between males and females. Generally, an odds ratio greater than 1.50 or less than 0.67 is considered

	Overall	Female	Male	Unknown
N (%)	101,746 (100.0)	68,492 (67.3)	32,547 (32.0)	707 (0.7)
Year (%)				
2004 ~ 2005	4180 (4.1)	2828 (4.1)	1339 (4.1)	13 (1.8)
2006 ~ 2007	4739 (4.7)	3159 (4.6)	1555 (4.8)	25 (3.5)
2008 ~ 2009	5364 (5.3)	3705 (5.4)	1603 (4.9)	56 (7.9)
2010 ~ 2011	13,503 (13.3)	10,201 (14.9)	3248 (10.0)	54 (7.6)
2012 ~ 2013	10,185 (10.0)	7556 (11.0)	2586 (7.9)	43 (6.1)
2014 ~ 2015	6951 (6.8)	4699 (6.9)	2164 (6.6)	88 (12.4)
2016 ~ 2017	9194 (9.0)	5849 (8.5)	3266 (10.0)	79 (11.2)
2018 ~ 2019	18,042 (17.7)	11,753 (17.2)	6154 (18.9)	135 (19.1)
2020 ~ 2021	15,008 (14.8)	9374 (13.7)	5546 (17.0)	88 (12.4)
2022 ~ 2023	14,580 (14.3)	9368 (13.7)	5086 (15.6)	126 (17.8)
Outcome (%)				
Death	8230 (8.1)	4019 (5.9)	4146 (12.7)	65 (9.2)
Life-threatening	3081 (3.0)	1616 (2.4)	1444 (4.4)	21 (3.0)
Hospitalization	52,093 (51.2)	35,107 (51.2)	16,659 (51.2)	327 (46.3)
Disability	1464 (1.4)	1007 (1.5)	445 (1.4)	12 (1.7)
Congenital anomaly	2 (0.0)	2 (0.0)	0 (0.0)	0 (0.0)
RPPI	202 (0.2)	105 (0.1)	96 (0.3)	1 (0.1)
Other / Outcome not specified	36,674 (36.1)	26,636 (38.9)	9757 (30.0)	281 (39.7)
Reporting country (%)				
United States of America	61,017 (60.0)	42,670 (62.3)	18,047 (55.4)	300 (42.4)
Canada	7969 (7.8)	5281 (7.7)	2656 (8.2)	32 (4.5)
United Kingdom	4416 (4.3)	2503 (3.7)	1770 (5.4)	143 (20.2)
France	4133 (4.1)	2766 (4.0)	1353 (4.2)	14 (2.0)
Japan	3937 (3.9)	2257 (3.3)	1589 (4.9)	91 (12.9)
Germany	3735 (3.7)	2135 (3.1)	1572 (4.8)	28 (4.0)
Other / Country not specified	16,539 (16.3)	10,880 (15.9)	5560 (17.1)	99 (14.0)
Age in report (Mean (SD))	70.4 (11.4)	69.8 (11.5)	71.5 (11.2)	74.9 (11.2)
Age level (%)				
50 ~ 65y	37,483 (36.8)	26,898 (39.3)	10,430 (32.0)	155 (21.9)
66 ~ 75y	27,651 (27.2)	18,176 (26.5)	9262 (28.5)	213 (30.1)
76 ~ 85y	26,422 (26.0)	16,893 (24.7)	9333 (28.7)	196 (27.7)
>85y	10,190 (10.0)	6525 (9.5)	3522 (10.8)	143 (20.2)
Top 10 Indications (%)				
Multiple sclerosis	11,730 (11.5)	9698 (14.2)	2011 (6.2)	21 (3.0)
Rheumatoid arthritis	7167 (7.0)	6258 (9.1)	889 (2.7)	20 (2.8)
Osteoporosis	7110 (7.0)	6653 (9.7)	440 (1.4)	17 (2.4)
Hypertension	5136 (5.0)	3384 (4.9)	1724 (5.3)	28 (4.0)
Atrial fibrillation	3119 (3.1)	1486 (2.2)	1611 (4.9)	22 (3.1)
Parkinson's disease	3021 (3.0)	1347 (2.0)	1667 (5.1)	7 (1.0)
Pain	2784 (2.7)	1966 (2.9)	801 (2.5)	17 (2.4)
Pulmonary arterial hypertension	2769 (2.7)	2113 (3.1)	654 (2.0)	2 (0.3)
Depression	2720 (2.7)	1995 (2.9)	713 (2.2)	12 (1.7)
Other / Unknown indications	56,190 (55.2)	33,592 (49.0)	22,037 (67.7)	561 (79.3)

Table 1. Characteristics of adverse event (AE) reports. N, the number of reports; RPPI, Required to prevent permanent impairment.

evidence of a strong difference, according to previous studies[19–21]. Among all shared signals, 33 were positively correlated with falls in females, and 38 with falls in males, whereas 48 showed no sex difference.

Cardiovascular system

Cardiovascular system (ATC code C) comprises substances used for the treatment of cardiovascular conditions. In the ATC classification cardiac therapy (C01), midodrine (F/M 0.32, 95%CI 0.24–0.42) and droxidopa (F/M 0.30, 95%CI 0.25–0.36) both presented stronger associations with falls in men than women (Fig. 4a). Also, there

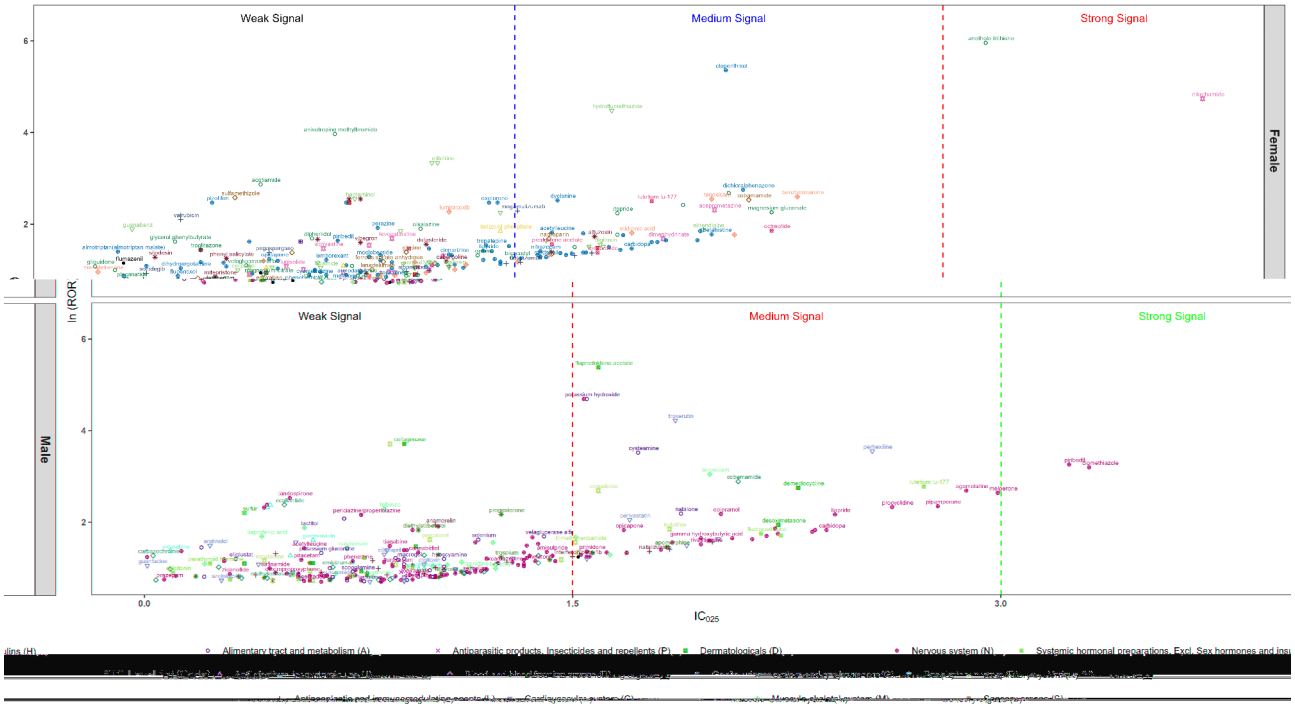

Fig. 2. The Scatterplot of signals distribution at the 1st-level Anatomical Therapeutic Chemical (ATC) classifications.

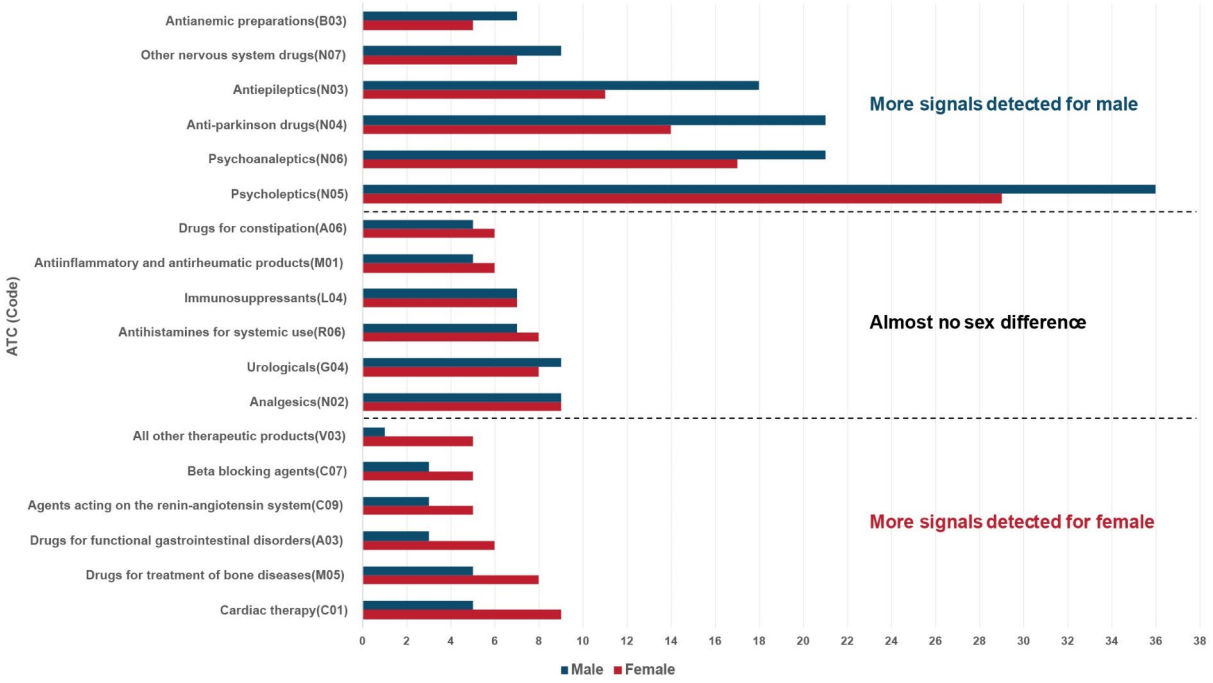

Fig. 3. The bar plot of signals at the Top 6 2nd-level Anatomical Therapeutic Chemical (ATC) classifications with / without sex differences.

Fig. 4. The values and 95% confidence intervals (CI) of F/M ratios for sex differences at the 2nd-level Anatomical Therapeutic Chemical (ATC) classification. (**a**) From A06 to C09. (**b**) From D07 to M09.

were similar sex difference results of prazosin (F/M 0.37, 95%CI 0.24–0.56) in Antihypertensives (C02) and torasemide (F/M 0.53, 95%CI 0.46–0.60) in Diuretics(C03).

Genito urinary system and sex hormones

Among Genito urinary system and sex hormones (ATC code G), tamsulosin (F/M 0.03, 95%CI 0.02–0.03) and alfuzosin (F/M 0.08, 95%CI 0.05–0.12) in urologicals (G04) were noted to have a significant higher risk of fall in men (Fig. 4b).

Systemic hormonal preparations, excl. Sex hormones and insulins

Systemic hormonal preparations, excl. sex hormones and insulins (ATC code H) comprise all hormonal preparations for systemic use. In pituitary and hypothalamic hormones and analogues (H01), lutetium lu-177 (F/M 0.25, 95%CI 0.12–0.54) revealed a stronger association with falls in men than women (Fig. 4b). In corticosteroids for systemic use(H02), fludrocortisone (F/M 0.33, 95%CI 0.24–0.43) also showed a strong difference for men, while cortisone (F/M 1.76, 95%CI 1.23–2.52) showed a high risk of fall in women. In Calcium homeostasis (H05), teriparatide revealed a strong association with females (F/M 6.65, 95%CI 5.85–7.55).

Antineoplastic and immunomodulating agents

Whether immunostimulants (L03) or immunosuppressants (L04) as shown in Fig. 4b, there seems to be a link for women between fall and immunomodulating agents, such as interferon beta-1α (F/M 2.66, 95%CI 2.46–2.87), dimethyl fumarate (F/M 2.40, 95%CI 2.03–2.83) or fingolimod (F/M 3.38, 95%CI 2.77–4.11).

Musculo-skeletal system

In drugs for treatment of bone diseases (M05), romosozumab (F/M 5.17, 95%CI 3.10–8.62), alendronate (F/M 7.36, 95%CI 6.51–8.33) and ibandronate (F/M 10.17, 95%CI 6.96–14.85) both revealed strong associations with female (Fig. 4b).

Nervous system

Among medications classified within the nervous system (ATC code N), we observed significantly sex-specific correlations for different agents. From Fig. 5a, in analgesics (N02), tilidine revealed a significantly difference for males (F/M 0.37, 95%CI 0.26–0.53), in contrast to dextropropoxyphene which revealed a strong association with females (F/M 2.69, 95%CI 1.56–4.66). In antiepileptics (N03), divalproex (F/M 0.49, 95%CI 0.36–0.65) showed a significantly difference for males, and almost all signals had similar results in anti-parkinson drugs (N04), except for safinamide. From Fig. 5b, with the categories of psycholeptics (N05) and psychoanaleptics (N06), some drugs displayed a marked predilection for male such as melperone (F/M 0.32, 95%CI 0.20–0.51) and memantine (F/M 0.71, 95%CI 0.61–0.83), while others exhibited a preferential association with females like prazepam (F/M 2.69, 95%CI 1.33–5.47) and mianserin (F/M 1.64, 95%CI 1.07–2.51). Meanwhile, other nervous system drugs (N07)

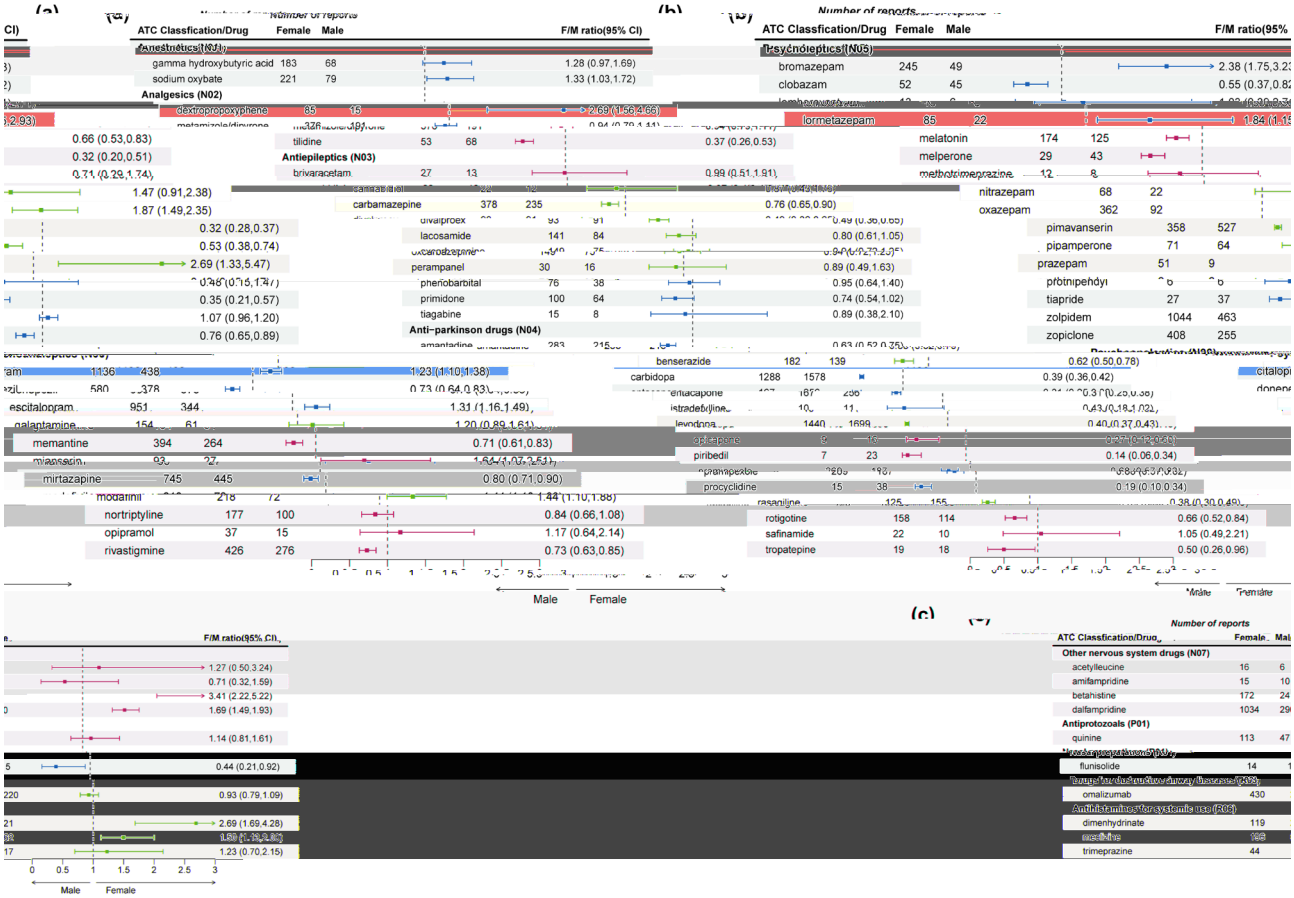

Fig. 5. The values and 95% confidence intervals (CI) of F/M ratios for sex differences at the 2nd-level Anatomical Therapeutic Chemical (ATC) classification. (**a**) From N01 to N04. (**b**) From N05 to N06. (**c**) From N07 to R06.

like dalfampridine (F/M 1.69, 95%CI 1.49–1.93) and betahistine (F/M 3.41, 95%CI 2.22–5.22) were noted to have a significant signal for female fall (Fig. 5c).

Miscellaneous medications

Cholecalciferol (F/M 1.70, 95%CI 1.57–1.85) in Vitamins (A11), meclizine (F/M 1.50, 95%CI 1.13-2.00) and dimenhydrinate (F/M 2.69, 95%CI 1.69–4.28) in antihistamines for systemic use (R06) were noted to have a significant signal for female fall. In addition, iron dextran (F/M 0.05, 95%CI 0.03–0.09) in antianemic preparations (B03) and flunisolide (F/M 0.44, 95%CI 0.21–0.92) in nasal preparations (R01) were noted to be significant for male.

Discussion

Regardless of whether they are middle-aged and elderly women or men, once the adverse event of a fall occurs, there will be a high risk of serious consequences such as hospitalization, life-threatening and even death[1], which is similar to our Table 1. Falling results from an interaction between factors within the individual (age-related changes, cognitive deficits, sensory deficits etc.) and the environment (medications, assistive devices, alcohol/drugs etc.)[8,22]. Therefore, it is very essential to prevent and reduce the occurrence of falls. Meanwhile, drugs with high risk of falls should be taken as little as possible, according to the disease condition and individual characteristics of middle-age and elderly patients. To our knowledge, there have been few previous studies that used the FAERS database to assess sex differences of FRIDs, with most studies focused on the classes of FRIDs. Additionally, in our study, ROR and BCPNN were both used to detect the FRIDs, which made it possible to obtain more reliable results when the number of AEs was low[23].

We delineated a potential association between immunomodulatory agents and the increasing risk of falls within the female population. It is well-acknowledged that limb weakness, especially the hands and arms, is believed to be driven by an immune-mediated process in many autoimmune disorders[24–26]. In contrast to robust elderly and youthful female counterparts, intramuscular total carnitine levels and short-chain acylcarnitine levels are decreased in pre-frail older females, which is associated with reduced physical performance, whereas no differences were observed in males[27]. Besides, in female but not male older adults, physical weakness was

characterized by a higher sex-specific expression of intramuscular inflammatory pathways, coupled with an infiltration of NOX2-expressing immune cells and a concomitant rise in VCAM1 expression[28]. However, there is a paucity of research examining the relationship between immunomodulators and falls across different sex, necessitating further investigation.

Teriparatide, bisphosphonates and romosozumab are existing drugs for the prevention or treatment of osteoporosis in internationally recognized clinical guidelines[29], and cholecalciferol is the preferred form of vitamin D exogenous supplementation[30], which were all observed to have significant associations with falls in women in this study. Nevertheless, considering the prevalence of bone diseases such as rheumatoid arthritis[31] and osteoporosis[32], sex differences of signals may be associated with significant sex characteristic differences of different indications as shown in Table 1. Research has demonstrated that cholecalciferol-calcium supplementation over an extended period of time reduces the odds of falling in ambulatory older women by 46%, but with a neutral effect in men[33]. Significantly, there were inconsistent results for Vitamin D supplementation interventions, with a high dose being associated with increasing risks of falls and fractures[34–36]. The crucial factor in determining the efficacy of vitamin D in preventing falls appears to be the dosage administered to each individual, regardless of sex. Nevertheless, women who take the medications mentioned above might need extra attention and care than men, no matter how the fall risk is brought from bone diseases conditions or high dosages of medications.

In the nervous system, sex differences in drug effects appear to be even more prominent. A recent study demonstrated a significant association between depressive symptoms and both the occurrence of falls and the dread of falling in the elderly. Interestingly, it highlighted a distinct sex disparity, as depression played a stronger role in women[37]. However, higher drugs use in females compared to males may be one of the reasons why sex differences were reported in some psychotropic drugs, of which antidepressants were the most frequently reported[38]. Furthermore, over 1000 transcripts with substantial interactions of sex and disease were discovered by Seney et al.[39], and these transcripts were impacted in opposite directions in men and women with major depressive disorder, leading to sex differences in the responsiveness to antidepressant medications. Antiparkinsonian medication may worsen cognitive impairment and different sex may exhibit various forms of cognitive impairment in Parkinson's patients. Sex differences may be attributed to differences in brain anatomy, chemistry, and function[40]. Antipsychotics and hypnotics, and sedatives might increase the risk of falling. Antipsychotic drugs induce falls owing to their negative effects on cognition, blood pressure management, or causing their extrapyramidal motor symptoms such as tremor, rigidity, and bradykinesia[41]. For psychotropic drugs, haloperidol and quetiapine were observed to be associated with falls, yet pipamperone and risperidone were not, indicating that falls may be associated with particular drugs rather than drug classes[42]. However, further research is needed to determine which individual drugs cause major sex differences.

By the way, tamsulosin, alfuzosin or other prostate-specific α antagonists in cardiovascular system have a minor but considerable increased risk of falls, fractures, and head injuries, most likely as a result of induced hypotension[43]. However, there is a lack of sufficient evidence to support sex difference results observed in our findings.

Some inherent limitations should be taken into consideration when interpreting the findings of our investigation. Firstly, our retrospective study design precludes the establishment of direct causality, which cannot be directly inferred from the observed results. The source of observed results was AE reports, which had various biases such as subjective judgments of the reporting personnel to FRIDs, missing data, and uneven reports quality. Secondly, because the denominator was not the total number of individuals treated with an interested drug, and the numerator did not represent the overall number of individuals who actually experience adverse drug reactions, the ROR or IC_{025} values were only rendered as metric of disproportionality of AE reporting, rather than a quantifier of relative risk. Finally, the FAERS database does not detail temporal information regarding the exposure of FRIDs and accordingly it is impossible to quantify the individual effect of multiple drug exposures. Additionally, due to the inherent limitations of disproportionality analyses in establishing causal relationships between drugs and AE, it solely provides an estimation of signal strength, which is statistically significant exclusively. However, to a certain extent, these results can provide reference for general practitioners, nursing staff, and other health professionals when making clinical medical decisions. In summary, to prevent drug-induced falling, we should not only pay attention to FRIDs categories, but drug sensitivity of different sex.

Conclusion

In a view of publicly available FAERS database, we provided a series of common drugs with fall-increasing-risks, and clearly suggested but did not prove, true and important underlying sex-related differences in falls. As there are limited studies on the effects of FRIDs with sex, it is imperative to improve the consideration of sex throughout the entire life-cycle of drug surveillance in the further. For example, in post-marketing clinical studies, it is warranted for balanced inclusions of women and men, as well as sex-stratified analyses for FRIDs.

Methods

Data source

OpenVigil 2.1-MedDRA-v24, a pharmacovigilance data analysis tool, extracts, filters and analyses preliminary cleansed AE reports which conveniently leads to precise drug safety results, whose data provided by medical practitioners were obtained from FAERS[44]. Throught Drugs@FDA and Drugbank, it has converted drug names (brand names, generic names, abbreviations, and so on) into unique drug names. Therefore, preliminary cleansed AE reports were allowed to be extracted through the query structure of drugs and/or AEs in OpenVigil 2.1. This enables users to directly obtain relevant data for specific time periods and populations based on various filtering criteria, which can then be exported for further analysis.

Reports inclusion/exclusion criteria

In this descriptive, cross-sectional study, reports were from January 2004 to March 2023 and the age of patients ranged from 50 to 100. Fall-related AEs were identified using the preferred term (PT) 'fall [10016173]' or 'drop attacks [10013643]', according to the Medical Dictionary for Regulatory Activities (MedDRA, version 24.1). The Search for drug entries was not restricted by the specified role in medication usage.

Individual safety reports (ISRs) are the frequencies statistical basis for AE reports extracted by OpenVigil 2.1. In this study, a duplicate report is considered if the ISR, reporting date, patient characteristics and drug used are all the same.

Signals inclusion/exclusion criteria

In pharmacovigilance, disproportionality analyses usually used to detect AE signals for a given drug or drug signals for a specific AE, which can be mainly divided into frequentist methods and Bayesian methods. Prevalent frequentist methods are the reporting odds ratio (ROR) and proportional reporting ratio (PRR). Contrasting to frequentist methods, Bayesian methods compare the probability of the joint occurrence of a drug-AE pair with its probability under the assumption that there is no association between the drug and the AE. The information component (IC) is provided by the Bayesian confidence propagation neural network (BCPNN), and the empirical Bayes geometric mean (EBGM) is also used[45]. However, each of these methods has benefits and drawbacks. Sakaeda et al.[18] compared above four methods and found that ROR had the highest sensitivity and detected the most signals, while EBGM had the highest specificity (followed by IC) and detected the fewest signals. Ordering to detect as many signals as possible with higher specificity, signals in our study must be satisfied both of two algorithms, ROR and BCPNN, which are based on the two-by-two contingency table (Supplementary Table S1). Besides, only drugs (such as prescription drugs, biosimilars, etc.) were included whereas vaccines, dietary supplements, or products were excluded.

For the ROR algorithm, the threshold for a signal is marked by a constellation of criteria: the count of drug–AE pairs ≥ 3, plus the value of the ROR ≥ 2, $\chi^2 \geq 4$, and the lower limit of the 95% confidence interval (95%CI) > 1[18]. In contrast, the BCPNN algorithm employs the IC value as a primary measure of the strength of the quantitative dependency between the specific drug and the reported AE. A signal was identified when the lower limit of information component (IC_{025}) > 0. Specifically, it was denoted as a weak signal if $0 < IC_{025} \leq 1.5$, with $1.5 < IC_{025} \leq 3$ characterized as medium, and $IC_{025} > 3$ considered as strong[46,47]. The equation and criteria of two algorithms are shown in Supplementary Table S2.

We filtered shared signals satisfying ROR and BCPNN between men and women simultaneously to indirectly describe their sex differences using the female/male (F/M) ratio for all of drugs. The number of fall related reports for women was divided by the number of female reports, and this proportion was subsequently divided by the similar proportion concerning men. The F/M ratio was calculated as a point estimate with a 95%CI. If the lower limit of the 95%CI of the F/M ratio was > 1, a drug was considered to have a statistically significant higher risk of falls in women than men. Conversely, if the upper limit of the 95%CI was < 1, it indicated a higher risk of fall in men. An example of how the F/M ratio was calculated is given in the equation as follows[21]:

$$F/M\ ratio\ macrogol = \frac{\frac{\text{DE reports for women}}{\text{reports concerning women}}}{\frac{\text{DE reports for men}}{\text{reports concerning men}}} = \frac{\frac{18}{68492}}{\frac{15}{32547}} = 0.57$$

$$F/M\ 95\%CI = e^{\ln \frac{F}{M}\ \text{ratio} \pm 1.96\sqrt{\frac{1}{18}+\frac{1}{68492}+\frac{1}{15}+\frac{1}{32547}}}$$

Classification of drugs

Nowadays, sanctified by the World Health Organization (WHO), the Anatomical Therapeutic Chemical (ATC) classification system is the most widely recognized classification system for medicinal substances. This system has 14 main anatomical or pharmacological groups, denoted by the 1st-level code, which serves as the foundational tier. As the system branches, the 2nd- to 4th-level ATC codes are often used to identify the therapeutic and pharmacological information of one drug[48]. Accordingly, the ATC classification emerges as an indispensable tool, facilitating the study of drug utilization and categorizing drugs based on their different purposes, therapeutic properties, chemical and pharmacological properties[49]. The ATC classification was given for each FRID in our study[50].

Statistical analysis

Data processing and statistical analysis were performed using Microsoft Excel 2019 and R statistical software version 4.3.1.

Data availability

Reports of falls-risk-increasing drugs in this study can be publicly assessed via: https://openvigil.sourceforge.net/. The ATC classification code for each drug can be referred to via: https://www.whocc.no/atc_ddd_index/. The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

Received: 16 August 2024; Accepted: 26 November 2024
Published online: 29 November 2024

References

1. Ye, P. et al. Burden of falls among people aged 60 years and older in mainland China, 1990–2019: Findings from the Global Burden of Disease Study 2019. *Lancet Public Health* **6**, e907–e918. https://doi.org/10.1016/S2468-2667(21)00231-0 (2021).
2. Wang, M. et al. Incidence and circumstances of falls among middle-aged women: a cohort study. *Osteopor. Int.* **32**, 505–513. https://doi.org/10.1007/s00198-020-05617-4 (2021).
3. Cross, A. J. et al. Interventions for improving medication-taking ability and adherence in older adults prescribed multiple medications. *Cochr. Datab. Syst. Rev.* **5**, CD012419. https://doi.org/10.1002/14651858.CD012419.pub2 (2020).
4. Zia, A., Kamaruzzaman, S. B. & Tan, M. P. Polypharmacy and falls in older people: Balancing evidence-based medicine against falls risk. *Postgrad. Med.* **127**, 330–337. https://doi.org/10.1080/00325481.2014.996112 (2015).
5. van Vries, M. et al. Fall-risk-increasing drugs: A systematic review and meta-analysis: I. Cardiovascular drugs. *J. Am. Med. Dir. Assoc.* **19**, 371e371-37e379. https://doi.org/10.1016/j.jamda.2017.12.013 (2018).
6. Seppala, L. J. et al. Fall-risk-increasing drugs: A systematic review and meta-analysis: III.. *J. Am. Med. Dir. Assoc.* **19**, 372 e371-372 e378. https://doi.org/10.1016/j.jamda.2017.12.099 (2018).
7. Seppala, L. J. et al. Fall-risk-increasing drugs: A systematic review and meta-analysis: II. Psychotropics. *J. Am. Med. Dir. Assoc.* **19**, 371 e311-371 e317. https://doi.org/10.1016/j.jamda.2017.12.098 (2018).
8. Phelan, E. A., Mahoney, J. E., Voit, J. C. & Stevens, J. A. Assessment and management of fall risk in primary care settings. *Med. Clin. North Am.* **99**, 281–293. https://doi.org/10.1016/j.mcna.2014.11.004 (2015).
9. Seppala, L. J. et al. STOPPFall (screening tool of older persons prescriptions in older adults with high fall risk): A Delphi study by the Eugms task and finish group on fall-risk-increasing drugs. *Age Ageing* **50**, 1189–1199. https://doi.org/10.1093/ageing/afaa249 (2021).
10. Osman, A. et al. Fall risk-increasing drugs and gait performance in community-dwelling older adults: A systematic review. *Ageing Res. Rev.* **77**, 101599. https://doi.org/10.1016/j.arr.2022.101599 (2022).
11. Pronk, A. C. et al. Candidate genetic variants and antidepressant-related fall risk in middle-aged and older adults. *PloS One* **17**, e0266590. https://doi.org/10.1371/journal.pone.0266590 (2022).
12. Mauvais-Jarvis, F. et al. Sex- and gender-based pharmacological response to drugs. *Pharmacol. Rev.* **73**, 730–762. https://doi.org/10.1124/pharmrev.120.000206 (2021).
13. Zucker, I. & Prendergast, B. J. Sex differences in pharmacokinetics predict adverse drug reactions in women. *Biol. Sex Differ.* https://doi.org/10.1186/s13293-020-00308-5 (2020).
14. Lacroix, C. et al. Sex differences in adverse drug reactions: Are women more impacted?. *Therapie* **78**, 175–188. https://doi.org/10.1016/j.therap.2022.10.002 (2023).
15. Chang, V. C. & Do, M. T. Risk factors for falls among seniors: Implications of gender. *Am. J. Epidemiol.* **181**, 521–531. https://doi.org/10.1093/aje/kwu268 (2015).
16. Ardaneh, M., Fararouei, M. & Hassanzadeh, J. Gender difference in the perceived cause of fall leading to fracture and its potentially contributing factors among older adults. *J. Inj. Violence Res.* **15**, 157–164. https://doi.org/10.5249/jivr.v15i2.1788 (2023).
17. Martinez-Cengotitabengoa, M. et al. Benzodiazepine prescriptions and falls in older men and women. *Revista De Psiquiatria Y Salud Mental* **11**, 12–18. https://doi.org/10.1016/j.rpsm.2017.01.004 (2018).
18. Sakaeda, T. et al. Data mining of the public version of the FDA adverse event reporting system. *Int. J. Med. Sci.* **10**, 796–803. https://doi.org/10.7150/ijms.6048 (2013).
19. Wang, D. Y. et al. Fatal toxic effects associated with immune checkpoint inhibitors: A systematic review and meta-analysis. *JAMA Oncol.* **4**, 1721–1728. https://doi.org/10.1001/jamaoncol.2018.3923 (2018).
20. Jing, Y. et al. association between sex and immune-related adverse events during immune checkpoint inhibitor therapy. *J. Natl. Cancer Inst.* **113**, 1396–1404. https://doi.org/10.1093/jnci/djab035 (2021).
21. Ekhart, C. et al. Sex differences in reported adverse drug reactions of selective serotonin reuptake inhibitors. *Drug Saf.* **41**, 677–683. https://doi.org/10.1007/s40264-018-0646-2 (2018).
22. Ham, A. C. et al. Medication-related fall incidents in an older, ambulant population: The B-PROOF study. *Drugs Aging* **31**, 917–927. https://doi.org/10.1007/s40266-014-0225-x (2014).
23. Setyawan, J. et al. Reporting of thromboembolic events with JAK inhibitors: Analysis of the FAERS database 2010–2019. *Drug Saf.* **44**, 889–897. https://doi.org/10.1007/s40264-021-01082-y (2021).
24. Umapathi, T. et al. Immunosuppressant and immunomodulatory treatments for multifocal motor neuropathy. *Cochr. Database Syst. Rev.* **2015**, CD003217. https://doi.org/10.1002/14651858.CD003217.pub5 (2015).
25. Park, H.-S. et al. Risk of fracture in patients with myasthenia gravis: A nationwide cohort study in Korea. *J. Bone Miner. Res.* **39**, 688–696. https://doi.org/10.1093/jbmr/zjae043 (2024).
26. Mahdi-Rogers, M. et al. Immunomodulatory treatment other than corticosteroids, immunoglobulin and plasma exchange for chronic inflammatory demyelinating polyradiculoneuropathy. *Cochr. Database Syst. Rev.* **5**, 003280. https://doi.org/10.1002/14651858.CD003280.pub5 (2017).
27. van der Hoek, M. D. et al. Intramuscular short-chain acylcarnitines in elderly people are decreased in (pre-)frail females, but not in males. *FASEB J.* **34**, 11658–11671. https://doi.org/10.1096/fj.202000493R (2020).
28. de Jong, J. C. B. C. et al. Evidence for sex-specific intramuscular changes associated to physical weakness in adults older than 75 years. *Biol. Sex Differ.* **14**, 45. https://doi.org/10.1186/s13293-023-00531-w (2023).
29. Khosla, S. & Hofbauer, L. C. Osteoporosis treatment: Recent developments and ongoing challenges. *Lancet Diabetes Endocrinol.* **5**, 898–907. https://doi.org/10.1016/S2213-8587(17)30188-2 (2017).
30. Sosa Henríquez, M., de Tejada, G. & Romero, M. J. Cholecalciferol or calcifediol in the management of vitamin D deficiency. *Nutrients* https://doi.org/10.3390/nu12061617 (2020).
31. Favalli, E. G. et al. Sex and management of rheumatoid arthritis. *Clin. Rev. Allergy Immunol.* **56**, 333–345. https://doi.org/10.1007/s12016-018-8672-5 (2019).
32. Wang, J. et al. The prevalence of osteoporosis in China, a community based cohort study of osteoporosis. *Front. Public Health* **11**, 1084005. https://doi.org/10.3389/fpubh.2023.1084005 (2023).
33. Bischoff-Ferrari, H. A., Orav, E. J. & Dawson-Hughes, B. Effect of cholecalciferol plus calcium on falling in ambulatory older men and women: A 3-year randomized controlled trial. *Arch. Intern. Med.* **166**, 424–430 (2006).
34. Guirguis-Blake, J. M. et al. Interventions to prevent falls in older adults: Updated evidence report and systematic review for the US preventive services task force. *JAMA* **319**, 1705–1716. https://doi.org/10.1001/jama.2017.21962 (2018).
35. Gallagher, J. C. Vitamin D and falls—The dosage conundrum. *Nat. Rev. Endocrinol.* **12**, 680–684. https://doi.org/10.1038/nrendo.2016.123 (2016).
36. Tan, L., He, R. & Zheng, X. Effect of vitamin D, calcium, or combined supplementation on fall prevention: A systematic review and updated network meta-analysis. *BMC Geriatr.* **24**, 390. https://doi.org/10.1186/s12877-024-05009-x (2024).
37. Park, Y. et al. Depressive symptoms, falls, and fear of falling in old Korean adults: The Korean longitudinal study on health and aging (KLoSHA). *J. Frailty Aging* **6**, 144–147. https://doi.org/10.14283/jfa.2017.21 (2017).
38. Watson, S. et al. Reported adverse drug reactions in women and men: Aggregated evidence from globally collected individual case reports during half a century. *EClinicalMedicine* **17**, 100188. https://doi.org/10.1016/j.eclinm.2019.10.001 (2019).
39. Seney, M. L., Glausier, J. & Sibille, E. Large-scale transcriptomics studies provide insight into sex differences in depression. *Biol. Psychiatry* **91**, 14–24. https://doi.org/10.1016/j.biopsych.2020.12.025 (2022).

40. Yang, K. et al. Cognitive characteristics in Chinese non-demented PD patients based on gender difference. *Transl. Neurodegener.* **7**, 16. https://doi.org/10.1186/s40035-018-0120-1 (2018).
41. Berry, S. D. et al. Antipsychotic and benzodiazepine drug changes affect acute falls risk differently in the nursing home. *J. Gerontol. A Biol. Sci. Med. Sci.* **71**, 273–278. https://doi.org/10.1093/gerona/glv091 (2016).
42. Janus, S. I. M. et al. psychotropic drug-related fall incidents in nursing home residents living in the eastern part of The Netherlands. *Drugs R. D.* **17**, 321–328. https://doi.org/10.1007/s40268-017-0181-0 (2017).
43. Welk, B. et al. The risk of fall and fracture with the initiation of a prostate-selective α antagonist: A population based cohort study. *BMJ* **351**, h5398. https://doi.org/10.1136/bmj.h5398 (2015).
44. von Hehn, L. et al. Clinical applications of the OpenVigil 2 pharmacovigilance analysis tool: Reverse disproportionality analyses and detection of drug-drug interactions. *Naunyn-Schmiedebergs Arch. Pharmacol.* **388**, S57–S58 (2015).
45. Huang, L. et al. A review of statistical methods for safety surveillance. *Therap. Innov. Regul. Sci.* **48**, 98–108. https://doi.org/10.1177/2168479013514236 (2014).
46. Carrer, P. et al. Dehydroepiandrosterone sulfate and fall risk in older people: Sex differences in the Pro.V.A. longitudinal study. *Maturitas* **128**, 43–48. https://doi.org/10.1016/j.maturitas.2019.07.003 (2019).
47. Noren, G. N. et al. Extending the methods used to screen the WHO drug safety database towards analysis of complex associations and improved accuracy for rare events. *Stat. Med.* **25**, 3740–3757. https://doi.org/10.1002/sim.2473 (2006).
48. Peng, Y. et al. Drug repositioning by prediction of drug's anatomical therapeutic chemical code via network-based inference approaches. *Brief Bioinform.* **22**, 2058–2072. https://doi.org/10.1093/bib/bbaa027 (2021).
49. Chen, L. et al. Predicting Anatomical Therapeutic Chemical (ATC) classification of drugs by integrating chemical-chemical interactions and similarities. *PLoS One* **7**, e35254. https://doi.org/10.1371/journal.pone.0035254 (2012).
50. WHO Collaborating Centre for Drug Statistics Methodology. *ATC/DDD Index*, <https://www.whocc.no/atc_ddd_index/.> (2023).

Author contributions

Ying Zhao and Weitao Lu contributed to the conceptualization and design of the study and wrote the original draft. Yuke Zhong took responsibility for the collection, integrity, and accuracy of the data. Liuqing Wu and Jiao Yan contributed to data curation. All authors contributed to the manuscript's revision and read and approved the submitted version.

Funding

No sources of funding were used to assist in the preparation of this study.

Declarations

Competing interests

The authors declare no competing interests.

Additional information

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-024-81342-w.

Correspondence and requests for materials should be addressed to W.L.