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# Women in pharmacoepidemiology 2021

**Edited by**
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# Women in pharmacoepidemiology: 2021

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# Editorial: Women in pharmacoepidemiology: 2021

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KEYWORDS

**women, pharmacoepidemiolgy, public healh, real world data (RWD), medicine**

Editorial on the Research Topic
Women in pharmacoepidemiology: 2021

This is the first Research Topic offering the opportunity to promote the work of women scientists at different stages of their careers, worldwide, and in all areas of pharmacoepidemiology. This Research Topic contains 11 studies led by women from different parts of the world, including five studies from Brazil, three from Canada, one from the United States, one from Switzerland and one from Romania. The work presented here highlights the diversity of research carried out across the breadth of pharmacoepidemiology research and presents advances in theory and methodology with applications to compelling problems. This current Research Topic includes studies related to chronic health conditions, including cardiovascular, renal, respiratory, and cancer diseases.

An important theme present in this Research Topic is the use of real world data (RWD) to generate evidence for decision-making. RWD has gained significant attention in the field of research as it provides a valuable data source beyond traditional clinical trials and lab-based experiments. RWD can come from various sources, including but not limited to healthcare administrative data, hospitalization databases, electronic health databases, surveys, data from government agencies and others. Healthcare administrative data refers to the information collected and maintained by healthcare organizations, insurers, and government agencies for the purpose of managing, tracking, and reimbursing various aspects of healthcare services. An interesting scoping review (Bukhtiyarova et al.) was conducted to explore the current state of existing research according to the application of Artificial intelligence (AI) to healthcare administrative data, including those involving medications. The application of AI to healthcare administrative data is heterogeneous in terms of areas of interest and methods. One of the points highlighted by the authors is that AI can significantly improve research on the utilization of healthcare administrative data. This phenomenon can be explained by the accumulation of large volumes of this type of data, improved access to such databases for AI researchers, further development of AI methods, improved computational capacities, and increased funding of interdisciplinary projects. The authors found that many studies were focused on data from hospitals and emergency departments which can be explained by better accumulation of data by large hospitals that are often affiliated to

universities, and their better accessibility for AI research. The most popular health areas for the application of AI include the prediction of health outcomes and the handling of large health datasets. These findings point to the need to improve data collection and accessibility for scientific research of outpatient data. Three studies (Barbosa et al., Frent et al., Okuyama et al.) used data from pharmacovigilance databases to generate safety data. Okuyama et al. analyzed cross-referenced information from three different healthcare administrative databases: official death records between 1996 and 2019 from the Mortality Information System in Brazil, hospitalizations between 2008 and 2020 from the Hospital Information System, and cases of poisonings between 2017 and 2020 in health services that have been notified to the National System for Vigilance of Notifiable Diseases. The analysis shows that the reports were more frequent among adults, particularly women, and due to accidents, with exposure to paracetamol identified as a concern for preventable intoxications, hospitalizations and deaths. Barbosa et al. identified early safety signals of antibacterial agents to support pharmacovigilance systems using data from a Brazilian database (Vigimed/VigiFlow) from December 2018 to December 2021. Vancomycin was the most reported antibiotic, followed by ceftriaxone and piperacillin and tazobactam. Three serious events were associated with ceftazidime and avibactam, a new drug in the Brazilian market. Frent et al. performed a descriptive analysis of cases of acute renal failure and nephrolithiasis reported from Sodium–Glucose Co-Transporter 2 (SGLT2) inhibitors in VigiBase to September 2021. The vast majority of acute renal failure and nephrolithiasis reports were considered serious. Canagliflozin was the gliflozin most involved in cases of acute renal failure and nephrolithiasis.

Healthcare records are another important source of real world data. Healthcare records play a crucial role in generating RWD in the field of healthcare and medical research. One way that healthcare records contribute to generating real-world evidence is through observational studies using de-identified patient data from healthcare records. A cross-sectional database study in Switzerland (Rachamin et al.) used medical records to determine patient age- and sex-specific prevalence rates of polypharmacy, and rates of prescribing of the most frequently used medication classes; they also explored practitioner variability in prescribing practices in Swiss general practitioners. The prevalence of polypharmacy in the adult Swiss general practice population was determined to be 24%, increasing with age: from 6% in patients aged 18–40 years to 65% in patients aged 81–92 years. Women had higher rates of polypharmacy than men. The difference was more pronounced at younger ages, and interestingly, hormonal contraceptives did not relevantly contribute to the difference. The most clear drivers of the differing rates of polypharmacy in the younger population were higher prescription rates of vitamins, mineral supplements, and antianemic preparations in female patients. Men were more often prescribed agents targeting the cardiovascular system (such as antihypertensive agents, antithrombotic agents, and lipid modifying agents), whereas most other medications were more often prescribed to women. A cohort study (Gorgui et al.) undertaken in Canada involving the linkage of three Quebec databases was undertaken to quantify the risk of babies being born small for gestational age (SGA) and very small for gestational age (VSGA) with the use of medically assisted reproduction. While no association was observed between medically assisted reproduction and SGA or VSGA in the study population; medically assisted reproduction was associated with an increased risk for SGA among preterm pregnancies; no increased risk of SGA was observed in term pregnancies. Another cohort study (Oh et al.) examined the association between gabapentin use and neurocognitive changes in older adults using the National Alzheimer's Coordinating Center Uniform Data Set (NACC UDS). The NACC UDS has rich data and is an example of how building a database with real world data focused on answering research questions can contribute to decision making in health. This data set provided a greater sample size compared with previous studies in this population and was able to measure the association between gabapentin initiation and neurocognition with various clinically relevant outcomes. The results provided evidence that gabapentin was associated with increased odds of global cognitive decline, functional status decline, and motor function change in the 2 years following gabapentin initiation. Considering that gabapentin may block calcium channels in the brain, it was hypothesized that it would have a neuroprotective effect, but these findings did not support this assumption. The authors concluded that further experimental studies are needed to examine the mediators of gabapentin use and neurocognitive changes.

On the other hand, systematic reviews with meta-analyses (SR-MA) also play a crucial role in informing healthcare decisions, policy-making, and advancing scientific knowledge. Two systematic reviews and meta-analyses published in this Research Topic were designed to complement the knowledge obtained from randomized control trials and observational studies of primary data to evaluate the real-world effectiveness of medications. These reviews (Castro et al., Queiroz et al.) summarized the evidence produced from observational studies involving administrative databases of different drug classes of disease-modifying drugs (DMARDs) in patients with rheumatoid arthritis (RA). The meta-analysis by Queiroz et al. did not suggest there is an increased risk of adverse events associated with the use of biologics for the treatment of RA, indicating a lower risk of cardiovascular events with abatacept than tumor necrosis factor inhibitors (TNFi) (low to very low certainty of the evidence). The meta-analysis by Castro et al. synthesized data on 182,098 RA patients across 21 studies included. They concluded that biologics effectively treat patients with RA, with higher effectiveness for non-TNFi and Janus kinase inhibitors (JAKi) than with TNFi. A policy brief is another type of evidence synthesis combining research evidence specific to stakeholders' contextual knowledge. The policy brief from Fulone et al. identified evidence-based strategies to improve adherence to preventive measures against COVID-19 at the community level. Three evidence-based strategies were identified: i) Risk communication; ii) Health education to the general public, and iii. Financial support and access to essential supplies and services. The evidence showed that an increase in knowledge, transparent communication, and public awareness about the risks of COVID-19 and the benefits of adopting preventive measures result in changes in people's attitudes and behavior, which can increase adherence. These strategies can guide future actions and the formulation of public policies to improve adherence to preventive measures in the community in future epidemics. Finally, this Research Topic also includes a protocol on a scoping review (Leal et al.) describing the methodology for assessing the available literature on emulation target trials to study outcomes in women exposed to medications in the preconception, perinatal, or postpartum periods.

To conclude, this first Research Topic on Women in Pharmacoepidemiology highlights the range of robust research that is being performed by women in science, and pharmacoepidemiology in particular, across the globe today. Research is varied, and complementary, and is being undertaken across the life course, from conception to adulthood. However, the lack of true global representation of women in science is a significant issue that has persisted for many years and requires a multi-faceted approach to address the issue. Efforts to increase the representation of women in science should be a priority for governments, educational institutions, scientific organizations, and society as a whole. By breaking down barriers and creating more inclusive environments, we can unlock the full potential of women in advancing scientific discovery and innovation. We need to do better in the future to promote the work of women scientists all over the world. It is with great pleasure that we are presenting *Women in pharmacoepidemiology: 2021*.

## Author contributions

LL: Conceptualization, Writing–original draft, Writing–review and editing. DM: Writing–review and editing. TD: Writing–review and editing. NG: Writing–review and editing. BM: Writing–review and editing. AB: Writing–review and editing.

## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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# Prescription Rates, Polypharmacy and Prescriber Variability in Swiss General Practice—A Cross-Sectional Database Study

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**Purpose:** The frequency of medication prescribing and polypharmacy has increased in recent years in different settings, including Swiss general practice. We aimed to describe patient age- and sex-specific rates of polypharmacy and of prescriptions of the most frequent medication classes, and to explore practitioner variability in prescribing.

**Methods:** Retrospective cross-sectional study based on anonymized electronic medical records data of 111 811 adult patients presenting to 116 Swiss general practitioners in 2019. We used mixed-effects regression analyses to assess the association of patient age and sex with polypharmacy (≥5 medications) and with the prescription of specific medication classes (second level of the Anatomical Therapeutic Chemical Classification System). Practitioner variability was quantified in terms of the random effects distributions.

**Results:** The prevalence of polypharmacy increased with age from 6.4% among patients aged 18–40 years to 19.7% (41–64 years), 45.3% (65–80 years), and 64.6% (81–92 years), and was higher in women than in men, particularly at younger ages. The most frequently prescribed medication classes were *antiinflammatory and antirheumatic products* (21.6% of patients), *agents acting on the renin-angiotensin system* (19.9%), *analgesics* (18.7%), and *drugs for acid related disorders* (18.3%). Men were more often prescribed agents targeting the cardiovascular system, whereas most other medications were more often prescribed to women. The highest practitioner variabilities were observed for *vitamins*, for *antiinflammatory and antirheumatic products,* and for *mineral supplements*.

**Conclusion:** Based on practitioner variability, prevalence, and risk potential, antiinflammatory drugs and polypharmacy in older patients appear to be the most pressing issues in current drug prescribing routines.

**Keywords: drug prescriptions, polypharmacy, clinical practice variation, demographic aging, sex differences, primary care, Switzerland**

# INTRODUCTION

A global increase in life expectancy has been observed in recent decades (GBD 2017 Mortality Collaborators, 2018), resulting in an older and more chronically ill population (Barnett et al., 2012; Cao et al., 2020). This demographic change is inevitably accompanied by an increasing need for medical interventions such as medication prescribing. Accordingly, the prevalence of polypharmacy (i.e., concurrent prescription of five or more medications) has climbed to over 25% among the older population in many healthcare systems (Guthrie et al., 2015a; Midão et al., 2018; Khezrian et al., 2020). This phenomenon is concerning because incremental health benefits tend to decrease with each additional medication, while the risk of adverse effects increases and may even outweigh the expected benefits (Kongkaew et al., 2013; Donaldson et al., 2017; Insani et al., 2021). The risk associated with prescribing varies greatly among different medication classes, with some medications (e.g., vitamins) posing minimal risks and others (e.g., anti-inflammatory drugs) posing substantial risks (Singh and Triadafilopoulos, 1999; McGettigan and Henry, 2011).

Given the potential negative health consequences of excessive prescribing and, in particular, polypharmacy, unwarranted variability in prescribing is of particular concern. Prescribing variability is unwarranted when it depends on physician factors (i.e., recognition of an indication) rather than patient factors (i.e., the presence of an indication) (Wennberg, 2011). Practitioner variability can thus serve as an indicator of issues with indication quality and potential healthcare inequity, which are particularly problematic in publicly funded healthcare systems like the Swiss.

Large primary care databases have been used before for measuring prescription rates and general practitioner (GP) variability in prescribing, but analyses have generally been limited to specific medication classes (e.g., antibiotics or opioids) (Guthrie et al., 2015b; Haastrup et al., 2016; Coyle et al., 2019) or populations (e.g., older patients) (Aubert et al., 2016; Schnegg et al., 2020). Comprehensive assessments across all medication classes and patient demographics are needed to identify the specific medication classes contributing to polypharmacy and to develop targeted initiatives to improve prescribing practices.

Therefore, the aim of the present study was to comprehensively describe medication prescribing in Swiss general practice and, in particular, to present patient age- and sex-specific prescription rates as well as practitioner variability in polypharmacy and the most common medication classes.

# METHODS

## Study Design, Setting, and Participants

We performed a retrospective cross-sectional study based on data from the large Swiss primary care database FIRE (FIRE is an acronym for Family Medicine ICPC Research using Electronic Medical Records) (Chmiel et al., 2011). Since the FIRE project started in 2009, over 700 individual GPs have voluntarily contributed anonymized clinical routine data from their electronic medical records to the FIRE database (>10% of all Swiss GPs (mfe Haus- und Kinderärzte Schweiz, 2020)). As of April 2021, the database holds over 11 million consultation records with administrative information, laboratory and vital signs measures as well as medication plans.

For this study, we included GPs of practices exporting medication data labelled with starting and stopping dates since at least the year 2018 and covering the full year 2019 (26.6% of FIRE practices in 2019). From included GPs, we considered all patients aged 18 years or older who had at least one consultation in the year 2019 (total number of considered patients: $n$ = 112 934). We grouped patients of the same sex and age (in years) into sex × age strata and excluded all patients in strata of less than 100 patients (i.e., all patients aged >92 years, $n$ = 1 123). This left 111 811 patients in 150 sex × age strata for analysis.

The local Ethics Committee of the Canton of Zurich waived approval for the present study because the FIRE project is outside the scope of the law on human research (BASEC-Nr. Req-2017–00797).

## Database Query and Definitions

We extracted GP- and patient-level data from the database. From GPs, we used sex and year of birth. From patients, we used sex, year of birth, and the list of active medication prescriptions at their last consultation in 2019. We labeled medication prescriptions with the anatomical therapeutic chemical (ATC) classification system (WHOCC, 2020). The ATC classification system organizes active substances in a hierarchy with five different levels, according to the organ or system on which they act and their therapeutic, pharmacological, and chemical properties. We identified ATC codes of all recorded prescriptions, and excluded non-systemic medications, namely: 1) dermatologicals (ATC code D) except antifungals for systemic use (D01B), antipsoriatics for systemic use (D05B), and anti-acne preparations for systemic use (D10B); 2) drugs targeting sensory organs (S), i.e., ophthalmologicals and otologicals; 3) stomatological preparations (A01); 4) antiinflammatory preparations for topical use (M02AA); 5) throat preparations (R02); 6) agents for treatment of hemorrhoids and anal fissures for topical use (C05A); 7) decongestants and other nasal preparations for topical use (R01A); and 8) heparins or heparinoids for topical use (C05BA). Lastly, we excluded vaccines (J02) because of inconsistent data capturing.

For each patient, the medication count was defined as the number of distinct, active ATC codes (considering all five levels of the code), and polypharmacy was defined as a medication count ≥5. For the remaining analyses, prescriptions were aggregated on the second level of the ATC code, which represents therapeutic or pharmacological subgroups. We referred to the aggregated prescriptions as "(medication) classes". We adopted the names of the classes as defined in the ATC classification system.

## Statistical Analysis

We used counts and proportions ($n$ and %) or medians with interquartile ranges (IQRs) to describe the data. Prescription rates

**TABLE 1 |** Description of patients overall and by age group.

| Variables | Overall (*n* = 111 811) | Age 18–40 years (*n* = 36 458) | Age 41–64 years (*n* = 44 167) | Age 65–80 years (*n* = 22 698) | Age 81–92 years (*n* = 8 488) |
|---|---|---|---|---|---|
| Female sex, % | 51.7 | 52.0 | 49.9 | 51.7 | 60.2 |
| Age, median (IQR) | 52 (35–66) | 30 (24–35) | 53 (47–58) | 72 (68–76) | 85 (83–88) |
| Number of consultations in 2019, median (IQR) | 4 (2–9) | 2 (1–5) | 4 (2–8) | 7 (3–13) | 10 (4–19) |
| Medication count, median (IQR) | 2 (0–4) | 1 (0–2) | 2 (0–4) | 4 (2–7) | 6 (3–10) |
| Prevalence of polypharmacy (≥5 medications), % | 24.0 | 6.4 | 19.7 | 45.3 | 64.6 |
| Prescription rates of medication classes, % | | | | | |
| Antiinflammatory and antirheumatic products | 21.6 | 16.5 | 23.9 | 26.3 | 18.6 |
| Agents acting on the renin-angiotensin system | 19.9 | 1.3 | 18.2 | 42.4 | 47.8 |
| Analgesics | 18.7 | 11.3 | 17.3 | 24.3 | 43.4 |
| Drugs for acid related disorders | 18.3 | 7.9 | 18.4 | 29.4 | 33.3 |
| Vitamins | 15.5 | 6.9 | 14.0 | 24.7 | 35.4 |
| Antithrombotic agents | 14.2 | 1.2 | 8.5 | 32.3 | 51.5 |
| Lipid-modifying agents | 12.1 | 0.3 | 9.7 | 30.8 | 25.9 |
| Beta blocking agents | 10.5 | 1.0 | 7.5 | 23.2 | 33.4 |
| Psychoanaleptics | 10.5 | 6.2 | 11.2 | 12.3 | 20.3 |
| Psycholeptics | 9.3 | 3.1 | 8.1 | 14.7 | 27.5 |
| Mineral supplements | 8.8 | 4.2 | 7.6 | 14.6 | 20.1 |
| Drugs for obstructive airway diseases | 8.7 | 6.8 | 8.5 | 11.4 | 11.0 |
| Antianemic preparations | 8.3 | 6.9 | 6.9 | 10.0 | 17.9 |
| Drugs for constipation | 6.7 | 2.5 | 4.7 | 10.8 | 24.1 |
| Antihistamines for systemic use | 6.0 | 6.7 | 6.1 | 5.1 | 4.7 |
| Calcium channel blockers | 5.5 | 0.3 | 3.9 | 11.7 | 19.0 |
| Diuretics | 5.1 | 0.1 | 2.1 | 10.4 | 28.2 |
| Drugs used in diabetes | 5.0 | 0.5 | 4.5 | 10.9 | 11.4 |
| Urologicals | 5.0 | 0.6 | 3.8 | 11.3 | 12.6 |
| Thyroid therapy | 4.4 | 1.9 | 4.3 | 6.9 | 9.1 |

*Abbreviations: IQR, interquartile range.*

and polypharmacy rates per stratum (overall, sex-specific, age-specific, sex × age-specific) were calculated as proportions of patients with a prescription within a specific medication class or with polypharmacy, respectively. Sex × age-specific prescription rates of the different medication classes as well as sex-specific and age-specific rates of polypharmacy were presented graphically.

For statistical modelling, patient age was categorized into the groups 18–40 years, 41–64 years, 65–80 years, and 81–92 years. For each medication class separately, we built a mixed-effects logistic regression model of whether a patient had a matching prescription, with demographic patient variables as fixed effects (age groups and sex, with interaction terms) and random GP effects. An analogous model was built for the presence of polypharmacy. For the regression analyses, only GPs with at least 500 patients in 2019 were considered ($n$ = 100 of total $n$ = 116).

To explore practitioner variability in prescribing, we reported crude distributions of GP-specific prescription rates (again considering only GPs with at least 500 patients). Also, using the 5th and 95th percentiles of the fitted random effects distributions, we quantified the variability unexplained by covariates, both of prescribing the various medication classes and of polypharmacy, using the odds ratios $OR_{lib/cons} = \exp(q_{0.95} - q_{0.05})$, which are interpreted as the odds ratio (OR) of prescribing the respective medication class or of polypharmacy, respectively, between a rather liberal prescriber (at the 95th percentile of the random effects distribution) and a rather conservative prescriber (at the 5th percentile of the random effects distribution) for a patient of the same sex and age group. We reported results for the 20 medication classes with the highest overall prescription rates in the main text (out of a total of 72 appearing in the database); the appendix expands results to all classes with overall prescription rates >1%. For statistical analysis and visualization we used the R software (R Core Team. R, 2019), Version 4.0.0. Significance was assumed for $p$-values < 0.005 (Benjamin et al., 2018); 99.5% confidence intervals (CIs) were reported.

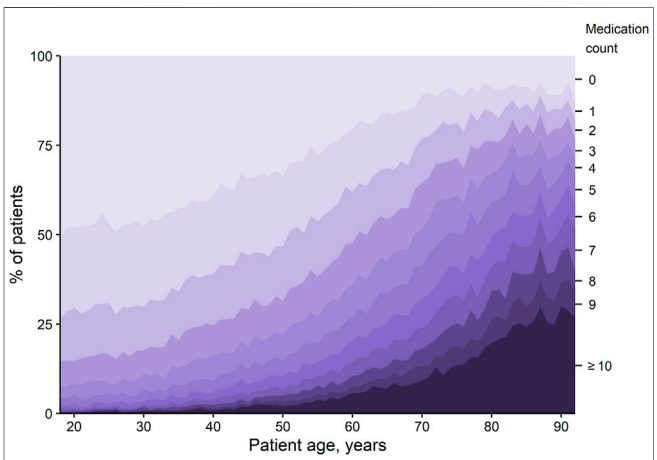


**FIGURE 1 |** Proportion of patients with the specified number of medications, depending on age. Each shaded region represents the overall percentage of patients with the respective number of medications.

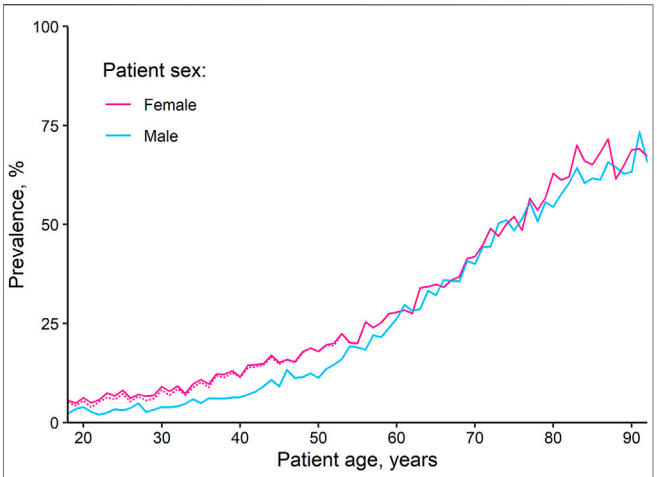


**FIGURE 2 |** Age-dependent polypharmacy rates, by sex. The dotted line represents the proportion of female patients with polypharmacy if hormonal contraceptives for systemic use are excluded.

# RESULTS

## Patient and GP Population

We analyzed 111 811 adult patients of 116 different GPs. Patients are described in **Table 1**, overall and by age group (for description of patients by sex, see **Supplementary Table S1**). Of GPs, 34.5% were female, the median GP age was 52 years (IQR 43–57), and GPs treated 923 patients (IQR 643–1 218) in median.

## Medication Counts and Polypharmacy

Overall, 28.9% of patients were without medication, 47.2% were prescribed one to four medications, and 24.0% had polypharmacy. The median medication count was 2 (IQR 0–4) overall and 3 (IQR 2–6) among patients with at least one medication. Medication counts (**Figure 1**) and, as a consequence, the likelihood of having polypharmacy (**Figure 2**), increased with patient age (see **Table 1** for crude numbers and **Supplementary Table S2** for regression analyses). Male patients exhibited considerably lower rates of polypharmacy than female patients in all age groups except 65–80 years (age 18–40 years: OR = 0.49 [99.5% CI 0.43 to 0.55], age 41–64 years: OR = 0.78 [99.5% CI 0.73 to 0.84], age 81–92 years: OR = 0.82 [99.5% CI 0.72 to 0.94], **Supplementary Table S2**). The difference remained even after hormonal contraceptives were excluded (**Figure 2**).

## Medication Classes

The most often prescribed medication classes were *antiinflammatory and antirheumatic products* (prescribed for 21.6% of patients), *agents acting on the renin-angiotensin system* (19.9%), *analgesics* (18.7%), and *drugs for acid related disorders* (18.3%; see **Supplementary Table S3** for all prescription rates >1%).

For the vast majority of medication classes, prescription rates significantly increased with age (**Figure 3**; **Supplementary Table S2** for regression models). Exceptions were *antihistamines*, which showed a decrease with age, *antianemic preparations*, which decreased in female patients at middle ages before increasing again at older ages, and *antiinflammatory and antirheumatic products* as well as *lipid modifying agents*, which increased up to a certain age before decreasing.

Prescription rates of all medication classes showed significant sex differences at certain ages (**Figure 3** and **Supplementary Table S2**). Men were more often prescribed agents targeting the cardiovascular system (such as *antihypertensive agents*, *antithrombotic agents*, and *lipid modifying agents*), whereas most remaining classes were more often prescribed to women. Consistently significant and unidirectional prescription rate differences across all age groups appeared in *antiinflammatory and antirheumatic products* (female > male), *analgesics* (female > male), *vitamins* (female > male), *lipid modifying agents* (male > female), *psychoanaleptics* (female > male), *mineral supplements* (female > male), *drugs for constipation* (female > male), *urologicals* (male > female), and *thyroid therapy* (female > male). Some medication classes exhibited sex differences only in older ages (*drugs for acid related disorders*, *drugs used in diabetes*), while for others, sex differences existed at younger ages and diminished with age (*drugs for obstructive airway disease*, *antianemic preparations*, and *antihistamines for systemic use*).

## Practitioner Variability

For polypharmacy, practitioner variability in terms of $OR_{lib/cons}$ was 4.4, meaning that patients of a given sex and age had 4.4 higher odds of having polypharmacy if they were treated by a liberal prescriber compared to a conservative prescriber. Among the medication classes, the highest practitioner variability was observed for *vitamins* ($OR_{lib/cons}$ = 8.8), followed by *antiinflammatory and antirheumatic products* ($OR_{lib/cons}$ = 5.6) and *mineral supplements* ($OR_{lib/cons}$ = 5.0). Lowest variability was observed for *antithrombotic agents* and *thyroid therapy* (both $OR_{lib/cons}$ = 2.0), followed by *psychoanaleptics* and *urologicals* (both $OR_{lib/cons}$ = 2.2). The crude practitioner variabilities of the medication classes (boxplots) along with the $OR_{lib/cons}$ are shown in **Figure 4**.

# DISCUSSION

Comprehensive displays of medication prescribing are scarce. Our study, designed to fill this gap, confirms patient age and sex differences in prescribing of specific medication classes and polypharmacy and reveals considerable practitioner variability in prescribing. In addition to providing epidemiologic insight, our findings uncover medication classes with high prescription rates and practitioner variability, thereby highlighting potential for improvement.

Overall, we found a polypharmacy prevalence of about 24% in the adult Swiss general practice population, increasing with age from 6% in patients aged 18–40 years to 65% in patients aged 81–92 years. Assessments of polypharmacy in younger individuals are scarce. In this context, our polypharmacy prevalence of 20% in patients aged 41–64 years, consistent with findings from Scotland (Guthrie et al.,

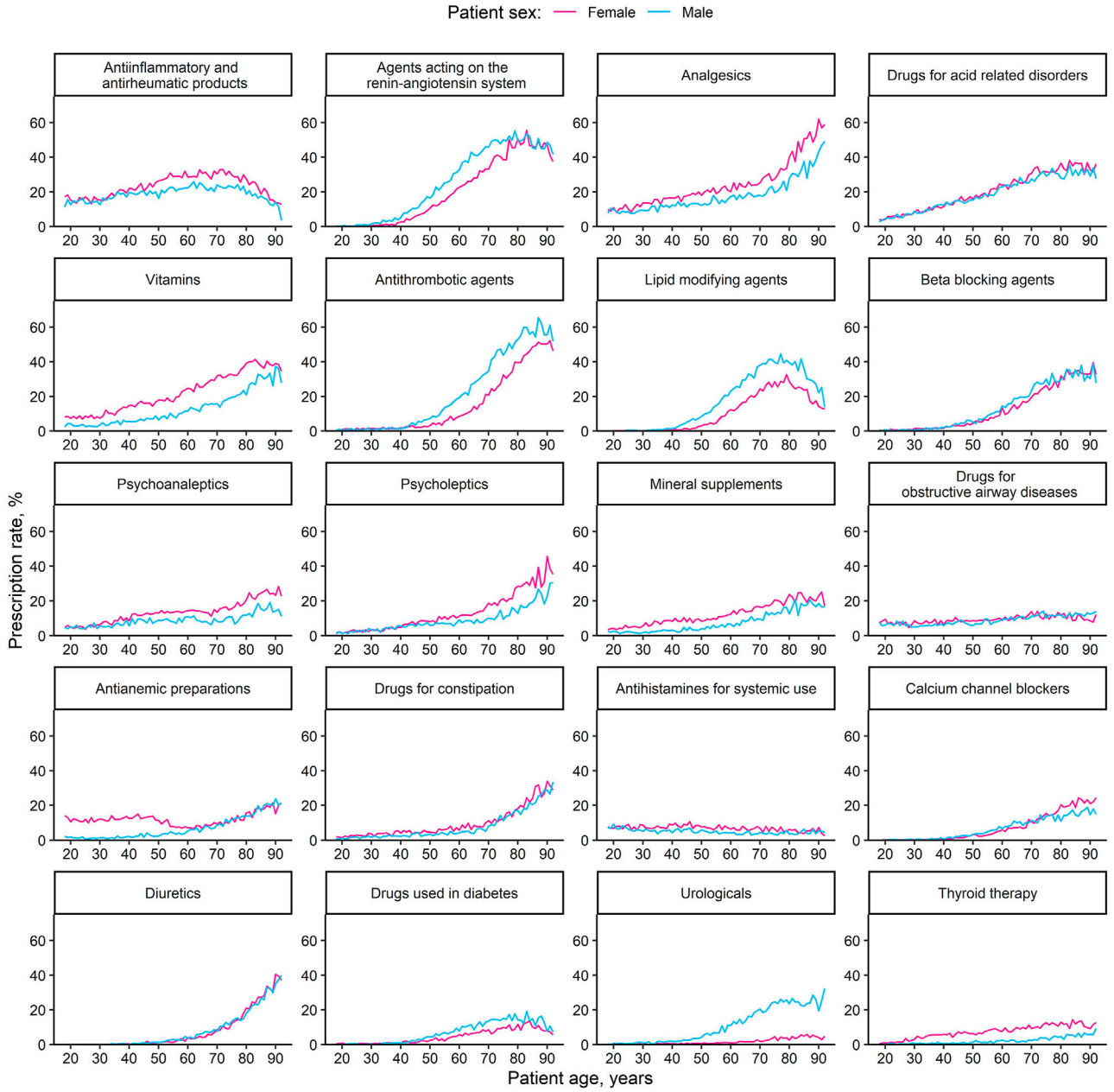


**FIGURE 3 |** Age-dependent prescription rates of different medication classes, by sex. The 20 most common medication classes (second level of the anatomical therapeutic chemical classification system) are displayed, ordered by decreasing overall prescription rate.

2015a), raises concerns that polypharmacy may be an important but underappreciated issue in this age group. For older patients, our findings are in line with those of two recent Swiss studies conducted in similar settings but with fewer GPs and patients (polypharmacy prevalence of 37% in a sample aged 75–80 years and of 60% in a sample aged over 75 years, respectively) (Aubert et al., 2016; Schnegg et al., 2020), as well as with general practice prescribing data from Scotland (Guthrie et al., 2015a). Moreover, two Swiss studies with a population-based sampling strategy and presumably less morbid patients than in our general practice-based study found lower polypharmacy rates compared to our results, as would be expected (Castioni et al., 2017; Schneider et al., 2019). With regard to prescription rates of specific medication classes, we found highest rates for pain and inflammation medication, medication for cardiovascular risk management, and medications to regulate gastric acidity. These prescription rates are highly concordant with those found in similar national (Schnegg et al., 2020; Muheim et al., 2021) and international (Guthrie et al., 2015a) studies.

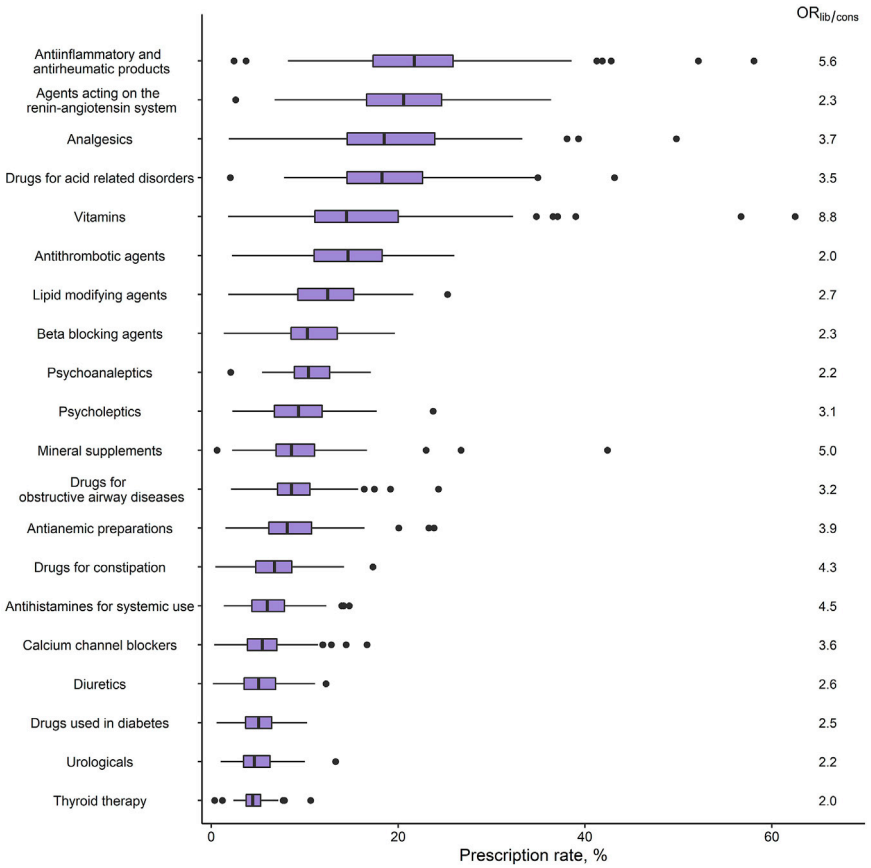


**FIGURE 4 |** Practitioner variability in medication class prescribing (GPs: $n$ = 100). Boxplots of the crude among-GP distributions of prescription rates, and the unexplained variability in terms of $OR_{lib/cons}$, for the 20 most common medication classes (second level of the anatomical therapeutic chemical classification system) ordered by overall prescription rate. Prescription rates were calculated for each GP as the percentage of their patients who had a prescription within the respective medication class; $OR_{lib/cons}$ represents the OR between a liberal prescriber (95th percentile of the random effects distribution) and a conservative prescriber (5th percentile). Abbreviations: GP, general practitioner; OR, odds ratio.

Our study provides relevant insights into the relationship between prescription rates and patient demographics. For age, we found a positive association with prescription rates for most medications, which we expected given the accumulation of chronic diseases with age. However, prescription rates of *lipid modifying agents* decreased markedly beyond 80 years of age in both sexes. This finding might be the result of many GPs' willingness to de-prescribe these medications for patients in primary prevention of cardiovascular diseases (Jungo et al., 2021). Similarly, the prescription rates of *antiinflammatory and antirheumatic products* decreased in the older. It is quite plausible that this is also partly due to de-prescribing, as there is a broad consensus that these drugs are potentially inappropriate for older patients (Holt et al., 2010; Panel et al., 2019). In this context, it is worth noting that we found high rates of *analgesics* in the oldest age group. One might thus hypothesize that antiinflammatory drugs are replaced by analgesics (mostly paracetamol) in the old, especially considering that pain was the most frequent complaint in a study of old, multimorbid patients in Swiss general practice (Neuner-Jehle et al., 2017). On another note, however, the age-dependent increase in the prescription rates of *diuretics* also in the very old population is of particular concern, given their association with preventable hospitalizations (Howard et al., 2007).

Regarding sex differences, we found a higher rate of polypharmacy in women, consistent with the literature (Guthrie et al., 2015a; Schnegg et al., 2020). The difference was more pronounced at younger ages, and interestingly, hormonal contraceptives did not relevantly contribute to the difference. The most decisive drivers of the differing rates in the younger population seemed to be higher prescription rates of *vitamins*, *mineral supplements*, and *antianemic preparations* in female patients. Physiological reasons may explain the higher prescription rates of *vitamins* for women (i.e., folic acid for the prevention of embryonal neural tube defects during reproductive age, or vitamin D to prevent osteoporosis at advanced age). For *mineral supplements*, the sex difference at older ages may also be partly explained by physiology (i.e., with calcium supplementation for the prevention of osteoporosis), but

this explanation does not readily apply to younger patients. For *antianemic preparations*, prescription rates are higher among women only during reproductive age, which is quite plausibly explained by iron deficiency caused by menstrual blood loss (Benson et al., 2021). Contrary, a higher prescription rate among male patients was observed for cardiovascular medications. While this finding is highly consistent with reports from other studies (Schnegg et al., 2020; Zhao et al., 2020), the higher intrinsic cardiovascular risk of male patients may not be the only explanation, as female patients have been found to receive less intensive cardiovascular care than men even when at similar risk (Rachamin et al., 2020a, 2020b, 2021).

Variability in prescribing can partly be explained by the GPs' patient populations (case mix). However, it can also hint at (in) appropriateness because some of the variability may be due to medication over- (or under-)use, and the risk of prescribing potentially inappropriate medications is higher among physicians with a more liberal attitude towards prescribing. (Martinez et al., 2021). Hence, several studies have investigated practitioner variability in polypharmacy: A study from Swedish general practice found that the prevalence of polypharmacy varied by a factor of six among all GPs, whereas studies from Germany and the Netherlands found factors of 3.6 and 2.4, respectively (Bjerrum et al., 1999; Grimmsmann and Himmel, 2009; Sinnige et al., 2016). These numbers are, however, sensitive to outliers and therefore of limited informative value. We quelled the influence of outliers by introducing the $OR_{lib/cons}$, which represents the central 90% of GPs. Our result of an $OR_{lib/cons}$ of 4.4 for polypharmacy is therefore a more conservative measure but still illustrates a large practitioner variability, suggesting that there may be much room for improvements in quality of care and potential cost savings.

Medication classes with both high overall prescription rates as well as high $OR_{lib/cons}$ are arguably of particular relevance and include *vitamins*, *mineral supplements*, *antiinflammatory and antirheumatic products*, *antianemic preparations*, and *antihistamins for systemic use*. The highest practitioner variability was found for *vitamins* which is—to our best knowledge—a novel finding. The high practitioner variability in vitamin prescribing is however in line with the high practitioner variability in vitamin testing observed both in Switzerland and internationally (Schumacher et al., 2020; O'Sullivan et al., 2018). Moreover, inappropriate prescribing of vitamins has been documented before, and in Switzerland specifically, a potential overuse of *antianemic preparations* has been suspected (Silverstein et al., 2019; Biétry et al., 2017; Meier et al., 2019). Interestingly, *vitamins*, *mineral supplements*, and *antianemic preparations* were also among those medications which were more often prescribed to (especially young) female patients. For *antiinflammatory and antirheumatic products,* high practitioner variability in prescribing has been acknowledged before, and is most relevant because of the well-known associated risks (Hawkey et al., 1997; Dreischulte et al., 2012). Furthermore, a medication class for which variability and potential overuse have often been investigated, due to their contribution to the emerging threat of multiresistant germs, are *antibacterials*. A recent Italian primary care-based study which investigated prescribing of a set of six frequently prescribed medications found the largest variability in antibiotics (Russo et al., 2020). In our study, antibiotics had a rather low prevalence (and are therefore not described in the main text), but practitioner variability in prescribing antibacterial medication was considerable ($OR_{lib/cons}$ = 4.9, **Supplementary Table S2**). In contrast, low practitioner variability was found in thyroid medications, antithrombotics, renin-angiotensin antagonists, beta blockers, and antidiabetic drugs. This consistent prescription behavior by GPs is reassuring especially in antithrombotic medication which convey high bleeding risks and require adherence to evidence-based treatment guidelines (Hutten et al., 1999).

## Strengths and Limitations

Strengths of this study lie in the comprehensiveness of medication classes assessed and of the population included, which together provide a large and detailed picture of medication prescribing activity in Swiss general practice. Moreover, we excluded topical medication in order to increase the relevance of our findings regarding polypharmacy. The data presented in this article is valuable for researchers as well as for policy makers and may help to inform assumptions, make comparisons, and set policy priorities. A limitation of this study are the unknown and potentially varying morbidities of the GPs' patient populations, which made it impossible to more precisely judge the appropriateness of prescribed medications. In addition, due to the cross-sectional design of our study, we could not follow up prescription dynamics and were therefore unable to distinguish between cautious prescribing and secondary de-prescribing. Moreover, since we analyzed patients at their last visits to their GPs in 2019, we measured prescriptions immediately following a medical consultation and our results are therefore bound to an episode of care which may not be fully representative for a full patient year and may have overestimated prescription rates. This limitation would primarily affect drugs prescribed for acute indications, such as *analgesics* and *antiinflammatory and antirheumatic products*. Analyzing data from last encounters in 2019 also caused an overrepresentation of the winter season and may have biased prescription rates for medication targeting seasonal illnesses, e.g., antibiotics (Hawes et al., 2018). Lastly, we did not consider prescribed medication doses, which is also a limitation for judging adequacy of prescriptions.

# CONCLUSION

Based on practitioner variability, prevalence and conveyed risks, the targets with the highest potential for subsequent initiatives to improve medication prescribing in Swiss general practice are antiinflammatory medications and polypharmacy in old and very old patients.

## DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because of institutional restrictions. Requests to access the datasets should be directed to thomas.rosemann@usz.ch.

## ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional requirements. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

## AUTHOR CONTRIBUTIONS

YR: Conceptualization, Methodology, Formal analysis, Visualization, Writing—original draft, Writing—review and editing. LJ: Methodology, Writing—review and editing. RM: Data curation, Writing—review and editing. TG: Methodology, Writing—review and editing. OS: Resources, Writing—review and editing. JMB: Writing—review and editing. SM: Conceptualization, Writing—original draft, Writing—review and editing, Supervision.

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## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2022.832994/full#supplementary-material

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# Estimates of Paracetamol Poisoning in Brazil: Analysis of Official Records From 1990s to 2020

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**Objective:** To assess the cases of paracetamol poisoning in Brazil. Methods: Analysis of official records of deaths between 1996 and 2019 from the Brazil Mortality Information System (SIM), admissions between 2008 and 2020 from the Hospital Information System (SIH), and cases of poisoning between 2017 and 2020 in health services, reported to the Brazilian Notifiable Diseases Surveillance System (SINAN). In SIM and SIH, records with ICD-10 were included: F55, T39, X40, X60, and Y10. In SINAN, commercial products containing paracetamol were identified. Records were stratified by age, sex, and intentionality. Mean and standard error were calculated for each stratum based on the annual data, by federation unit. Poisoning reports by 1,000,000 inhabitants were calculated from each state and compared to the national average. Results: In total, 492 deaths, 5,666 hospital admissions, and 17,031 cases of paracetamol poisoning were recorded in the period. Deaths occurred mostly among adults (71.3% ± 3.0) and in suicide attempts (37.3% ± 2.7). Hospital admissions were more frequent in adults (69.7% ± 1.4), women (57.1% ± 2.5), and unintentional poisoning (80.2% ± 4.2). Poisoning reports was more also frequent among adults (71.4% ± 1.2), women (74.2% ± 0.6), and due to accidents (79.6% ± 1.8). The South and Southeast regions of the country presented the highest frequencies in all outcomes, above the national average. Conclusion: Paracetamol exposure is a concern for preventable poisonings, hospital admissions and deaths. More accurate data about paracetamol poisoning are required to support surveillance actions and the development of mechanisms to reduce poisoning, particularly related to adults, women and suicide attempts.

**Keywords: admission, acetaminophen, suicide, paracetamol, poisoning**

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## INTRODUCTION

Paracetamol is one of the most popular over-the-counter medicines worldwide. As a nonopioid analgesic and antipyretic agent, paracetamol is one of the best-selling drugs in Brazil (Brasil, 2019b). It is commercially available as tablets or oral solutions, isolated or associated with other active ingredients (Brasil, 2019a). It can be easily bought with or without a prescription, representing a common cause of accidental or intentional poison exposure (Park et al., 2015).

Reports of paracetamol poisoning are frequent and studied in several countries (Sheridan et al., 2017; Benlamkaddem et al., 2018; Parry et al., 2018). Drug abuse and self-medication for the treatment of chronic pain are associated with accidental poisoning (Ghanem et al., 2016). In cases of suicide attempts, the over-the-counter accessibility of paracetamol and high risk of hepatotoxicity, emergency interventions are frequently required (Stravitz and Lee, 2019).

**TABLE 1 |** Characteristics and strategies for the identification of paracetamol poisoning information in official databases.

| | Mortality Information System | Hospital Information System | Brazilian Notifiable Diseases Surveillance System |
|---|---|---|---|
| Study period | 1996–2019 | 2008–2020 | 2017–2020 |
| Origin of collected data | SUS IT Department (DATASUS)—SIM | DATASUS—SIH | DATASUS—SINAN |
| Website | https://datasus.saude.gov.br/mortalidade-desde-1996-pela-cid-10 | https://datasus.saude.gov.br/acesso-a-informacao/producao-hospitalar-sih-sus/ | https://datasus.saude.gov.br/acesso-a-informacao/doencas-e-agravos-de-notificacao-de-2007-em-diante-sinan/ |
| National representativeness | Yes | Restricted to SUS | Yes |
| Estimates | All paracetamol-related deaths | All SUS paracetamol-related admissions | All paracetamol poisoning cases treated in health services |
| Definitions adopted | Data processed according to ICD-10: F55[1]; T39[2]; X40[3]; X60[4]; Y10[5] | Data processed according to ICD-10: F55[1]; T39[2]; X40[3]; X60[4]; Y10[5] | Circumstance of exposure/contamination: 02 (accidental); 05 (inadequate prescription); 06 (administration error); 07 (self-medication); 08 (abuse); 10 (suicide attempt); 12 (violence/homicide); 13 (other); 99 (ignored) |
| Causes | **Suicide:** X60[4] (ICD-10)<br>**Unintentional:** F55[1]; T39[2]; X40[3]; Y10[5] (ICD-10) | **Suicide:** X60[4] (ICD-10)<br>**Unintentional:** F55[1]; T39[2]; X40[3]; Y10[5] (ICD-10) | **Suicide:** 10 (suicide attempt)<br>**Unintentional:** 02 (accidental); 05 (inadequate prescription); 06 (administration error); 07 (self-medication); 08 (abuse); 12 (violence/homicide) |
| | — | — | **Ignored/Other:** 13 (other); 99 (ignored) |

*Notes: [1]Abuse of non-dependence-producing substances; [2]Poisoning by nonopioid analgesics, antipyretics and antirheumatics; [3]Accidental poisoning by and exposure to nonopioid analgesics, antipyretics and antirheumatics; [4]Intentional self-poisoning by and exposure to nonopioid analgesics, antipyretics and antirheumatics; [5]Poisoning by and exposure to nonopioid analgesics, antipyretics and antirheumatics, undetermined intent.*

Paracetamol is in the list of essential medicines and, in general, it is considered a safe drug (WHO, 2019b). However, acute liver injury is observed when used in doses above 10 g/day (Buckley et al., 1999) and, depending on nutritional or clinical conditions, lower doses can also cause hepatotoxicity (Kwan et al., 1995). The lowest acute dose capable of causing toxicity in adults is 7.5 g and in children 150 mg/kg (Bizovi and Smilkstein, 2002). In cases of paracetamol overdose, the adverse effect observed is acute liver failure, the main cause of fulminant hepatitis. The mechanism of hepatotoxicity is associated with the production of N-acetyl-*p*-benzoquinone imine, glutathione depletion and liver cell necrosis (Miner and Kissinger, 1979).

Warnings or educational campaigns highlighting the inadequate uses of paracetamol proposed by regulatory bodies have been conducted to reduce poisoning rates in the United States (FDA, 2017). Although the risks of paracetamol are well known, estimates of paracetamol poisoning have been poorly investigated in Brazil. The risk of this exposure does not seem to be lower in the country, as the Brazilian National Health Surveillance Agency (ANVISA) warned in 2021 to the risk of drug-induced hepatitis after prolonged use or drug abuse in situations of indiscriminate use of paracetamol to relieve the adverse events of vaccines against COVID-19 (Brasil, 2021).

This study aimed to identify and analyze paracetamol poisoning in Brazil.

# METHODS

## Study Design

This is a descriptive retrospective study that used different information systems to obtain representative data about paracetamol poisoning in Brazil. Three database systems were assessed: the Brazilian Mortality Information System (SIM), the Hospital Information System (SIH), and the Brazilian Notifiable Diseases Surveillance System (SINAN). **Table 1** summarizes the data collected from these three information systems.

## Background

SIM was created by the Informatics Department of the Unified Health System (DATASUS) and implemented in Brazil in 1975 by the Ministry of Health. The system combines statistical information from death forms recorded at the municipal, state and federal levels of public health management. The death form is standardized, filled in by the physician and collected by the Municipal or State Health Department. It is a free file transfer protocol (FTP) system, and allows users to view files and join files from different periods as a historical series, combining them into the same file.

SIH processes hospital admission records from the Unified Health System (SUS) patients in Brazil. Each record has a Hospital Admission Authorization, allowing the payment of fixed amounts for hospital and medical procedures by the SUS. This system displays municipal and state data obtained from the Ministry of Health website by free FTP system.

SINAN receives data from disease investigations of compulsory reporting; its updating is mandatory at the municipal, state, and federal levels. Poisoning cases treated at health services involve compulsory reporting in Brazil, which must be made in SINAN system. Consolidated data can be freely accessed via DATASUS. The poisoning agent insertion in the system happens by free text and up to three agents under the trade name and three active ingredients can be provided, which may involve spelling mistakes.

## Participants

This study assessed the cases of death from paracetamol poisoning between 1996 and 2019 from SIM under the codes of the 10th revision of the International Classification of Diseases (ICD-10) as primary and secondary causes and probable circumstances of unnatural death, as follows: F55 (abuse of non-dependence-producing substances), T39 (poisoning by nonopioid analgesics, antipyretics and antirheumatics), X40 (accidental poisoning by and exposure to nonopioid analgesics, antipyretics and antirheumatics), X60 (intentional self-poisoning by and exposure to nonopioid analgesics, antipyretics and antirheumatics), and Y10 (poisoning by and exposure to nonopioid analgesics, antipyretics and antirheumatics, undetermined intent); SUS admissions from 2008 to 2020 with primary and secondary diagnosis registered in SIH as F55, T39, X40, X60, and Y10, according to ICD-10; and cases of paracetamol poisoning between 2017 and 2020 reporting it as the toxic agent. The period defined was feasible considering data availability in FTP for each database system.

## Variables

The primary outcomes were death (1996–2019), SUS admission (2008–2020), and poisonings treated and reported in health services (2017–2020). The independent variables were age (in years: <6, 6-16, 17-64, ≥65) and sex (male, female). For a better understanding of the poisoning causes, they were classified as "unintentional" (accidental, inadequate drug prescription, medication administration error, self-medication, drug abuse, and violence or homicide), "suicide attempt," and "not informed/ignored." The variable "state of residence" was also assessed in SINAN poisoning reports.

## Data Source and Measurement

Data were obtained from the repositories and compiled in a Microsoft Excel® spreadsheet.

Because the toxic agent information is manually inserted in the SINAN form, paracetamol poisoning was identified by searching all names and spelling variations for paracetamol. We created a list of commercial presentations with paracetamol based on an inquiry in active and discontinued drug registries on the ANVISA website (https://www.gov.br/anvisa/pt-br/acessoainformacao/dadosabertos/informacoes-analiticas) for this purpose. This inquiry was performed in September 2019 in both expired drug registrations and registrations in force.

The reports of poisoning cases in the SINAN were grouped by state and calculated by the respective population official estimate according to the Brazilian Institute of Geography and Statistics (http://ibge.gov.br). The rate of poisonings per million inhabitants for each state (federation unit) was calculated for 2017 to 2020.

## Statistical Analysis

We used the SIM, SIH and SINAN databases to address different hypothesis about paracetamol poisoning. We investigated whether there is a difference in terms of age, sex and causes for each outcome. For each stratum, we calculated the percentage for each group by year and calculate the mean and standard error of these percentages over each assessed year. We performed two-tailed analysis of variance (ANOVA) for independent samples to detect any difference in each stratum and considered an alpha level of 0.05 to assign statistical significance. The rate of poisoning per 1 million inhabitants was described by federation unit and compared to the national average. The state rate was also plotted in map. All analyzes were performed in Microsoft Excel®.

# RESULTS

A total of 492 deaths from paracetamol poisoning were identified in Brazil between 1996 and 2019, of which 183 were cases of suicide and 123 were accidental deaths ($p < 0.004$). Deaths were more frequent in the population over 17 years of age ($p < 0.001$, **Table 2**).

From 2008 to 2020, 5,666 admissions to due to paracetamol poisoning occurred in SUS hospitals. Women, adults and unintentional reason were the most affected stratum ($p < 0.001$, **Table 2**). Intentional use of paracetamol in suicide attempts represented 19.8% of admission in Brazilian public hospitals ($p < 0.001$, **Table 2**).

From 2017 to 2020, 515,539 poisoning cases were reported by Brazilian health services, of which 17,031 (3.3%) were paracetamol poisonings. Women and people aged between 17 and 64 years ($p < 0.001$) were more frequently seen in poisoning cases (**Table 2**). Suicide attempts accounted 20.4% of the reports ($p < 0.001$).

In the whole country, it was reported 20.3 cases of paracetamol poisoning per million inhabitants in this period. Paracetamol poisoning reports were concentrated in the South and Southeast regions (**Figure 1**). The state of Espírito Santo (ES), Southeast Region, had 2.3 times more cases than the national average (45.8 per million). In the South Region, the state of Paraná (PR) had 3.3 times more (67.2 per million) and Santa Catarina (SC), had 3.0 times more (61.6 per million) than the national average.

# DISCUSSION

In Brazil, paracetamol exposures leading to poisonings and hospital admissions were higher among women and adults. When compared to unintentional poisoning, deaths from paracetamol exposures due to suicide were significantly higher. This research represents the first effort to bring an overall assessment of the dimension of paracetamol exposure in Brazil.

Despite the completeness of present investigation, our results are limited by the quality of the records. Although the mortality system (SIM) includes all deaths in Brazil, we suspect that there is underreporting. The ICD-10 included probably refers to acute exposures and/or more severe cases, with better investigations. It is also possible that suicides are underestimated, due to life insurance and inheritance issues. Only hospitalizations funded by the SUS were included. Hospitalizations paid for by the patient or by private health insurance could not be included. Brazil has 270,880 general beds, of which 66% are available for the SUS (Noronha et al., 2020). On the other hand, the first urgent and

**TABLE 2 |** Summary of paracetamol poisoning data obtained from different official records.

| Variables | Mortality (1996–2019) | | Admissions (2008–2020) | | Poisoning reports (2017–2020) | |
|---|---|---|---|---|---|---|
| | Mean ± SE | *p*-value | Mean ± SE | *p*-value | Mean ± SE | *p*-value |
| Age (years) | — | <0.001* | — | <0.001* | — | <0.001* |
| <6 | 7.3 ± 1.6 | — | 12.6 ± 0.9 | — | 6.2 ± 0.8 | — |
| 6–16 | 5.1 ± 1.2 | — | 13.4 ± 0.9 | — | 21.5 ± 0.6 | — |
| 17–64 | 71.1 ± 3.0 | — | 69.7 ± 1.4 | — | 71.4 ± 1.2 | — |
| ≥65 | 16.6 ± 2.0 | — | 4.4 ± 0.4 | — | 0.9 ± 0.1 | — |
| Sex | — | 0.611** | — | <0.001** | — | <0.001** |
| Male | 50.9 ± 2.5 | — | 42.9 ± 2.5 | — | 25.8 ± 0.6 | — |
| Female | 49.1 ± 2.5 | — | 57.1 ± 2.5 | — | 74.2 ± 0.6 | — |
| Cause of exposure | — | <0.004*** | — | <0.001*** | — | <0.001*** |
| Suicide | 37.3 ± 2.7 | — | 19.8 ± 4.2 | — | 20.4 ± 1.8 | — |
| Unintentional | 25.7 ± 3.5 | — | 80.2 ± 4.2 | — | 79.6 ± 1.8 | — |
| Not reported/ignored/ other | 37.0 ± 3.1 | — | — | — | — | — |

*p *value from ANOVA, for age;* **p *value from ANOVA, for sex; and* ***p *value from ANOVA, for cause.*

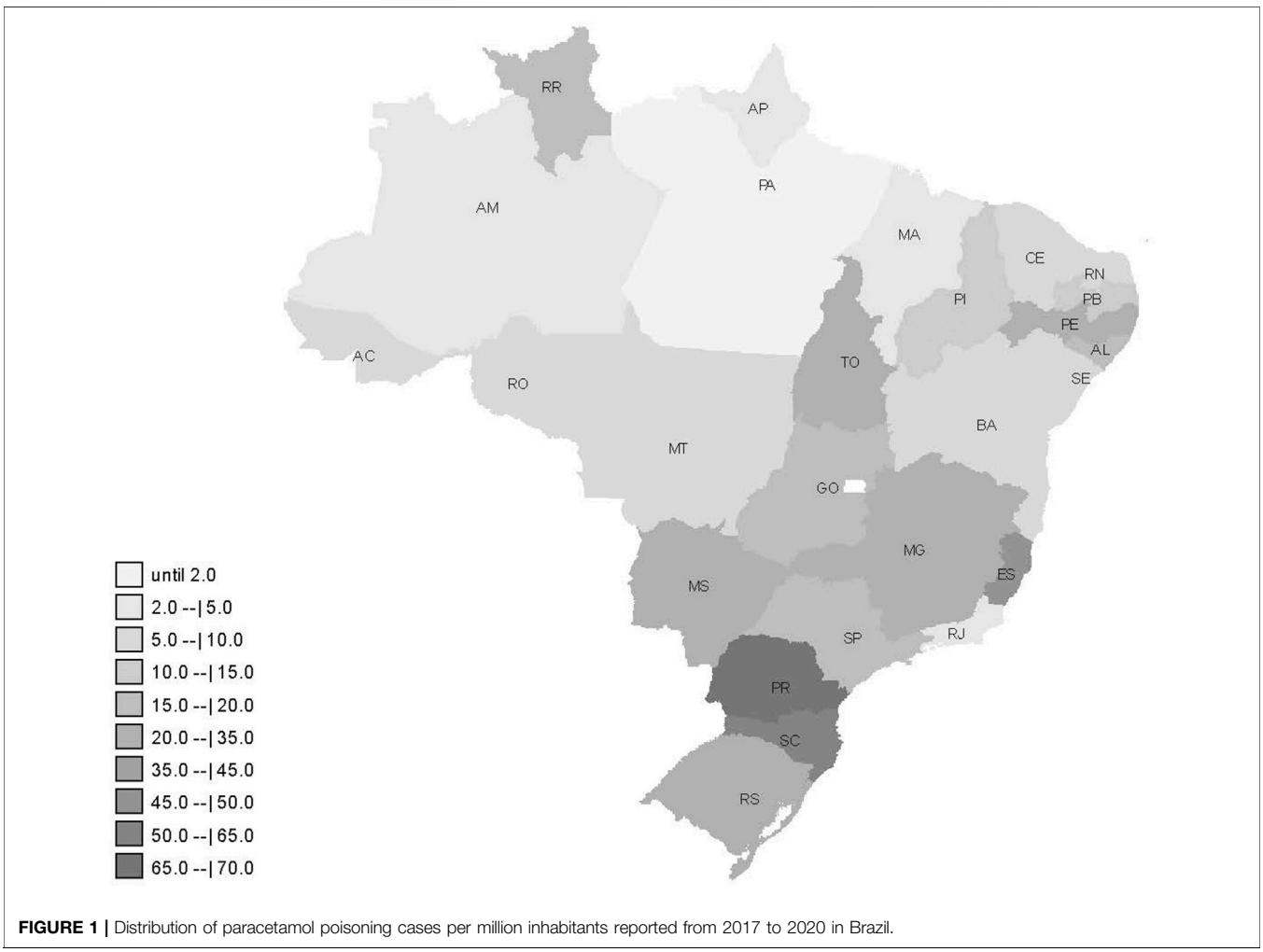


**FIGURE 1 |** Distribution of paracetamol poisoning cases per million inhabitants reported from 2017 to 2020 in Brazil.

emergency care, common in cases of intoxication, is virtually covered only by the SUS. Reports of poisoning treated in Brazilian health services—public or private—are mandatory and would include more serious cases requiring medical care, and lack representativeness of all poisoning cases. Non-standardization of the SINAN form in its toxic agent information field may lead to

failed records and possible information bias. The retrospective design based on administrative databases also impacts the reliability of the findings. Poisoning data identification and analysis in official databases, similar to present effort, are widely used as a surveillance method in other countries (Nourjah et al., 2006; Gedeborg et al., 2017) and are considered valuable sources to assess the magnitude of the problem.

Deaths, hospital admissions, and poisoning reports due to paracetamol exposure were predominant among adults, a scenario that is similar to what was observed in Sweden in 2000–2013 (Gedeborg et al., 2017), Germany in 2007–2018 (Daly et al., 2020), England in 2004–2014 (Casey et al., 2020), and Algeria in 2010–2017 (restricted to one hospital) (Chefirat et al., 2020).

Paracetamol administration above the maximum recommended dose of 4 g/day and chronic use for pain control are the main causes of poisoning among adults in the United States (Blieden et al., 2014). Therapeutic effects of paracetamol such as analgesia and antipyretics are considered safe and accepted (Bertolini et al., 2006), which makes it possible to use it in a wide age range, from young children to elderly people, to control fever and pain (WHO, 2019b), preferable to non-steroidal anti-inflammatory drugs (NSAIDs), to avoid gastric irritation. It was considered a first choice drug for pain control by the American Pain Society in conjunction with the American College of Physicians along with NSAIDs in pain control (Chou et al., 2007). Easy access, no prescription required, and self-medication favor poisoning. The use of paracetamol to control pain in osteoarthritis is known and often indicated due to its safety when compared to NSAIDs (Shah and Mehta, 2012). Chronic pain management in these conditions should use a combination of pharmacological and non-pharmacological treatments (physical and occupational therapies, behavioral and cognitive therapies, nutritional therapy, among others) (Borenstein et al., 2017), which can help patients live with chronic pain and avoid opioid dependence or drug poisoning (Kjartansdottir et al., 2012; Conaghan et al., 2019).

Regulatory agencies in settings with high rates of suicide attempts and suicide with paracetamol propose alternatives such as limitations to the amount sold over-the-counter, restricting sales to medical prescription, and changes in commercial packaging to mitigate the risks (Gunnell et al., 2000). In Brazil, drug combinations of paracetamol with opioid analgesics has special control, such as the compounds of paracetamol associated with tramadol and codeine (Brasil, 1998). During the opioid overdose crisis, the United States Food and Drug Administration decreased the concentration of paracetamol in the commercial presentation of paracetamol and hydrocodone after a public consultation to reduce cases of paracetamol poisoning (Blieden et al., 2014).

Hospital admissions caused by paracetamol poisoning were more frequent among women in Brazil. In a multicenter study conducted in England from 2011 to 2014, women presented higher rates of paracetamol poisoning than men (Casey et al., 2020). Men had a higher death rate despite lower admissions than women due to higher doses of paracetamol. Mental health problems such as depression are more frequent in women (WHO, 2013) than men. Factors such as social context, failure to seek help for mental health issues, and skills and access to weapons between men and women (Möller-Leimkühler, 2003) explain the double rate of consummated suicide in men (WHO, 2019a), while the frequency of suicide attempts is higher in women (Canetto and Sakinofsky, 1998). Psychological and social factors and cultural characteristics also influence the means used in suicide attempts by men and women, which are more lethal in men (Varnik et al., 2011; Mergl et al., 2015).

Hospital admissions due to unintentional poisoning were more frequent than intentional exposure to paracetamol. On the other hand, when analyzing deaths, suicide attempts were more frequent. The indiscriminate use of medication to control pain increases unintentional poisoning, with simultaneous administration of two or more formulations with paracetamol (Larson et al., 2005). Poor knowledge of consumers about adverse events related to the drug may also increase risks and unintentional poisoning (Daifallah et al., 2021). In addition to the consumption of different compounds with acetaminophen, easy access without a prescription, and self-medication, the concomitant use with alcohol further damages the liver function and increases the risk of unintentional poisoning (Kane et al., 2012; Kjartansdottir et al., 2012; Hawton et al., 2019). In 2016, unintentional poisoning using different toxic agents caused 100,000 deaths worldwide (WHO, 2019c) and medicines were the main cause of admissions, mainly among adults (Yehya et al., 2020).

Paracetamol poisoning in Brazil was more concentrated in the South and Southeast regions. These regions have higher Human Development Index and per capita income (Organização das Nações Unidas, 2021). They also have more Poison Control Centers. These aspects culturally influence the number of reports in health services, recognition the importance of this condition and its mandatory reporting. In the American context, population characteristics–such as ethnicity, race, educational level, population with the largest number of children, and per capita income–influenced the number of toxic exposure reports in the Poison Control Centers (Litovitz et al., 2010). Differences in the accessibility and structure of services can also affect reporting rates and types (Laborde, 2004). Unlike the United States, Brazil has a public healthcare system, accessible to all Brazilians, despite its budgetary underfunding.

Given the consumption of paracetamol in the Brazilian population, further studies on paracetamol poisoning could assess data from all Poison Control Centers in Brazil such as performed for pesticides in 2017 (Okuyama et al., 2020) and the association of paracetamol with other drugs, such as codeine and tramadol, which are used to control moderate pain.

## CONCLUSION

The results found in this study indicate that cases of paracetamol exposure are a reality in the Brazilian scenario and exposure are a

concern for avoidable poisoning, hospital admission and deaths. The adult population was more affected by paracetamol poisoning leading to death, and was also the most frequent group in SUS admissions and healthcare services due to paracetamol poisoning in Brazil. Women and unintentional causes were more common in public hospital admissions and in poisonings treated in Brazilian healthcare services. Deaths were higher due to suicide. Estimates of paracetamol poisoning should be based on more accurate data that allows surveillance, monitoring and mechanisms to avoid cases of chronic exposure and suicide.

## DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

## AUTHOR CONTRIBUTIONS

JO, TG and MS designed the work, analyzed and interpreted the data, and drafted the manuscript.

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# Major areas of interest of artificial intelligence research applied to health care administrative data: a scoping review

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**Introduction:** The ongoing collection of large medical data has created conditions for application of artificial intelligence (AI) in research. This scoping review aimed to identify major areas of interest of AI applied to health care administrative data.

**Methods:** The search was performed in seven databases: Medline, Embase, CINAHL, Web of science, IEEE, ICM digital library, and Compendex. We included articles published between January 2001 and March 2021, that described research with AI applied to medical diagnostics, pharmacotherapy, and health outcomes data. We screened the full text content and used natural language processing to automatically extract health areas of interest, principal AI methods, and names of medications.

**Results:** Out of 14,864 articles, 343 were included. We determined ten areas of interest, the most common being health diagnostic or treatment outcome prediction (32%); representation of medical data, clinical pathways, and data temporality (i.e., transformation of raw medical data into compact and analysis-friendly format) (22%); and adverse drug effects, drug-drug interactions, and medication cascades (15%). Less attention has been devoted to areas such as health effects of polypharmacy (1%); and reinforcement learning (1%). The most common AI methods were decision trees, cluster analysis, random forests, and support vector machines. Most frequently mentioned medications included insulin, metformin, vitamins, acetaminophen, and heparin.

**Conclusions:** The scoping review revealed the potential of AI application to health-related studies. However, several areas of interest in pharmacoepidemiology are sparsely reported, and the lack of details in studies related to pharmacotherapy suggests that AI could be used more optimally in pharmacoepidemiologic research.

KEYWORDS

**artificial intelligence, health care administrative database, pharmacotherapy, scoping review, natural language processing**

## Introduction

Healthcare sectors generate a huge amount of complex data such as hospital records and examination results, medical insurance claims, and data from medical imaging and monitoring with medical devices (Raghupathi and Raghupathi, 2014). The emergence of digitized data provides a radical improvement of the health system in terms of efficiency and costs (Khan et al., 2019). Health care administrative database has gained particular interest in research, and notably in pharmacoepidemiology. These data are primarily collected by government institutions or other types of organizations and represent a rich source of information (Kone Pefoyo et al., 2009). They are classically generated through a physician's office registration, a prescription transaction and record keeping at a community pharmacy, an admission to hospital, or a delivery of diagnostic service (Timofte et al., 2018). Health care administrative databases are typically vast, covering very large population samples over a lengthy period. The fact that this type of data is regularly and continuously collected through a consistent way without requiring extra resources is a significant advantage for research and allows for more advanced research questions (Timofte et al., 2018). Furthermore, health care administrative databases have been successfully used for disease surveillance (Blais et al., 2014). As those databases get larger and technology improves, new analysis methods are needed to exploit them correctly.

Artificial intelligence (AI)-based algorithms and tools such as deep learning, machine learning, and reinforcement learning have been successfully used in a variety of health data research and development projects (Bates et al., 2014). AI-based strategies have been designed to transform data into meaningful and actionable insights that help stakeholders to take action or make a clinical decision (Raghupathi and Raghupathi, 2014). For example, AI can be used to predict outcomes, understand pharmacotherapy, or evaluate spatio-temporal models. Compared to classical statistical techniques, novel AI-based strategies can be more accurate, efficient, precise, and impactful (Gubbi et al., 2013; Mehtaa et al., 2019), though this is not always the case, depending on the context (Sessa et al., 2021). The potential of health care administrative databases analyzed with this type of tools remains to be elucidated.

This scoping review was conducted to explore the current state of existing research according to the application of AI to health care administrative data, including those involving medications. The objectives were to identify:

1. The major areas of interest of current studies related to the application of AI to health care administrative data.
2. The principal AI methods applied to research involving health care administrative data.
3. Main clinical and pharmacotherapeutic interests of AI-based research.

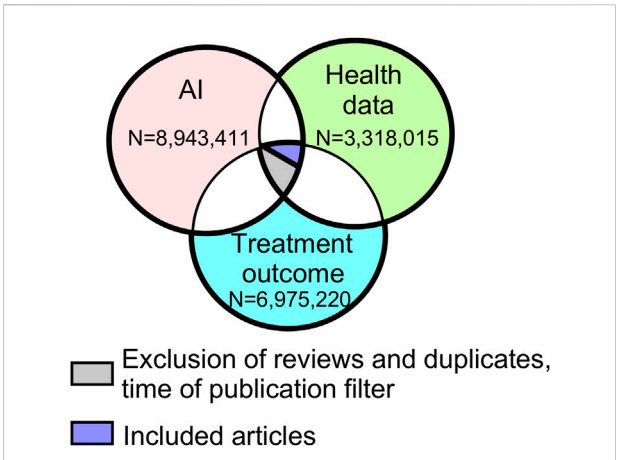



FIGURE 1
Venn diagram of the initial database search results. Legend: Each circle represents the number of articles related to each topic. There were 14,864 articles that overlapped the three topics. AI, artificial intelligence.

## Materials and methods

### Overview

The planning of the search strategy was performed with a research librarian, who was involved at all stages of planning and bibliographic research. The initial search was performed in Medline, Embase, CINAHL, Web of science, IEEE, ICM digital library, and Compendex. We searched for articles published between January 2001 and March 2021, that described original research in AI applied to medical diagnostics, pharmacotherapy, and health outcomes data (Figure 1, additional files). The list of key words and results of the search of each of the seven databases can be found in Supplementary Material.

We performed a three-step procedure for the scoping review: abstract review, full text review, and data extraction. The first two steps were performed with Covidence (Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. Available at www.covidence.org). Each abstract and full text was reviewed by two researchers (OB, AA, YC, SS, MS). In case of conflict, consensus was reached by a vote of a third researcher or by mutual agreement of at least two team members.

### Abstract review

The reviewed abstracts had to correspond to the following criteria to be included in further steps of the review: 1) be based on original study of real-world data. (Protocols and reviews of previously published studies, theoretical approaches, studies

based exclusively on synthetic data, as well as description of architecture of medical information systems (e.g., web-based, cloud-based solutions) were excluded); 2) include application of AI methods. (Studies based on descriptive statistics, pre-defined medical algorithms (rules), and solely regression analysis were excluded); 3) be based on large health databases with an arbitrary threshold of at least 1,000 observations. (Clinical essays and clinical trials were excluded due to the relatively small number of participants and the exclusive use of classical descriptive statistics); 4) be based on data types that can be found in health care administrative databases (clinical diagnoses, prescribed medications, medical procedures, hospital services).

Therefore, we excluded studies that were based **exclusively** on the following types of data: medical imaging (e.g., fMRI, CT, X-ray, PET, cell histology); synthetic data; genomics; time-series data (e.g., continuous recordings of vital signs, ECG, EEG); laboratory tests (e.g., glucose, cholesterol); surveys and questionnaires (e.g., depression scales, surveys on quality of life); social media data; free texts without extraction of data comparable to health care administrative database.

When abstracts did not contain enough information about correspondence to inclusion or exclusion criteria, the article was considered for full text review.

## Full text review

In addition to the criteria described above, at this stage we filtered out items that fell under our exclusion criteria. We excluded documents that were not full-text articles (e.g., abstracts from scientific meetings), duplicate publications, or articles that did not have full description of purpose of the study, methods used, or data types (e.g., use of a "cardiology dataset").

## Data extraction

We applied two different approaches for data extraction that served for different purposes. In objective 1, we used the *classic approach,* that involved reading the article by at least two reviewers. We determined the principal area of interest for the application of AI methods. Each article was categorized into one or more areas which were defined based on agreement between the reviewers. In objectives 2 (determining the principal AI methods used in the research) and 3 (determining main clinical and pharmacotherapeutic interests of AI-based research), we used the *automated* approach, which was based on Natural Language Processing (NLP), an AI method used for automatic extraction of useful information from free texts. This approach helped to retrieve AI methods applied in the included studies, and health data-related and pharmacotherapy-related terms. The procedure was performed in Python with the use of NLTK (Natural Language Toolkit). It consisted of the following steps: import of titles, abstracts, "Methods" and "Results" sections of the articles, text preprocessing (tokenization, lemmatization, parts-of-speech analysis to retain nouns, substitution for synonyms), creating vocabulary of terms for retrieval, and determining number of articles in which the terms from the vocabularies were used.

## Data analysis

In objective 1, we described the proportion of articles that pertained to the major areas of interest that were identified in the extraction process. In objectives 2 and 3, the frequency of use of the terms was determined based on three different custom-created vocabularies. First, the names of selected statistical and AI methods and their commonly used acronyms were targeted in objective 2. In order to do so, we created a vocabulary of 24 popular AI methods that contained their names (e.g., 'regression') and commonly used acronyms (e.g., 'rnn' for 'recurrent neural network' or 'svm' for 'support vector machine') based on preliminary screening of the articles. We also investigated evolution of use of AI methods in three-year-long periods from 2001 to 2021.The second custom-created vocabulary was related to the objective 3, and pertained to health data related terms that included clinical diagnoses, terms related to medical and hospital services, and names of socio-demographic variables. Finally, the third custom-created vocabulary was also related to objective 3 and comprised pharmacotherapy-related terms based on Anatomical Therapeutic Chemical (ATC) codes and American Hospital Formulary Service (AHFS) Pharmacologic-Therapeutic Classification System. We manually defined pairs of words that could be considered as synonyms in the context of this study (such as, for example, illness and disease, electronic patient record and electronic health record), and performed replacement of the words that had close meaning with their synonyms. We displayed the frequency of use of health data-related and pharmacotherapy-related terms as WordCloud to provide insights into relative popularity of each term.

# Results

## Overview

Results from our initial database search are presented in Figure 1. After applying the filters for the presence of all three areas of interest, time of publication, and automatic exclusion of reviews and duplicates, the search resulted in 14,864 abstracts (Figure 1, additional files). With further abstract screening based on inclusion and exclusion criteria, the number of articles selected for full text review was narrowed to 1,126, and after their review, 343 articles were included for further analysis (Figure 2). Only 336 articles were included in objectives 2 and

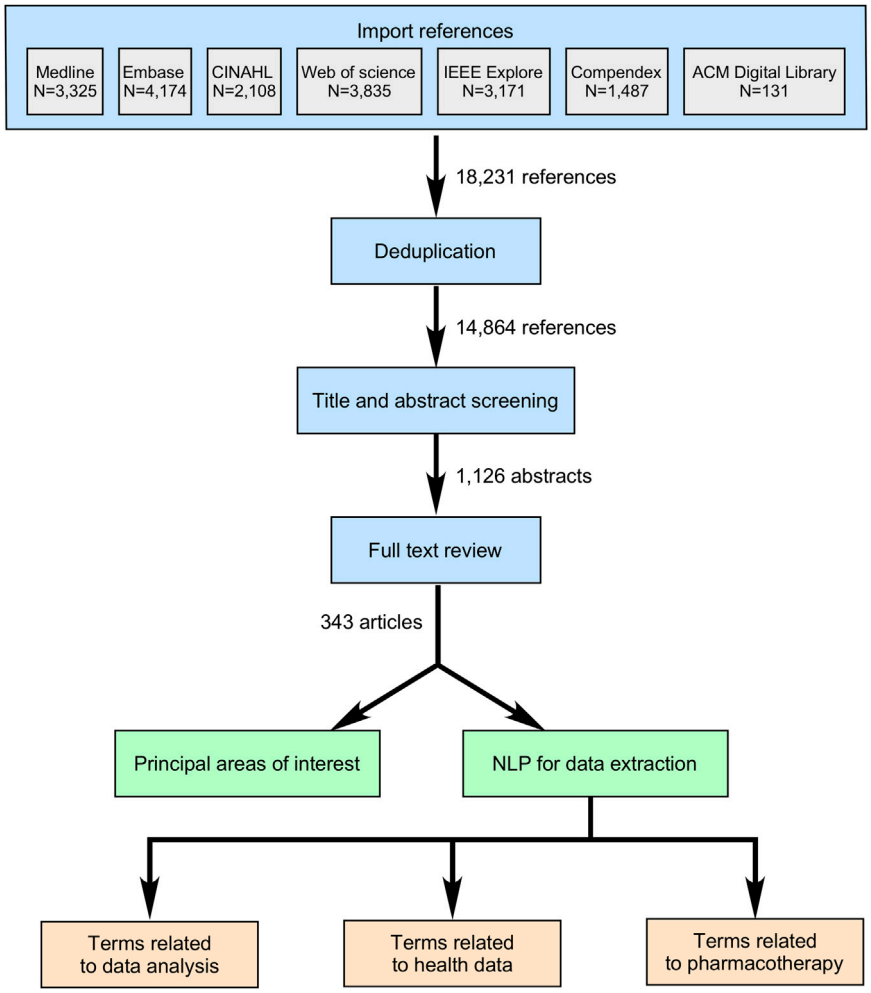



FIGURE 2
Article selection and data extraction strategy. Legend: The three main steps for article selection included titles and abstract screening, full test reviews, and data extraction. Classic (manual) approach allowed categorizing publications according to the principal areas of applied AI research. Automated method with the use of NLP allowed extraction of terms from three different groups, and their quantification.

3 due to the exclusion of 7 articles that could not be successfully imported from PDF format.

The first full-text articles applying AI to health care administrative databases were published in 2003 (Figure 3). Their frequency increased gradually and reached nearly 70 publications per year in 2020. A proportion of 67% of the articles were published between 2017 and March 2021. More than half of the studies have been published after 2018.

## Principal areas of artificial intelligence application

With the classic review approach, we determined ten principal areas of interest of AI application to health data (Table 1). The most common task for AI methods (N = 111; 32.1%) was to evaluate health state or predict health outcomes, such as predicting hospital length of stay (Azari et al., 2012), readmissions (Yang et al., 2016; Yu and Xie, 2020) or mortality (Melton et al., 2014; Lopez-de-Andres et al., 2016). This category also includes articles that focused on predicting the development of important health problems, such as stroke occurrence within a five-year period (Hung et al., 2017), cancer (Wang H. H. et al., 2019; Wang Y. H. et al., 2019), complications of diabetes (Liu et al., 2020), or adverse outcomes in COVID-19 patients (Shao et al., 2021).

The second most common objective of the studies (N = 74; 21.5%) aimed to develop AI for medical data representation including describing clinical pathways and taking into consideration time domain of medical data. These studies

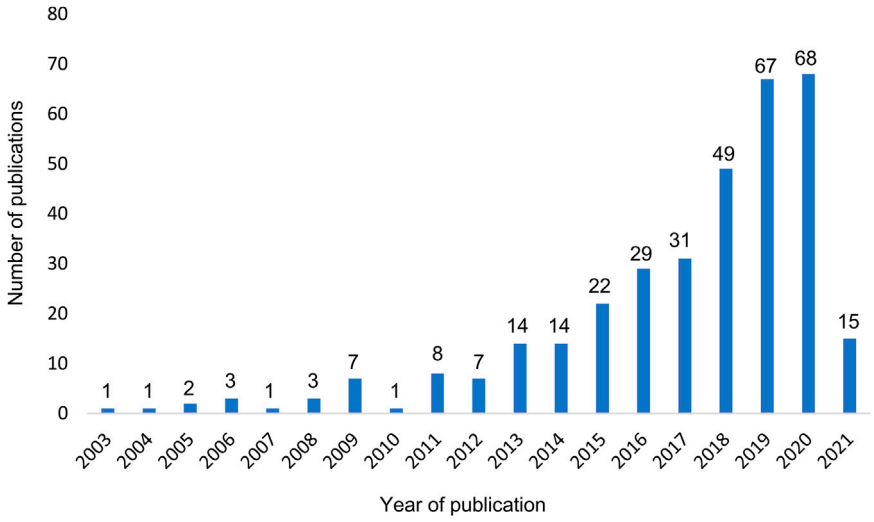



FIGURE 3
Number of published original articles on AI research applied to health care administrative database per year. Legend: The period 2003–2012 was characterized by a few publications per year and points to an emerging interest in the field. These research topics were rapidly growing in popularity in the following years, most significantly since 2018.

TABLE 1 Principal areas of AI application for health care administrative database.

| Area of interest | Number of articles | % from total |
|---|---|---|
| Health diagnostics or health outcome prediction | 110 | 32.0 |
| Medical data representation, clinical pathways, and temporality | 74 | 21.5 |
| Medication patterns, ADE, DDI | 52 | 15.1 |
| Medical data clustering | 47 | 13.7 |
| Multimorbidity | 45 | 13.1 |
| Combination of medications and treatment patterns | 23 | 6.7 |
| Subpopulations | 9 | 2.6 |
| Polypharmacy | 6 | 1.7 |
| Missing or biased medical data | 3 | 0.9 |
| Reinforcement learning | 3 | 0.9 |

ADE, adverse drug events; DDI, drug-drug interaction.

used sophisticated mathematical methods applied to longitudinal and heterogenous data (Zhang et al., 2018) to describe sequence of clinical events (Esteban et al., 2015) or inpatient services (Han et al., 2020), or to model disease progression (Powell et al., 2019).

A total of 52 articles (15.1%) focused on medication sequence patterns, adverse drug events (ADE), and drug-drug interactions. Examples of research topics of these studies are specific complications of pharmacotherapy, such as drug interaction effects on myopathy (Chasioti et al., 2019) or role of diabetes medications in the development of renal failure (Davazdahemami and Delen, 2019a; Davazdahemami and Delen, 2019b). This group of articles also includes those that used AI methods to extract information about ADE from such sources as Electronic Health Records (Bagattini et al., 2019) and health care administrative databases (Jin et al., 2008).

A significant share of included studies focused on regrouping medical data. These studies were mostly dedicated to mathematical approaches for: data clustering and evaluation of similarity between patients (13.7%) (Santana-Velásquez et al., 2020), combining analysis of patients with multiple medical diagnoses—multimorbidity (13.1%) (Bueno et al., 2018), or analysis of specific socio-demographic or geographic subpopulations (2.6%).

Only a few articles were using AI to determine combinations of medications in use and treatment patterns (6.7%). The least

TABLE 2 Principal AI methods applied to health care administrative database.

| Methods | Years | | | | | | Total (%) |
|---|---|---|---|---|---|---|---|
| | 2003–2005 | 2006–2008 | 2009–2011 | 2012–2014 | 2015–2017 | 2018–2020 | |
| Regression | 1 | 2 | 4 | 9 | 35 | 88 | 150 (44.6) |
| Correlation | 1 | 1 | 5 | 4 | 26 | 52 | 105 (31.3) |
| Decision tree | 4 | 0 | 3 | 10 | 28 | 48 | 102 (30.4) |
| Cluster analysis | 0 | 1 | 3 | 10 | 22 | 58 | 101 (30.1) |
| Random forest | 0 | 1 | 0 | 3 | 16 | 33 | 59 (17.6) |
| Support vector machine | 0 | 0 | 0 | 4 | 9 | 24 | 41 (12.2) |
| Recurrent neural network | 0 | 0 | 0 | 0 | 6 | 32 | 39 (11.6) |
| Bootstrap | 0 | 0 | 1 | 5 | 9 | 18 | 36 (10.7) |
| Naïve Bayes | 0 | 0 | 1 | 4 | 6 | 21 | 31 (9.2) |
| Long short-term memory | 0 | 0 | 0 | 0 | 4 | 24 | 29 (8.6) |
| Apriori | 3 | 3 | 4 | 5 | 6 | 8 | 28 (8.3) |
| Boosting | 0 | 0 | 0 | 1 | 2 | 20 | 26 (7.7) |
| k-Nearest neighbors | 0 | 0 | 1 | 1 | 5 | 15 | 24 (7.1) |
| Multi-layer perceptron | 0 | 0 | 1 | 0 | 4 | 14 | 21 (6.3) |
| Principal component analysis | 0 | 0 | 2 | 3 | 3 | 10 | 18 (5.4) |

Note: Linear discriminant analysis, cox models, hierarchical clustering, autoencoders, hidden Markov models, adaboost, reinforcement learning, generative adversarial networks, and self-organizing maps were mentioned in less than 5% of the articles and thus not included in Table 2.

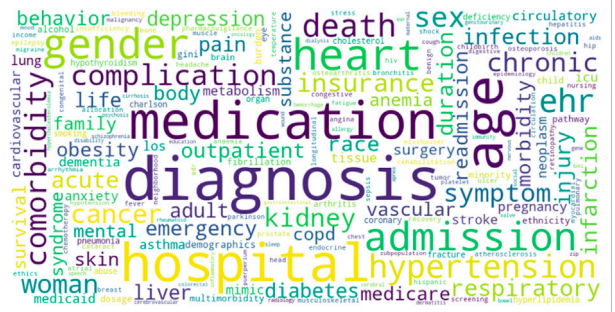



FIGURE 4
Principal health-related terms mentioned in AI applied studies. Legend: The larger font corresponds to the higher number of research articles where the terms were found.

frequent objectives of the studies were related to polypharmacy (1.7%), to solving problems of missing or biased medical data (0.9%), or to building treatment recommendations based on reinforcement learning (0.9%).

## Principal artificial intelligence methods applied to health care administrative data

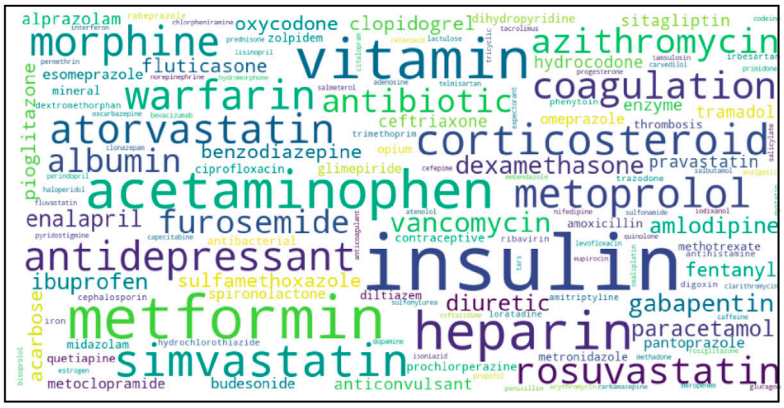
The top five most frequently used AI methods were decision trees, cluster analysis, random forests, support vector machines and recurrent neural networks (Table 2). Their popularity started to grow from 2012 to 2014 and has continued to increase until present. Regression and correlation analyses remained widely used in combination with AI methods, mainly for comparison of the research results or for data preparation (e.g., exclusion of highly correlated variables).

## Automated extraction of health-related terms from scientific articles

After performing all the steps of text processing described in the Methods section, we obtained 16,532 unique words that were defined as nouns and a corresponding number of articles in which these words were found. We chose the most frequently used terms related to health data, which resulted in a vocabulary of 190 words (Figure 4).

The word cloud in Figure 4 represents frequency of principal health-related terms extracted from scientific articles. The larger size of the words correlates with the larger number of articles in which the term was used. The terms “diagnosis” (N = 289) and “medication” (N = 215) were among the most frequently used. Most of the data was related to hospitals (N = 220), with particular interest in hospital admissions (N = 121) and emergency rooms (N = 52), while fewer articles focused on outpatients (N = 51). The most common clinical topics of interest were related to heart (N = 146, including hypertension, N = 115), cancer (N = 75) and kidneys (N = 70). Other common topics were respiratory

**A**




**B**

| ATC level 1 | Number of references | Number of medications (ATC level 5) | Examples of most frequently cited medications |
|---|---|---|---|
| A Alimentary tract and metabolism | 172 | 50 | insulin (N=33), metformin (N=18) |
| B Blood and blood forming organs | 57 | 17 | heparin (N=14) |
| C Cardiovascular system | 139 | 53 | simvastatin (N=10), atorvastatin (N=8), metoprolol (N=8) |
| D Dermatologicals | 46 | 24 | dexamethasone (N=6), fluticasone (N=5) |
| G Genitourinary system and sex hormones | 34 | 23 | Ibuprofen (N=5), metronidazole (N=3) |
| H Systemic hormonal preparations, excluding sexual hormones and insulins | 12 | 7 | dexamethasone (N=6) |
| J Antiinfective for systemic use | 87 | 41 | azitromycin (N=7), vancomycin (N=6), sulfamethoxazole (N=5) |
| M Antineoplastic and immunomodulating agents | 26 | 15 | ibuprofen (N=5) |
| L Musculo-skeletal system | 39 | 29 | methotrexate (N=3) |
| N Nervous system | 157 | 69 | acetaminophen (N=14), morphine (N=8), gabapentin (N=6) |
| P Antiparasitic products | 9 | 5 | metronidazole (N=3), permetrine (N=2), mebendazole (N=2) |
| R Respiratory system | 61 | 28 | dexamethasone (N=6), ibuprofen (N=5), fluticasone (N=5) |
| S Sensory organs | 35 | 20 | vancomycin (N=6), dexamethasone (N=6) |
| V Various | 3 | 3 | mannitol (N=1) |

FIGURE 5
Frequently used pharmacotherapy-related terms. Legend: **(A)** The larger font of the word cloud corresponds to a larger number of articles where the terms were found. **(B)** The table presents information about the number of mentions belonging to ATC level 1 classes, the number of ATC level 5 medications found in the articles, and examples of the most frequently mentioned medications. Some medications may be included in more than one ATC class (for example, dexamethasone appears in classes D, H and R), since the medication indications were not extracted. Some level 1 ATC classes are thus overrepresented (for example, the circumstances in which ibuprofen was studied may not belong to class G (intravaginal use), but rather to class M (anti-inflammatory agent), but ibuprofen has been listed in every ATC class to which it may belong).

diseases, infections, injuries, pain, and diabetes. Many articles considered not just single diagnosis, but also comorbidities (N = 95). The research was more often focused on chronic diseases (N = 78) than on acute conditions (N = 65). Socio-demographic data was often taken into consideration, with a special emphasis on age (N = 231), gender/sex (N = 135/91, correspondingly), particularly women and race (N = 55).

## Automated extraction of pharmacotherapy-related terms from scientific articles

The reviewed articles were presenting results of interdisciplinary research of AI applied to health. However, they were often lacking in detail on health-related input data and health-related results. In particular, even though many articles used the words "medication" or "drug", they were commonly missing information of what medications exactly were included in the study.

Our analytic NLP-based method allowed to directly quantify the use of pharmacotherapy-related terms. We performed automatic extraction of single word terms found in ATC and AHFS classifications, that composed a vocabulary of 1,129 terms. The terms most frequently used are presented in Figure 5. Active substances most frequently mentioned were related to following anatomical and pharmacological groups (ATC level 1): alimentary tract and metabolism (172 mentions of 50 different substances), nervous system (157 mentions of 69 substances) and cardiovascular system (139 mentions of 53 substances). The least represented in the AI-based studies were antiparasitic products (9 mentions of 5 substances) and systemic hormonal preparations excluding insulins (12 mentions of 7 substances). More specifically, the most frequent terms were "insulin" (N = 33), "metformin" (N = 18), "vitamin" (N = 16), "acetaminophen" (N = 14), and "heparin" (N = 14). They were followed by such medication names as simvastatin, warfarin, atorvastatin, morphine, and metoprolol.

# Discussion

The review demonstrated the growing popularity of AI research in health domain, specifically in application to health care administrative data. This phenomenon can be explained by accumulation of large volumes of this type of data, improved access to such databases to AI researchers, further development of AI methods, improving computational capacities, and increased funding of interdisciplinary projects. Application of AI to health care administrative data is heterogenous in terms of areas of interest and methods. We discerned ten areas subdivided into a wide range of sub-areas involving 25 principal statistical and AI methods, 190 terms pertaining to health and 1,129 terms pertaining to pharmacotherapy. We showed that some areas are more popular (e.g., health diagnostics or outcome prediction) while others are still vastly underrepresented (e.g., reinforcement learning or missing or biased medical data).

We identified a trend towards extensive use of methods based on decision trees, cluster analysis, and random forests. The popularity of these methods could be explained by the fact that they are generally associated with a greater potential for explainability of the results, which facilitates their translation into clinical practice. Other methods, such as support vector machine and recurrent neural networks, have also gained popularity in recent years, as they are known to show better performance for certain tasks (Paquette et al., 2021). Traditional statistical methods are also widely used. Regression methods remain especially popular for comparing the performance of AI methods, and correlation analysis may be useful for data preparation, such as excluding highly correlated variables to reduce the dimensions of the dataset. Although both types of methods (AI and statistical) produce useful results, no general framework exists for practical use. Future studies using AI models should therefore also include traditional statistical methods (e.g., Poisson or logistic regressions when using random forests or neural networks) in order to better define conditions of performance and to help create guidelines of AI methods applied to health care administrative data.

The majority of the articles covered medical diagnoses and treatment, which corresponds to the keywords used for the search in literature databases. Many studies were focused on hospital data and emergency departments that can be explained by better accumulation of data by large hospitals that are often affiliated to universities, and their better accessibility for AI research. These findings point to the need to improve data collection and accessibility for scientific research of outpatient data.

Interestingly, the word cloud revealed that different features describing socio-demographic characteristics were of different levels of interest in the reviewed studies. For example, "age" of patients was mentioned more frequently than "race". Terms "gender" was found more frequently than "sex", however, we think that in the context of health care administrative databases, those terms might be inter-replaceable, and most likely represent the value of sex. We decided not to replace them with one synonym to illustrate the weakness of currently available databases that do not allow distinguishing between these socio-demographic categories. Our results also revealed a wide range of features with an imbalance in the levels of interest (e.g., hypertension vs. pneumonia).

The most common health topics were related to chronic conditions including cardiovascular, renal, and respiratory diseases, cancer, and diabetes. The high number of research publications focused on these topics may be explained by their high prevalence in the population and heavy burden on the health care system, as well as the availability of surveillance

data (Blais et al., 2014; Ke et al., 2022). These findings also correspond to the most frequent medications mentioned in the articles, such as metformin, heparin, and simvastatin. The commonly used term "insulin" could refer not only to pharmacotherapy, but also to clinical conditions such as insulin resistance or even to laboratory tests. However, our automatic analysis used to extract data, in its current form, does not allow distinguishing the contexts in which the term "insulin" was used in the articles.

### Strengths and limitations of the study

A librarian was involved in all stages of the review to define our search strategy and to strengthen the review process. The large number of abstracts included in the review helped to provide a global view on the state of the art of AI applied to health care administrative data that would focus on clinical problems and/or pharmacotherapy, as well as on the results of the treatment. However, manual data extraction from such a large number of articles was complicated and could have led to human errors. To avoid these errors and to facilitate data extraction at the last stage of the review we applied NLP-based method to automatize the procedure.

This search was limited to single-word terms and common acronyms of multi-word terms, and therefore some health and pharmacotherapy-related data might have been missed. Exclusion of studies based on databases with fewer than 1,000 observations could exclude studies using AI methods for a narrow or highly specific patient population. We suspected that the number of such studies excluded is small as AI methods are commonly used in large real-world databases.

## Conclusion

This scoping review revealed the potential of AI application to health-related studies. The most popular health areas for the application of AI include prediction of health outcomes and handling of large health datasets. Some areas of great importance for pharmacoepidemiology are, however, under-represented, such as health of specific socio-demographic groups and health effects of polypharmacy. With AI methods becoming increasingly popular, the extent to which they add value (in terms of efficiency, precision, or impact) is yet to be clarified.

## Author contributions

Conception of the study—CS, OB, and YC; abstract and full text reviews—OB, AA, YC, SS, and MS; natural language processing—OB; data analysis—OB, AA, YC, MS, and CS; writing the article—OB, AA, YC, MS, SS, and CS.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



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## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2022.944516/full#supplementary-material

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# The Use of the Target Trial Approach in Perinatal Pharmacoepidemiology: A Scoping Review Protocol

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**Background:** Pregnant and postpartum women have been historically excluded from clinical trials, with data on the safety of drugs relying on observational research. Methodological concerns regarding the timing and dosing of medications, data sources, study designs, and methods used for estimating associations are still problematic in observational studies. Answering causal questions is even more complex. Despite the increased interest in emulating target trials using observational data, little is known about this approach in perinatal pharmacoepidemiology.

**Objective:** This scoping review protocol aims to describe the methodology for assessing the available literature concerning emulating target trials for studying outcomes in women exposed to medications in the preconception, perinatal, or postpartum periods.

**Methods and Analysis:** We will follow the methods detailed in the Joanna Briggs Institute reviewer's manual. We will adopt the six-stage framework recommended by Arksey and O'Malley and Levac and others. Web scraping techniques will be used for identifying relevant studies. Two authors will select articles based on the title and abstract, with discrepancies resolved by consensus, by a third reviewer. Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews flow diagram will be presented to reflect the search process. We will use existing statements to identify quality gaps in the current literature. Variables related to the content for perinatal pharmacoepidemiologic research will be included. The Risk Of Bias In Non-randomised Studies - of Interventions (ROBINS-I) will guide the assessment of the target trial emulation (i.e., treatment strategies compared, assignment procedures, follow-up period, outcome, and causal contrasts).

**Discussion:** Data regarding the safety of drugs taken, prior to and during pregnancy and while lactating are lacking and it is necessary to understand how we can answer these questions using rigorous methods in observational research. Through this scoping review, we intend to understand to what extent the target trial approach is being used in perinatal pharmacoepidemiology and provide recommendations to improve its use in this field.

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**Ethics and Dissemination:** Secondary data from published scientific articles will be used, not requiring approval by the Research Ethics Committee with human beings. Findings will be submitted to a peer-reviewed journal.

**Keywords: scoping review, target trial emulation, preconception, perinatal, postpartum, pharmacoepidemiogy**

## BACKGROUND

Research in women's health is usually focused on specific periods of a women's life such as the reproductive or perinatal period (World Health Organization, 2009). Pregnancy and childbirth are normal physiological and social processes that carry health risks and require follow-up and care. Pregnancy may unmask or worsen a pre-existing condition (Torgersen and Curran, 2006), leading to interventions to reduce the burden and risk of long-term morbidity (Neiger, 2017). Although pharmacotherapy is typically the first-line therapy, questions relating to the effectiveness and safety of medications used in pregnancy and lactation, still remain.

The physiological changes that occur during pregnancy affect both the pharmacokinetics of drugs (i.e., absorption, distribution, metabolism, and elimination) and the pharmacodynamics, influencing the mechanism of action and magnitude of observed pharmacological effects (Zhao et al., 2014). Other factors might also contribute to the change in pharmacokinetics/pharmacodynamics during pregnancy including pre-existing comorbidities, maternal age, race, ethnicity, body weight, singleton vs. multiple gestations, gestational age, smoking history, alcohol usage, dietary habits, and illegal drug use, as well as other behavioral changes (Moya et al., 2014; Zhao et al., 2014). Teratogenic effects are the leading concern for medication use prior to and during pregnancy; while their use following delivery and while lactating raises concerns for the health of neonates and the long-term development of the child (Wecker et al., 2019). Given the lack of data on use of medications during pregnancy, little guidance exists for practitioners to determine whether the benefit outweighs the risks of pharmacological treatments (Ansari et al., 2016). Pregnant women have been historically excluded from clinical trials (Food and Drug Administration, 2018; van der Graaf et al., 2018; Yakerson, 2019; Bianchi et al., 2021), with data on the safety of newly marketed drugs relying on post-marketing surveillance (Huybrechts et al., 2021). There is, therefore, a need for rigorous observational research, to elucidate the effects of drugs in this population.

Nevertheless, evaluating the effectiveness and safety of medications during pregnancy presents major challenges. Methodological concerns regarding the timing and dosing of medications, data sources, study designs, and methods used for estimating associations are still problematic in observational studies (Horton et al., 2019; Huybrechts et al., 2019). Answering causal questions is even more complex. More recently, Hernan and others (Hernán and Robins, 2016) have proposed a framework for conducting comparative effectiveness research. More specifically, they proposed the use of large databases to emulate hypothetical pragmatic randomized trials, also called target trial emulation (Hernán and Robins, 2016).

The use of observational studies analyzed like randomized experiments was first demonstrated in 2008 (Hernán et al., 2008). Briefly, this method advocates the adoption of seven key components that should be clearly outlined in a target trial protocol: the eligibility criteria, treatment strategies being compared (including their start and end times), assignment procedures, follow-up period, outcome of interest, causal contrast(s) of interest, and analysis plan (Hernán and Robins, 2016). Despite the increased interest in emulating target trials using observational data, gaps have been identified, such as the misalignment of start of follow-up, eligibility, and treatment assignment, as well as the lack of complete knowledge on confounders (Hernán et al., 2016). Additionally, little is known about use of target trial emulation in perinatal pharmacoepidemiology research, in which key elements including, exposure ascertainment and etiologically relevant time of exposure are fundamental for interpreting outcomes (Fell et al., 2021).

Two recent articles have adopted the target trial approach to estimate the comparative effectiveness and safety of treatments before conception (Caniglia et al., 2018; Yland et al., 2022). However, the use of this method is likely more readily adopted by pharmacoepidemiologists working in perinatal research. Through a scoping review, we aim to understand the use of the target trial approach to answering causal questions in perinatal pharmacoepidemiology.

## SCOPING REVIEW AIMS

The aim of this protocol is to describe the methodology for assessing the available literature concerning emulating a target trial for studying outcomes in women exposed to medications in the preconception, perinatal, or postpartum periods. The specific objectives will be *i*) to describe the identified studies by type, year, and country *ii*) to describe the inclusion of the components of the target trial protocol of included studies *iii*) to identify knowledge gaps (i.e., reporting of the components of a target trial protocol, data sources availability, quality, research located in few centers etc.), and, *iv*) to provide recommendations for future research relating to the target trial approach.

## METHODS AND ANALYSIS

The proposed scoping review will follow the methods detailed in the Joanna Briggs Institute (JBI) reviewer's manual (Peters et al.,

2020). We will adopt the six stage framework recommended by Arksey and O'Malley (Arksey and O'Malley, 2005) and Levac and others (Levac et al., 2010).

## Stage 1: Identifying the Research Question

The Population, Concept and Context (PCC) elements (Peters et al., 2020) will guide the title, objective of the scoping review, question, and inclusion criteria. The question for the scoping review is: What is known from the existing literature about emulation of randomised trials using observational data (i.e., target trial emulation) for assessing outcomes related to medication exposure before, during or after pregnancy (post-delivery and during lactation)?

## Stage 2: Identifying Relevant Studies

A three-step search strategy for identifying relevant studies is recommended according to JBI (Peters et al., 2020): *i)* searching online databases, followed by an analysis of the text words contained in the title and abstract of records identified as relevant, and of the index terms used to describe the articles; *ii)* using all identified keywords and index terms across all included databases; *iii)* searching the reference list of all identified reports and articles for additional studies.

For our study, the first two steps will be automated using Web scraping techniques (Najork et al., 2018), data cleaning and deduplication (Ganti et al., 2018; Kaushik et al., 2018) developed by our group using the Python programming language (Python Software Foundation, https://www.python.org/) and previously used for various types of reviews, including scoping reviews (Mota et al., 2020). Briefly, Web scraping is a technique for extracting Web contents. Through this process a software agent, also known as a Web robot (scraper), mimics the browsing interaction between human and Web servers in a conventional Web navigation, extracting and combining contents of interest from the Web in a systematic way (Glez-Peña et al., 2013). The structure and content of a Web page are encoded in Hypertext Markup Language (HTML). A scraper is built to fit the web page's HTML to parse its content and extract information from it. A common scraping task involves iterating over every possible URL (sometimes called 'crawling') and storing data from each page without the risk of human error during extraction. Once the program is complete, all available and desired data can be captured from the web page. This process can be repeated continuously, assuming the web page structure remains mostly the same. (DeVito et al., 2020). Web scraping enables automated identification and extraction of data of interest available on a web page, resulting in scale gain and agility in searching for keywords or text of interest.

For our work, the scraping task will be carried out in PubMed, Science Direct, Ovid Embase, Scientific Electronic Library Online (Scielo), Latin American and Caribbean Health Sciences Literature (Lilacs) databases, and WHO Global Index Medicus between January 2013 to May 2022. The initial year was defined based on the first study describing a target trial emulation (Danaei et al., 2013). The search strategy for scientific articles will be tailored according to the database requirements. Health sciences descriptors (DeCS)/ Medical Subject Headings (MeSH) and combined keywords and other indexing terms (i.e., EMTREE), according to the PCC structure, limiting the searches to the concept, will be used. Our interest is to identify what type of publications have mentioned the use of target trial emulations for assessing outcomes in women of reproductive age or the perinatal period exposed to medications. In this regard, we did not limit our search using additional filters for the type of study. The scraping task will be carried out through the fields: title, summary, and keywords. In Scielo, the search will take place using the standard field "All indexes", which includes the search in the title and abstract of publications. No restrictions on language will be made. Appendix 1 provides the search strategy adopted for this protocol, as well as the description of the data scraping process.

Grey literature will be also retrieved through Web scraping techniques on Google Scholar, which retrieve information from conference proceedings, such as from Epidemiology, Pharmacoepidemiology, and Maternal Health [e.g., Society for Epidemiologic Research [SER] Conference, The Society for Pediatric and Perinatal Epidemiologic Research [SPER] Meeting, Conference on Pharmacoepidemiology and Therapeutic Risk Management, The Canadian National Perinatal Research Meeting (CNPRM)].

Box 1 shows the variables that will be requested at the web scraping stage. Duplicates will be removed through the use of DOI. The automated process will generate an output file with the data provided in an Excel® spreadsheet format to be used in the subsequent phases of this review.

The inclusion criteria will be based on the PCC elements:

### Population

We will select studies including women of childbearing age, pregnant or postpartum (prior to, during, or after pregnancy). Studies will not be restricted by the range of maternal age. Eligible studies will include primary research studies, systematic reviews, meta-analyses, letters, guidelines, etc.

### Concept

Emulation of a hypothetical randomised trial using observational data is an approach in which one carefully specifies a causal question and a strategy to minimize the sources of bias in observational research (Hernán and Robins, 2016). However, even if researchers have a high-quality data source, e.g., a database from electronic medical records with millions of patients, emulating a target trial is not a technically trivial exercise, in terms of knowledge, infrastructure or programing skills. Additionally, in pregnancy studies we usually deal with rare outcomes with small numbers of exposed women and consequently limited sample size, as well as relatively short time windows for pregnancy. In this regard, we want to understand what the limitations are in implementing these studies, what questions are being answered, and their respective outcomes in the perinatal period.

**BOX 1 | |** Variables that will be requested at the web scraping stage.

| Variable | Definition |
|---|---|
| DT | Day/time extraction |
| TITULO | Title of the article |
| TIPO_ARTIGO | Type of article - according to the journal classification |
| PERIODICO | Journal's name |
| DIA | Day publication |
| MES | Month publication |
| ANO | Year of publication |
| URL | Uniform Resource Locator |
| AUTOR_COMPLETO | Complete list of authors |
| PAIS_AUTOR | Country of the first author |
| INFO_AUTOR_1 | Name first author |
| DOI | Digital Object Identifier System |
| DOWNLOAD | website for download of the article |
| ABSTRACT | Abstract |
| KEYWORDS | Keywords |
| BASE | data source |

### Context

We want to understand the use of target trial emulation in the preconception, perinatal or postpartum periods. Thus, we will evaluate studies regardless of the data source or country in which they may have been carried out.

Observational studies of medication exposure in the preconception, perinatal and postpartum periods will be eligible for inclusion. We are also planning to assess opinion papers, oral presentations, conference notes, and abstracts. Observational studies comparing pharmacological treatments that have not used a target trial approach will be excluded.

## Stage 3: Study Selection

The authors (LFL and DMM), independently, will select the potentially eligible scientific articles based on the title and abstract, and full text, when necessary, to confirm the relevance of the review question. Through videoconference, the authors will use a sample of two studies to ensure that there was a common understanding of the inclusion and exclusion criteria.

Discrepancies will be discussed and resolved by consensus, by a third reviewer (SMG). The selected studies in this stage will comprise a single database that will be used in the fourth phase of this scoping review. Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) flow diagram (Tricco et al., 2018) will be followed to reflect the search process.

## Stage 4: Charting the Data

In the single database containing only the eligible studies, we will classify the types of scientific articles according to Lapeña et al. (Lapeña and Peh, 2019): *i)* Primary or original research articles; *ii)* Secondary or review articles; *iii)* Special articles; *iv)* Tertiary literature; and *v)* Grey literature. For articles classified as primary research, we will extract information related to the seven key components of the target trial protocol (Hernán and Robins, 2016). Information to evaluate the characteristics of reporting will be also included. For this, we will use the reporting of studies conducted using observational routinely collected health data statement for pharmacoepidemiology (RECORD-PE) (Langan et al., 2018). Additionally, we will include variables related to the content for perinatal pharmacoepidemiologic research recommended by Margulis et al. (2022). Although evaluating risk of bias in scoping reviews is not currently recommended, we will extract information on characteristics of the target trial emulation, such as treatment strategies being compared (including their start and end times), assignment procedures, follow-up period, outcome, and causal contrast(s) adopted according to Nguyen et al. (2021). The Risk Of Bias In Non-randomised Studies - of Interventions (ROBINS-I) (Sterne et al., 2016) will be used. The variables included represent efforts to identify gaps in the current literature related to the reporting and methods adopted.

## Stage 5: Collating, Summarizing and Reporting the Results

The studies will be grouped according to the variables contained in the single database and characteristics of included studies will synthesized using descriptive statistics, such as absolute numbers and frequencies and measures of central tendency (median) and dispersion (interquartile interval).

## Stage 6: Consultation

We will carry out two consultations. The first consultation will be held at the start of the scoping review to explore experts' opinions. Researchers experienced with the target trial approach will be consulted on the objectives of our review and asked to provide feedback on whether our aims capture existing knowledge gaps in the field. Researcher's input may give rise to additional, or modified aims. The findings of the review will be shared with experts (second consultation) to identify any additional gaps not identified in the scoping review. Recommendations for future research will be based on findings of the scoping review and through our consultations with experts.

# DISCUSSION

This protocol presents the background, objectives, and planned methodology for conducting a scoping review to analyze the available literature on the target trial approach for evaluating outcomes in women exposed to medications in the preconception, perinatal or postpartum period.

Data regarding the safety of drugs taken, prior to and during pregnancy and while lactating are lacking and it is necessary to understand how we can answer these questions using rigorous methods in observational research.

We anticipate that, perhaps, few studies will be found, and this may be a possible limitation. However, even if a limited number of studies exist, we will be able to understand to what extent the target trial approach is being used in perinatal

pharmacoepidemiology and provide recommendations to improve its use in this field.

## DATA AVAILABILITY STATEMENT

The raw data supporting the conclusion of this article will be made available by the authors, upon request.

## AUTHOR CONTRIBUTIONS

LL and RP devised the research question. DM and PF elaborated the methods. DM and GG provided input for search strategies. LL wrote the manuscript with support from SG, DM and PF. All authors contributed to the design and the frameworks for this protocol, provided critical feedback, and approved the final manuscript.

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## SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2022.904824/full#supplementary-material

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# Improving the adherence to COVID-19 preventive measures in the community: Evidence brief for policy

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**Objectives:** To identify evidence-based strategies to improve adherence to the preventive measures against the coronavirus disease (COVID-19) at the community level.

**Method:** This is an evidence brief for policy, combining research evidence specific to contextual knowledge from stakeholders. A systematic search was performed in 18 electronic databases, gray literature, and a handle search, including only secondary and tertiary studies that focused on the adherence of the general population to COVID-19 preventive measures in the community. Two reviewers, independently, performed the study selection, data extraction, and assessment of the quality of the studies. Relevant evidence has been synthesized to draft evidence-based strategies to improve adherence. These strategies were circulated for external endorsement by stakeholders and final refinement. Endorsement rates >80%, 60–80% and <60% were considered high, moderate, and low respectively.

**Results:** Eleven studies, with varying methodological qualities were included: high ($n = 3$), moderate ($n = 3$), low ($n = 1$), and critically low ($n = 4$). Three evidence based strategies were identified: i. Risk communication; ii. Health education to the general public, and iii. Financial support and access to essential supplies and services. The rates of endorsement were: 83% for risk communication, 83% for health education, and 92% for financial support and access to essential supplies and services. The evidence showed that an increase in knowledge, transparent communication, and public awareness about the risks of COVID-19 and the benefits of adopting preventive measures results in changes in people's attitudes and behavior, which can increase adherence. In addition, the guarantee of support and assistance provides conditions for people to adopt and sustain such measures.

**Conclusions:** These strategies can guide future actions and the formulation of public policies to improve adherence to preventive measures in the community during the current COVID-19 pandemic and other epidemics.

KEYWORDS

**COVID-19, health policy, pandemic, evidence-informed policy, knowledge translation**

## Introduction

In 2020, the coronavirus disease 2019 (COVID-19) quickly spread around the world, causing a global health and economic crises, unprecedented and, uncertain prospects for the period post-pandemic (1, 2).

COVID-19 is an infectious disease caused by the a novel coronavirus, severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2), that was first identified in December 2019 in China (2). With its rapid spread globally, the World Health Organization (WHO) declared the COVID-19 pandemic as an emergence of global importance. Since then, society, scientists, decisionmakers, and health systems have been challenged (3).

So far, there is no prophylactic drug treatment. As such, the disease is mostly controlled through non-pharmacological community measures and vaccination (4, 5). Vaccinations started in December 2020 in the United Kingdom, and the vaccination coverage rates vary considerably between countries. While some countries have achieved high vaccination coverage, others still lag behind. Furthermore, the emergence of several variants of the novel coronavirus, which worries the global scenery, highlights the importance of adopting the preventive measures at the community level, as these are the most effective and accessible measures currently (6, 7). The main community measures for the prevention of COVID-19 implemented in most countries include social distancing, quarantine, hand hygiene, and the use of facemasks (7, 8).

The combination of these non-pharmacological interventions aims to delay/decrease the spread of the virus and avoid the overburdening of health systems (9). Despite being simple, cheap, and effective, these measures have not achieved homogeneous adherence in the communities (10, 11). Adherence varied among the studies and mainly between the types of measures adopted (12). Furthermore, these measures were implemented differently in the countries (7) and efforts have been made to increase and sustain their acceptability, adherence, and public awareness.

The implementation and adherence to these measures are particularly more difficult in low and middle-income countries, especially in vulnerable populations, as observed in the previous epidemics (13). The poorest population, including those dependent on public transport, informal workers, homeless, people living in slums or crowded houses without adequate ventilation or without basic sanitation, are at a high risk of being infected and affected by serious crisis economic crisis (14).

In this context, it is crucial to contain the pandemic by improving the population's adherence to effective community measures for the prevention and control of COVID-19. However, the results and impact depend on collective behavior and interventions from government agencies. This study identified the best available evidence and described strategies to improve adherence to COVID-19 preventive measures in the community.

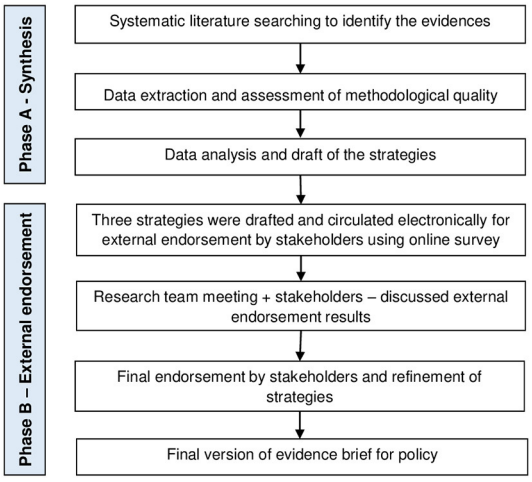


FIGURE 1
Phases to produce the evidence synthesis and its external endorsement.

## Methods

We conducted an evidence brief for policy (study that package research evidence to inform deliberations among policymakers and stakeholders) (15) combining two phases: (A) synthesizing the evidence from systematic literature searching around effective strategies (interventions) to improve the adherence to COVID-19 preventive measures in the community and (B) external endorsement and evidence brief final refinement by stakeholders, Figure 1.

### Phase A: Searching and identifying the literature, data extraction and assessment of methodological quality

#### Elegibility criteria for studies

Studies were selected based on the following inclusion criteria:

#### Type of studies

We included systematic reviews (SR), rapid reviews (RR), overviews, evidence brief, clinical practice guidelines and policy guidelines. Guidelines were only considered if GRADE Evidence to Decision (EtD) was used.

#### Type of participants

Studies involving the general population exposed to COVID-19 and other severe acute respiratory syndromes (SARS).

### Type of interventions

Any type of strategy to promote or improve adherence to community measures, such as handwashing, quarantine, social distancing, and use of facemasks for the prevention and control of COVID-19 and other SARS.

Studies that only suggested interventions to increase adherence but did not measure these were excluded.

### Type of comparisons

There were no restrictions on the types of comparisons.

### Type of outcome measures

Primary outcomes: number/proportion of people who adhere to community measures for the prevention and control of COVID-19 and other SARS; reduction of incident cases, hospitalizations, and mortality.

Secondary outcomes: cognitive or behavioral changes; changes in the knowledge, awareness, attitudes, acceptability, and behavior; factors associated with adherence or not adherence; knowledge/understanding of concepts or skills relevant to the critical appraisal of health claims.

## Information sources and search strategy

A systematic search was conducted in the following databases: MEDLINE, LILACS, The Cochrane Library, Health System Evidence, Health Evidence, EMBASE, CINAHL, Global Index Medicus, Epistemonikos, International Initiative for Impact Evaluation (3ie), Campbell Collaboration, Clinical Trial Registry, WHO ICTRP—International Clinical Trials Registry Platform (ICTRP) and GIN Guidelines International Network**.** It was also searched in some specific database for COVID-19: Coronavirus (COVID-19) Special Collections from Cochrane, COVID19 Study register from Cochrane, COVID-END from McMaster and COVID-19 Evidence database from Epistemonikos.

In addition, reference lists, gray literature and handle searches were also performed using a search strategy developed by two specialists. The supplement (Supplementary Data Sheet 1) shows the search strategy for MEDLINE which was adapted for each of the other databases. Electronic searches were conducted between January 28 to February 06, 2021.

### Screening and selection of studies

A pilot exercise was conducted using 50 abstracts for the entire screening team to calibrate and test the review form. Subsequently, titles and abstracts were screened independently according to the selection criteria by pairs of reviewers (CB, SBF, JOMB, TB). Disagreements regarding the eligibility of studies were resolved by discussion, and a third reviewer (LCL) was consulted when necessary.

The full texts of the potentially relevant papers were retrieved for examination. The inclusion criteria were then independently applied to the full-text version of the papers by the same pairs of reviewers. Conflicts were resolved by discussion, and a third reviewer (LCL) was consulted when necessary.

### Data extraction

The following data were extracted from the included studies: study objectives, designs, number of studies included, number and type of participants, intervention/strategy, main findings, country of study, and date of the last search. Data extraction was performed independently by the same pairs of reviewers and checked by another reviewer. Disagreements were resolved through discussion and consensus.

### Assessment of methodological quality

The qualities of SRs were independently assessed by a pair of reviewers, using the A MeaSurement Tool to Assess systematic Reviews (AMSTAR 2) (16). The quality of RR was assessed by pair of reviewers, independently, using an adaptation of the Cochrane checklist for rapid reviews (17). See all items assessed in Supplementary Table S1.

To assess the quality of clinical practice guidelines or policy recommendations, three reviewers used the AGREE checklist (18). The AGREE II analyses of 23 items divided into 6 quality domains and two global classification items, in which the raters used a scale from 1 to 7 points (1- corresponds to "strongly disagree" and 7 "strongly agree"). The quality score was individually assigned by the reviewers and the total percentage of each domain was obtained from the following calculation: [(obtained score—minimum possible score) divided by (maximum possible score—minimum possible score)]. Scores >80%, 60–80%, and <60% were considered to be of high, sufficient and low quality, respectively. The guidelines' overall rating and recommendation were independently determined by each rater and a consensus was reached.

### Data analysis and drafting the strategies

After extracting data, pairs of reviewers independently categorized the strategies using the taxonomy from Health Systems Evidence (19). It consists in taxonomy of governance, financial and delivery arrangements and implementation strategies within health systems[20]. We chose the topic "implementation strategies."

Conflicts and disagreements during this process were resolved through discussion and consensus.

Data from the included studies were synthesized using tables and a narrative summary.

## Phase B—External endorsement—Incorporating knowledge from stakeholders

Key people from the health departments and committees dealing with COVID-19 from Brazil and civil society with contextual knowledge were identified. Among 29 people who were invited, 20 agreed to participate in Phase B.

We circulated the recommendations electronically to this same group of 20 stakeholders (including policymakers, frontline health professionals, researchers and civil society organization representatives) for external endorsement using an online survey.

We asked stakeholders whether they fully endorsed, did not endorse, or had no opinion about recommendations. Participants were also invited to provide comments. We considered endorsement rates of >80% as high, 60%—80% as moderate, and <60% as low levels of endorsement. The results were discussed during an online meeting with the research team and stakeholders, and the results were incorporated into the final version of the evidence brief and refinement of the strategies.

## Patient and public involvement

We had stakeholders (policy-makers, health professionals, researchers, and civil society organization representatives involved in the phase B of this project.

# Results

Of the 11.376 identified studies, eleven studies met the inclusion criteria, Figure 2. In the full text stage, fifty-eight studies were excluded, and their reasons are shown in the Supplementary Material (Supplementary Table S2).

Of the 11 studies, 6 were RR (11, 20–24), 4 SR (25–28), and one guideline for policy (29). From these studies, we identified 3 strategies and categorized them as followed: i. Risk communication (6 studies included it); ii. Health education to the general public (4 studies included it), iii. Financial support and access to essential supplies and services (2 studies included it), Table 1. Characteristics of included studies, see Supplementary Table S3.

The methodological quality of studies was varied. Of the 4 SR, 2 were moderate-quality (26, 28), 1 low-quality (25), and 1 critically low quality (27). Of the 6 RR, 2 were high-quality (11, 23), 1 moderate quality (20), and 3 critically low quality (21, 22, 24), Table 2.

The only guideline included had high quality (Supplementary Table S4).

## Strategies identified

### Strategy 1— Risk communication

Six studies, with varying methodological qualities qualities (three high quality, three moderate quality), were included. Risk communication is defined as the "exchange of information, advice and opinions, in real-time, among experts, community leaders or officials, and people at risk who face threats to their health and social well-being" (29). This strategy should be based on three pillars, as shown below (29):

#### Building trust

The information must be easily found in legitimate/reliable sources, and it should be clear, consistent, unified, practical, and up-to-date. It should discuss the risks (dissemination, contagion, and severity of COVID-19), the benefits, the need, the effectiveness and the rationality of adopting community measures to prevent COVID-19 (11, 29). The population must receive practical information on what they should do and for how long.

These messages must be constantly reinforced (29) and disseminated widely across different media, including traditional, social, local, and mobile media (25). It is also important to maintain proactive communication from government and official authorities and monitor public perception, uncertainties, concerns, and inconsistencies in the population (23).

#### Transparency

Communicating and recognizing uncertainties, errors, and changes in information. Negative information, such as the number of victims, should not be occulted (11, 29).

#### Community participation

Identification and involvement of people that the community trusts (trusted leaders, be it a health professional or a public health leader) in the development and dissemination of the messages (11, 29). The messages should be customized according to the target audience, the cultural context, and their understanding, involving stakeholders to ensure the flow, integrating the community into practice (23, 29). These should also be tested in advance using a small group from the community (29). The messages should reinforce social responsibility and a sense of altruism to increase the population's motivation to adhere to the preventive measures (22).

In this way, risk communication is effective as it produces cognitive changes in the perception of disease risk, which in turn encourages behavior change and increases adherence

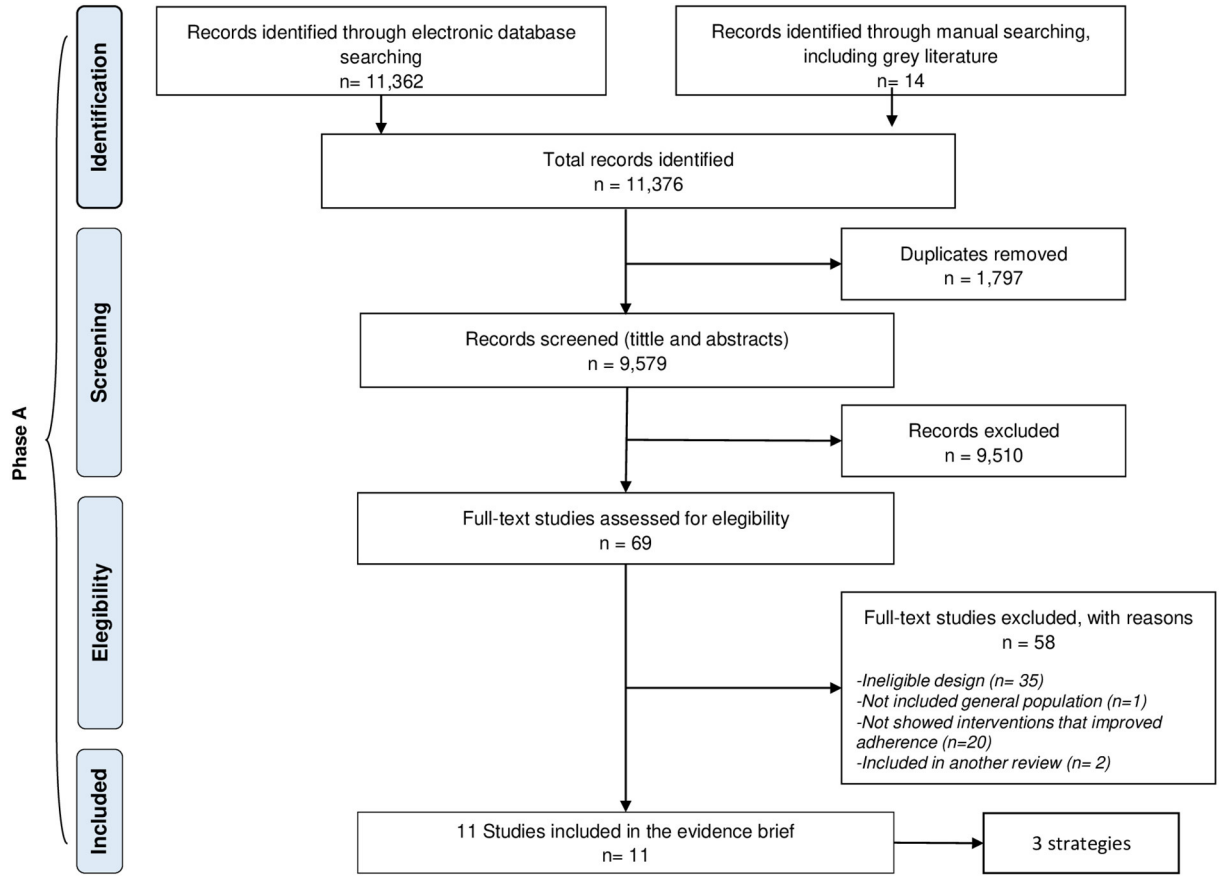


FIGURE 2
Selection of studies.

to preventive measures (24). Repeatedly providing clear information on how the virus is transmitted, the risk of contagion, the health risk, the severity of the disease (perception of risk), as well as the effectiveness and benefits at the individual and community (perception of benefit) levels of the preventive measures allowed people to understand and adopt preventive measures (11, 22, 23). Trust in science, local and/or national government institutions, and in the person delivering the message, and the sense of altruism (protecting oneself and others) are important in influencing behavior and increasing adherence (11, 22, 23).

Failures in communication can have negative effects on the acceptability and adherence to preventive measures (22, 23). Conflicting or confusing information taints the credibility and reliability of the information, which can cause "information fatigue" (22). The public is skeptical, and messages are considered alarmists (23). Delays in the transmission of messages by officials and agencies, government failure, and misinterpretation reduce public trust and discourage the population from continuing to adhere to preventive measures (22, 23).

## Strategy 2—Health education to the general public

Four studies with varying methodological qualities (three moderate quality and one critically low) were included.

Health education refers to any type of combination of learning experiences designed to help individuals and communities improve their health, increase their knowledge, and/or influence their attitudes (30). It is a permanent pedagogical process of building knowledge. However, it is not only limited to the dissemination of information related to health (30) as it must involve the promotion of motivation, skills, trust, and necessary autonomy to act and improve health and adopt healthy and preventive practices.

This strategy plays a key role in the prevention and control of emerging infectious diseases (27). It should be broad, consistent, released as early as possible. Furthermore, it should be focused on public awareness of COVID-19 (risk of transmission, symptoms, and measures to reduce the spread of virus), prevention (the benefits and

TABLE 1 Characteristics of the studies included for identifying policy strategies.

| Author, year | Number/type of studies included in the review | Number of participants | Main outcomes | Which preventive measure does study refer to? | Taxonomic classification of policy strategy[&] |
|---|---|---|---|---|---|
| Winograd et al. (24) | 31 studies: *14 RCTs, 17 nonRCTs* | 40,183* | Cognitive or behavioral outcomes | Multiples[#] | Risk communication |
| Webster et al. (21) | 14 studies: *6 qualitative studies, 8 quantitative studies* | 52,029 | Factors associated with adherence or non-adherence | Social distancing | Support/access |
| Li et al. (20) | 24 *cross-sectional studies* | 35,967 | Knowledge, attitude, practice or awareness | Multiples[#] | Health education |
| Mills et al. (22) | 89 *cross-sectional studies* | Not reported | Factors contributing to facemask use | Facemasks use | Risk communication |
| NCCMT (11) | 17 studies: *9 secondary studies, 5 primary studies, 3 guidances* | Not reported | Change in knowledge, attitudes and behavior | Multiples [#] | Risk communication |
| Ryan et al. (23) | 31 studies: *16 primary studies, 1 RR, 1 review of guideline, 8 SR, 3 guidelines, 2 reviews/meetings analyses* | Not reported | Increased acceptability and adherence to social distance | Social distancing/ quarantine | Risk communication Support/access |
| Cusack et al. (28) | 24 studies: *14RCTs, 10 non-RCTs* | 16,530* | knowledge or understanding of concepts/skills relevant to evaluating the effects of, or claims about, health interventions | Multiples[#] | Health education |
| WHO (29) | 13 studies: *12 SR, 1 RR* | Not reported | Adoption of preventive behavior | Multiples[#] | Risk communication |
| Solhi et al. (27) | 16 studies: *4 before-and-after studies, 12 intervention-control studies* | 10,960 | Prevention or reduction of the incidence of infectious diseases | Multiples[#] | Health education |
| Nordheim et al. (26) | 8 studies: *1 RCT, 7 non-RCTs* | 1,148* | Critical appraisal abilities for health claims | Multiples[#] | Health education |
| FitzpatrickLewis et al. (25) | 24 studies: *21 quantitative studies, 3 qualitative studies* | 3,546 | Awareness, knowledge, attitude or behavioral change | Multiples[#] | Risk communication |

*One of the studies did not report the number of participants. [#]Preventive measures defined in this evidence brief and others types; [&] the classification of strategies was done according to the Health Systems Evidence Taxonomy; RCT, randomized controlled trial; non-RCT, non-randomized controlled trial; RR: rapid review; SR, systematic review.

effectiveness of adopting adequate preventive measures), adoption of adequate face mask use (how to use and wash them), hand hygiene (wash your hands well with soap and water or use alcohol gel). Lastly, it should utilize of reliable information and sources related to the pandemic (20, 27).

Health education increases knowledge and public awareness, which improves attitudes, practices, and behaviors during the pandemic (20). It also contributes to maintaining optimistic attitudes and reducing the level of anxiety, tension, fear, and depression. As such, it may be more effective in the most vulnerable groups or in those who commonly adopt risk behaviors, such as young people (20). The most recommended types of educational interventions in this current pandemic involve raising awareness through national media campaigns and web-based educational programs (20, 27). This strategy is also effective in improving the understanding of key concepts related to health and skills in critically assessing health issues, including the general public (28) and teenagers (26).

TABLE 2 Methodological quality of systematic reviews and rapid review according to AMSTAR 2 and adapted Cochrane checklist respectively.

| Author, year | Q1 | Q2 | Q3 | Q4 | Q5 | Q6 | Q7 | Q8 | Q9 | Q10 | Q11 | Q12 | Q13 | Q14 | Q15 | Q16 | Ranking of Quality |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Strategy 1: risk communication** | | | | | | | | | | | | | | | | | |
| ***Rapid reviews*** | | | | | | | | | | | | | | | | | |
| Winograd et al. (24) | 🔴 | 🔴 | 🟡 | 🟢 | 🟡 | 🟢 | 🟢 | 🟢 | 🔴 | 🟢 | 🔴 | ○ | - | - | - | - | Critically low |
| NCCMT (11) | 🟢 | 🔴 | 🟡 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | ○ | - | - | - | - | High |
| Ryan et al. (23) | 🟢 | 🔴 | 🟡 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | ○ | - | - | - | - | High |
| Mills et al. (22) | 🔴 | 🔴 | 🟡 | 🔴 | 🟡 | 🟢 | 🟢 | 🟡 | 🔴 | 🟢 | 🔴 | ○ | - | - | - | - | Critically low |
| ***Systematic review*** | | | | | | | | | | | | | | | | | |
| Fitzpatrick-Lewis et al. (25) | 🟢 | 🔴 | 🔴 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | 🔴 | ○ | ○ | 🟢 | 🟡 | ○ | 🟢 | Low |
| **Strategy 2: health education to the general public** | | | | | | | | | | | | | | | | | |
| ***Rapid reviews*** | | | | | | | | | | | | | | | | | |
| Li et al. (20) | 🔴 | 🔴 | 🟡 | 🔴 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | ○ | ○ | ○ | - | - | - | - | Moderate |
| ***Systematic reviews*** | | | | | | | | | | | | | | | | | |
| Cusack et al. (28) | 🟢 | 🟢 | 🔴 | 🟢 | 🟢 | 🟢 | 🟡 | 🟢 | 🟢 | 🔴 | ○ | ○ | 🟢 | 🟢 | 🟢 | 🟢 | Moderate |
| Solhi et al. (27) | 🟢 | 🔴 | 🔴 | 🟡 | 🟢 | 🟢 | 🔴 | 🟢 | 🔴 | 🔴 | ○ | ○ | 🔴 | 🔴 | 🔴 | 🔴 | Critically low |
| Nordheim et al. (26) | 🟢 | 🟢 | 🔴 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | 🔴 | ○ | ○ | 🟢 | 🟢 | ○ | 🟢 | Moderate |
| **Strategy 3: financial support and access to essential supplies and services** | | | | | | | | | | | | | | | | | |
| ***Rapid reviews*** | | | | | | | | | | | | | | | | | |
| Ryan et al. (23) | 🟢 | 🔴 | 🟡 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | 🟢 | ○ | - | - | - | - | High |
| Webster et al. (21) | 🔴 | 🔴 | 🟡 | 🔴 | 🟡 | 🟢 | 🟢 | 🟢 | 🔴 | 🔴 | ○ | ○ | - | - | - | - | Critically low |

🟢 yes, 🔴 no; 🟡 partially yes, ○ not applicable (meta-analysis not performed).





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### Strategy 3—Financial support and access to essential supplies and services

Two studies with varying methodological qualities (one high-quality and one critically low quality).

Several practical elements need to support or sustain behavior change and the population's response to certain preventive measures, especially quarantine or social distancing. The population may have the desire, motivation, and knowledge to adhere to preventive measures, but if there are no means to do so, they will not adhere (31).

It is essential to offer certain types of support/assistance to the population, especially those most affected by the pandemic, and ensure that they know clearly which are available and how they can be accessed (23). This should include: financial support and access to basic supplies, such as food and medicines; facilitation of access to usual and specialized medical services; maintenance of direct lines for support and communication with a team of healthcare professionals, including online services or by telephone; and implementation of measures to compensate for financial losses or job loss (21, 23).

Despite the economic and social impact, ensuring of financial support and access to essential supplies increases adherence to preventive measures and mitigates long-term effects on the physical and mental health of the population. Hard-to-access support services cause stress and non-adherence (23), and the fear of losing one's job and family income were the main nonadherence factors (21).

## External endorsement results

Twenty stakeholders participated and completed the online endorsement survey, of which 2 (10%) were policy-makers, 2 (10%) frontline health professionals, 13 (65%) were researchers (professionals who work in research institutes focused on decision making), and 3 (15%) were civil society organization representatives. The rates of total endorsement for the recommendations were: 83% for risk communication, 83% for health education, and 92% for financial support and access to essential supplies and services.

Emphasis was placed on the importance of customizing risk messages according to the target audience and on empowering the primary health care team in the elaborating and disseminating these messages. Participants tended to endorse the health education, but they highlighted that it would be the most challenging recommendation during a pandemic. Furthermore, e-learning, one of the most commonly used forms, could have difficulties impacting a specific part of the population. Support was considered the most important because it enables the adoption of preventive measures during the pandemic.

# Discussion

This evidence brief presented strategies for improving the adherence to COVID-19 prevention measures in the community using complex knowledge synthesis of evidence from literature and contextual expert knowledge from stakeholders. The available evidence from 11 studies identified three strategies that may be useful in dealing with non-adherence, which was highly endorsed by stakeholders.

The time required to produce evidence is not always the same for decision making. Sometimes, robust evidence obtained from studies of high methodological quality may not be available when decision-makers need it, as in this case. The strategies were derived from some low-quality studies with varied evidence levels. As such, we included information on uncertainties and gaps.

There were more studies for strategy 1 than for other strategies; however, the quality was quite varied. Different approaches to risk communication were promising, but it was not possible to determine the best approach (24, 25). Evidence has showed that interventions targeting a specific population were more effective than the ones that do not (24). Another point highlighted in all the studies included was the importance of community involvement in the elaboration and transmission of risk messages, which increases acceptability, trust, and adherence to preventive measures (11, 23, 29).

Despite the relevance of the role of the strategy 2 in emerging diseases, the format of the educational process became more complicated in a pandemic scenario. The studies only suggested providing health education by media campaigns, telephone, or web-based programs (20, 27). In general, the format was variable, and little information about the educating agent was provided in the studies. The long-term effects of health education are still unknown because the studies assessed immediately after or shortly (after 28 weeks) (27). The lack of health education and low health literacy (32) poses a big risk in the COVID-19 pandemic due to the proliferation of false information (misinfodemic). When misinformation or false news is disseminated repeatedly, the marginal impact of true information on the population is limited (22), which might influence people's health decisions and encourage unhealthy behaviors. As health information and misinformation have become more abundant in recent years, through mass media or the internet, it has become increasingly crucial to have general knowledge and skills to assess whether claims about health interventions are trustworthy (28). Studies have shown that educational interventions can improve knowledge and skills in the critical appraisal of health claims at least in the short term (26, 28).

Strategy 3 shows the essential elements to support and sustain preventive measures, especially quarantine. Financial support and access to essential supplies (food and medicines) and services (usual and specialized medical services) result in

significant economic and social impacts, but robust economic assessments are needed (23). Some other positive support/access strategies were cited in some studies, but they did not assess their effectiveness in improving adherence, such as the provision of stations for handwashing, water, soap, or alcohol-gel to increase adherence to hand hygiene, whether in a public environment or domicile (13), distribution of masks in order to increase adherence to the use of masks (13); provision of quarantine or isolation centers (13); and control/reduction in the number of passengers on public transport (33).

The impact of strategy 3 may be even greater in low-income countries groups, or places that are potentially at a disadvantage. These include populations without clean water and those unable to buy masks, soap, or alcohol, or to keep their distance in crowded houses or slums.

The diverse group of stakeholders engaged in the endorsement process ensured the review, assessment of the feasibility, and refinement of the strategies in real practice. This phase was important as it weighed the research evidence with the knowledge, values, insights, and experiences of stakeholders. The approach of including stakeholders in the process has grown in the past several years and is critical for implementing promising interventions and improving the health of communities (34).

Bringing together evidence producers and users contributes to the dissemination and application of global and local evidence in real-world settings, reducing the gap between research and practice.

Although it was not the focus of our research and was not discussed among stakeholders, it is important to note that both strategies 1 and 2 could also help in the vaccination adherence to COVID-19. Vaccine hesitancy is another major challenge that countries are facing probably due negative and unclear information spread by media, lack of education and health literacy (35, 36).

Observational studies conducted in some countries identified that high adherence to COVID-19 preventive measures was associated with willingness to vaccinate against the disease (36, 37). The known major predictors that affect the adherence to preventive measures are similar to vaccination adherence, such as age, socioeconomic status, education level, health literacy level, trust in their government and in their healthcare system (36, 37). Women, older age, with chronic disease, higher education levels, higher health literacy, life satisfaction were associated positively to adherence to preventive measures and to vaccination (37).

Risk communication and health education could contribute to address positive and true information about the COVID-19 vaccination, to avoid the spread of misinformation, reduce disbeliefs, hesitancy and resistance, increase the confidence within the population about the benefits of vaccination and the percentage of vaccine definite people (35, 36).

Finally, our findings could be used by practitioners and policy-makers working in the field of prevention and control of COVID-19 to improve the adherence to COVID-19 preventive measures and the willingness of the community to vaccine and combat COVID-19.

## Strengths and limitations

To our knowledge, this was the first study to address this objective and involved relevant stakeholders for the endorsement of effective strategies.

While the three strategies are well outlined, it is important to mention that social influences could be a key motivation for some people's adherence to COVID-19 preventive measures. For instance, people have more motivation to adherence when their close social circle did (38).

The variability in the quality of the included studies may cause some uncertainties and limit the confidence in the findings. Further studies should be conducted to assess the effectiveness of interventions to improve adherence to preventive measures in the community for future epidemics. Furthermore, rigorous methods in order to provide high-quality evidence.

The majority of the studies also focused on high-income countries. This limits their application in low-income countries, which face different challenges, mainly in relation to its implementation. Additionally, if those implementing the strategy do not take into account and nurture the local culture, the project is doomed. Therefore, more studies need to be conducted in low- and middle-income countries.

# Conclusion

Based on the best available evidence, this evidence brief identified three strategies for improving adherence to preventive measures against COVID-19 in the community, which may guide future actions and policymaking during this pandemic or future epidemics. In addition, two of these strategies could contribute to improve the vaccination adherence and reduce the hesitancy and resistance in the community.

The intention is not to recommend specific strategies but to inform policymakers and stakeholders and contribute to assertive decision-making in public health, according to the needs, financial resources, feasibility, local reality, and the engagement of the main actors. This evidence brief provides relevant information for planners and policymakers to choose the most effective strategy.

## Data availability statement

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author.

## Ethics statement

The studies involving human participants were reviewed and approved by the Research Ethics Committee of the University of Sorocaba, on 15 October 2020, (CAAE: 38351620.9.0000.5500) according to Resolution CNS 466/12 of the National Health Council. The patients/participants provided their written informed consent to participate in this study.

## Author contributions

IF and LL led the conceptual design of the original study, acquisition of funding, drafted the manuscript and conducted the methodological quality assessment. JB, SB-F, CB, and IF selected tittles and abstracts and extracted data from included studies. All authors read and approved the final manuscript.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpubh.2022.894958/full#supplementary-material

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# A Description of Acute Renal Failure and Nephrolithiasis Associated With Sodium–Glucose Co-Transporter 2 Inhibitor Use: A VigiBase Study

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**Background:** The Food and Drug Administration issued a warning on the risk of acute kidney injury and a signal of nephrolithiasis for patients using sodium–glucose co-transporter 2 inhibitors (SGLT2i). We performed a descriptive analysis on acute renal failure (ARF) and nephrolithiasis cases reported to SGLT2i in the VigiBase®, in the scope of characterizing the patients and reactions and to report on the disproportionality analysis.

**Methods:** We analyzed all ARF and nephrolithiasis reports for SGLT2i in VigiBase from inception to September 2021. ARF cases were defined as reports containing at least one of the preferred terms (PTs) included in the ARF narrow Medical Dictionary for Regulatory Activities Standardised Queries (MedDRA SMQ). SGLT2i exposure was considered for reports with at least one gliflozin as a suspected/interacting drug. We characterized the patients, reporters, and reactions, and we present the proportional reporting ratio (PRR).

**Results:** Of 27,370,413 total reports in VigiBase, we found 3,972 ARF reactions to gliflozins as suspected/interacting drugs in 3,751 patients and 231 nephrolithiasis reactions in 227 patients. Most cases were reported from American regions (3057; 81.49%), for patients of age group 45–64 years (1590; 59%). About 30% (1156) of the ARF reports were registered in 2018, most from spontaneous reporting, and from consumers followed by healthcare professionals (2,235; 61% and 1440; 38%, respectively). Canagliflozin was the most involved gliflozin in the ARF and nephrolithiasis cases (2,640; 67% and 109; 47%, respectively). The great majority of ARF and nephrolithiasis reports were serious (3,761; 95% and 182; 79%, respectively). Of the total ARF cases reported, 51 had fatal outcome, while 152 had not recovered/not resolved outcome. No fatal outcome was reported for nephrolithiasis. Disproportionality analysis in full database showed a PRR of 4.68 (95% CI 4.53–4.83) for all gliflozins–ARF and a PRR of 3.44 (95% CI 3.00–3.95) for all gliflozins–nephrolithiasis.

**Conclusion:** Most of ARF reports associated with gliflozins were serious, with an important number of cases with fatal outcome. A drug safety signal was found

between ARF narrow SMQ and gliflozins. Also, gliflozins were associated with an increase in the proportion of nephrolithiasis reports compared to other medications.

**Keywords: SGLT2I, acute kidney injury, acute renal failure, nephrolithiasis, drug-induced acute kidney injury, drug-induced nephrolithiasis, disproportionality analysis, VigiBase**

## 1 INTRODUCTION

The benefit–risk balance of sodium–glucose co-transporter 2 inhibitors (SGLT2i, gliflozins), a relatively new glucose-lowering agent (GLA) class, was extensively studied over the last years. SGLT2i have proven to have beneficial effects beyond glycemic control, on metabolic, cardiovascular, and renal outcomes (Minze et al., 2018). Three cardiovascular clinical trials, (EMPA-REG, CANVAS, and DECLARE-TIMI 58 trial), reported beneficial renal outcomes (AY et al., 2018). Two kidney clinical trials (CREDENCE and DAPA_CKD) demonstrated that SGLT2 inhibitors can reduce the risk of worsening chronic kidney disease (CKD) (Giorgino et al., 2020). In contrast to this renoprotective benefit proven during clinical trials, several case reports on acute kidney injury (AKI) associated with SGLT2i were reported and triggered a strengthening of the warning on the risk of AKI issued by the Food and Drug Administration (FDA) (U.S. Food and Drug Administration, 2015; U.S. Food and Drug Administration, 2016). In addition, nephrolithiasis is another possible adverse drug reaction (ADR) of SGLT2i at the renal level. FDA also issued a warning on this potential risk, raising concerns regarding renal safety of these medications (U.S. Food and Drug Administration, 2017).

AKI is defined by an abrupt decrease in kidney function with important clinical consequences, including increased risk of death. AKI includes, but is not limited to, acute renal failure (ARF) and other, less severe conditions (Kellum et al., 2012). As a syndrome, AKI includes patients without actual damage to the kidney but with functional impairment (Kellum et al., 2012). Patients with diabetes are known to have a higher susceptibility to AKI/ARF (Wang et al., 2021), but also medications are a common cause of AKI/ARF, especially for patients admitted to hospital wards and the intensive care unit (Perazella and Rosner, 2022a).

The risk of developing renal impairment with SGLT2i and the role of plausible mechanisms have to be established yet (Szalat et al., 2018). SGLT2i may induce excessive diuresis which can lead to intravascular volume depletion, particularly in hemodynamically unstable and volume-depleted patients (Perlman et al., 2017; Szalat et al., 2018). Reduced trans-glomerular pressure with a modest decline in kidney function, a characteristic of SGLT2i, is on the long-term renal protective. The acute decrease in estimated glomerular filtration rate (eGFR) was attributed to the effect of proximal tubular natriuresis on tubuloglomerular feedback, leading to reversible intrarenal hemodynamic effects, including afferent arteriole vasoconstriction (Cherney et al., 2014; Sridhar et al., 2020; Meraz-Muñoz et al., 2021). Lastly, SLGT2i increase medullary oxygen consumption, increasing the risk for hypoxia (Perlman et al., 2017), especially with concomitant use of agents impairing medullary oxygenation, such as nonsteroidal antiinflammatory drugs (NSAIDs) and radiocontrast agents (Szalat et al., 2018).

The clinical implications of the acute decrease in eGFR were unknown and led to concerns about the safety of SGLT2i because observational reports suggested an increase in the risk of AKI (Perlman et al., 2017). On the other hand, a retrospective cohort study found that there were no differences observed in the incident AKI in SGLT2i versus other GLAs (Rampersad et al., 2020). A systematic review and meta-analysis showed that SGLT2i even reduced the odds of suffering AKI with and without hospitalization in randomized trials and in the real-world setting, despite the fact that more AEs related to hypovolemia are reported (Menne et al., 2019). In addition, some propensity score analysis comparing SGLT2i with other antidiabetics (dipeptidyl peptidase 4 inhibitors) reported that AKI risk was reduced in SGLT2i users, but the mechanism is unknown yet (Nadkarni et al., 2017; Sridhar et al., 2020).

In addition, SGLT2i treatment could lower the risk for incident and recurrent kidney stones in people with type 2 diabetes, as recent evidence suggests (Kristensen et al., 2021). SGLT2i induce osmotic diuresis, increased urinary flow, polyuria, and urine dilution that may even reduce the risk of nephrolithiasis (Kristensen et al., 2021). However, a potential signal of nephrolithiasis was detected earlier by the FDA in patients using SGLT2 inhibitors (U.S. Food and Drug Administration, 2017). It was also suggested that SGLT2i can cause hyperuricosuria (Chino et al., 2014; Novikov et al., 2019), which may confer a greater risk for specific types of kidney stones. Diabetes mellitus is also a known risk factor for nephrolithiasis (Aune et al., 2018).

Despite the fact that the risk of AKI and nephrolithiasis was not confirmed by observational database studies of large cohorts, reports of AKI and nephrolithiasis associated with SGLT2i use continue to be submitted to VigiBase (2487 and 231 reactions, respectively, by September 2021), the World Health Organization (WHO) unique global database of individual case safety reports (ICSRs). VigiBase includes reports from around 140 countries representing over 90% of the world's population and is maintained by the Uppsala Monitoring Centre (Uppsala, Sweden). The database contained more than 27 million ICSRs that has been submitted by national pharmacovigilance centers since 1967. Although VigiBase data cannot offer evidence on the causality relationship between the gliflozins and the events, analysis on the disproportionality of events reported for a particular drug versus the rest of the database and versus a restrictive diabetic therapeutic area can still be informative and add value to better characterize the safety profile of this class of drugs. Also, specific information on patients and reactions reported may help in contouring the common ground of the

reactions reported. The objective of our study was to perform such analyses in the VigiBase®, on ARF and nephrolithiasis reported to SGLT2i versus all ADRs and ADRs of all antidiabetics, in the scope of characterizing the patients and reactions and to investigate their relationship through disproportionality analysis in the largest international pharmacovigilance database.

# 2 METHODS

## 2.1 Study Population and Design

This is an observational study that characterizes the reported ARF and nephrolithiasis reactions related to gliflozins use and presents their disproportionality analysis when compared to all ADRs and to ADRs of all antidiabetics (ATC A10) in the VigiBase from inception to 31 August 2021.

The adverse events captured in the ICSRs have been coded according to the latest version of the Medical Dictionary for Regulatory Activities (MedDRA) at the time of reporting.

## 2.2 Information

Following variables on the reports were received from WHO: region of origin, date of report, reporter qualification, report source, serious, seriousness criteria per reaction, patient's characteristics (sex and age group), drugs (indication, start and end dates, dosage, and route of administration), and reactions reported (MedDRA terms, onset date and end date, time to onset, reaction outcome, and dechallenge/rechallenge action). One ICSR can include more than one adverse reaction and more than one suspected or interacting drugs.

## 2.3 Data Management

All ARF and nephrolithiasis reactions with canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, ipragliflozin, and/or luseogliflozin as suspected or interacting drugs until 31 August 2021 were received from VigiBase. In addition, the disproportionality analysis of each preferred term (PT, the term used to describe an adverse event in MedDRA) associated with each of the gliflozins as compared to all ADR reports and compared to all antidiabetics reports were received from VigiBase. We hypothesized that it is possible that some cases could be reported with a PT different from AKI or ARF, and decided to use MedDRA Standardised Medical Queries (SMQs), which are validated, predetermined sets of MedDRA terms grouped together to support safety analysis.[1] We identified the acute renal failure SMQ broad and narrow and we decided to use the narrow search as this is more specific (cases highly likely to be related to a specific condition). Narrow search on SMQ "Acute Renal Failure" yielded 19 PTs as follows: Acute kidney injury, Acute phosphate nephropathy, Anuria, Azothemia, Continuous hemodiafiltration, Dialysis, Fetal renal impairment, Hemodialysis, Hemofiltration, Neonatal anuria, Nephropathy toxic, Oliguria, Peritoneal dialysis, Prerenal failure, Renal failure, Renal failure neonatal, Renal impairment, Renal impairment neonatal, and Subacute kidney injury. All these PTs were included in the analysis.

The reports of ARF with fatal outcome were further analyzed with the aim of identifying and characterizing co-suspect/concomitant medications, concurrent conditions and potential risk factors for fatal ARF.

Regarding nephrolithiasis, we used only the PT with the same name.

Exposure to gliflozins was defined as the mention in the report of at least one of the following: canagliflozin, dapagliflozin, empagliflozin, ertugliflozin, ipragliflozin, and/or luseogliflozin as suspect or interacting medication.

## 2.4 Data Analysis

Descriptive statistics were used to summarize the baseline characteristics of the reports, patients, drugs, and reactions for the ICSRs containing adverse events from the ARF SMQ narrow (ARF reactions hereafter) and nephrolithiasis reactions. The comorbidities of the patients were retrieved from the field of indication for all drugs included in the analyzed ICSRs.

The disproportionality of selected reactions associated with the use of the six gliflozins was studied in a case–non-case analysis individually for each PT. The proportion of ARF/nephrolithiasis reactions reported for gliflozins was compared with the proportion of the ARF/nephrolithiasis reactions reported for all other drugs in VigiBase. Additionally, as diabetes mellitus itself is a known risk factor for development of kidney disease, a sensitivity analysis was performed and the database was restricted to the diabetic therapeutic area (i.e., considering only medicines used in diabetes) as the background, to take into account the increased baseline risk of ARF and nephrolithiasis. Furthermore, we excluded from the database all reactions with co-suspected drugs to limit the innocent bystander effect with gliflozins.

The proportional reporting ratio (PRR) was used as a measure of disproportionate reporting. The data were provided by the Uppsala Monitoring Centre for individual gliflozins and PTs. We calculated the PRR for the gliflozin class and ARF reactions and nephrolithiasis as described in the **Supplementary Tables 1, 2** on the data provided by the WHO Uppsala Monitoring Center(Proportional Reporting Ratio, 2022).

A PRR value $\geq 1$ associated with $\geq 5$ cases was considered a positive association between the reaction and gliflozins (Slattery et al., 2013).

Microsoft Excel was used to compute the PRR values that were not provided by WHO Uppsala Monitoring Center and to tabulate relevant data.

# 3 RESULTS

## 3.1 Case Selection

A flowchart of the study is presented in **Figure 1**. VigiBase contained 27,370,413 reports until 31 August 2021. Exposure to gliflozins as suspected/interacting drug was found in 69,352 reports.

## 3.2 Reports and ADR Characteristics

We identified 3972 ARF reports to gliflozins as suspected/interacting drugs in 3751 patients and 231 nephrolithiasis

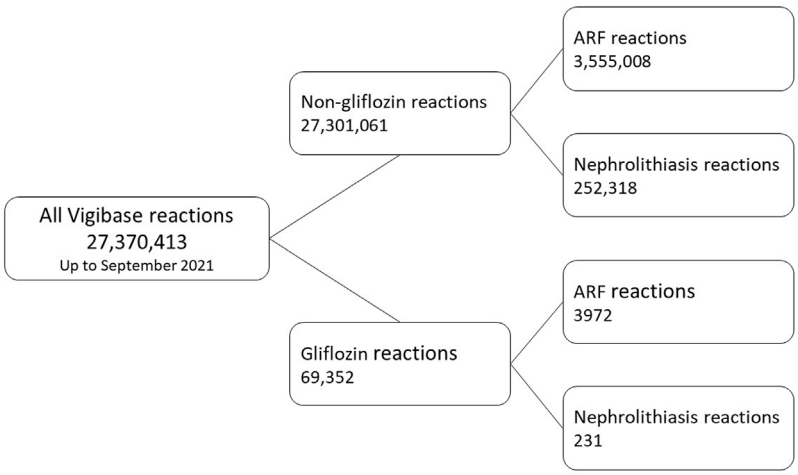


**FIGURE 1 |** Flowchart of the ICSRs included in the analysis.

reactions in 227 patients (more than one gliflozin may be suspected for one reaction and more than one PT may be reported in case of ARF SMQ).

The characteristics of reports, patients, and reactions are shown in **Table 1**. The most cases with available information were reported in the regions of America (3057; 81.49%), in the category of 45–64 years of age (1590; 59%) and male gender was more frequent (1852; 57% and 114; 56% in ARF and nephrolithiasis reports, respectively).

Most of the ARF reports came from spontaneous reporting, the majority from consumers followed by healthcare professionals (2235; 60.86% and 1.440; 38.09% from available data, respectively with 59.57% coming from consumers only). The first ARF reports were registered in 2011 and their number increased until 2018 (1156, around 31% of the total reports) and then declined until 2021 (169 reports by September) (**Table 1**). For nephrolithiasis, the highest number of reports were registered in 2015 (53 cases) and slightly decreased in the years after.

For the ARF analysis, we found that canagliflozin was the most frequently involved gliflozin (2640 cases; 66.81%) followed by dapagliflozin (622 cases; 15.74%) and empagliflozin (606 cases; 15.33%). Canagliflozin was the most involved gliflozin in the nephrolithiasis cases as well (109 cases; 47.18%), followed by empagliflozin (65 cases; 28.13%) and dapagliflozin (55 cases; 23.80%) (**Table 1**).

Of the 19 PTs included in the ARF SMQ narrow, we found 12 PTs reported for gliflozins. AKI (2387: 62.61%), renal failure (907; 22.83%), and renal impairment (501; 12.61%) were the most reported PTs for each gliflozin. Most of the reports were with canagliflozin (1750 AKI, 599 renal failure and 160 renal impairment), followed by empagliflozin (280 AKI, 128 renal impairment and 122 renal failure) and dapagliflozin (245 AKI, 138 renal impairment and 136 renal failure), (**Table 1**; **Figure 2**).

Information on time-to-onset of the reaction was available in 322 (8%) cases for ARF and in 158 reports ARF occurred after the first 8-week period of starting therapy (49% of the cases with this information available). In 45% of the 141 cases with available information, the reaction duration was less than 1 week for ARF. In 23 cases with information available for nephrolithiasis, we found the most cases reported within 6–12 months from treatment start (6 cases) followed by the interval within first week (5 cases) (**Table 1**).

The great majority of ARF reports were serious (95.79%) with more than half (57.7%) causing/prolonging hospitalization. Of the total ARF reported, 51 had fatal outcome (2.7% from available data), while 152 (8.07%) had not recovered/not resolved outcome. However, the vast majority of the cases have a favorable outcome, recovered or recovering at the moment of reporting (88.2% of known data). In 1724 of the ARF reactions, reaction abated after gliflozin withdrawal (positive de-challenge in 43.40% of the total ARF reactions) and also 3 cases with positive re-challenge were reported (**Table 1**).

The most frequent co-suspect and interacting drugs reported in the 3751 ARF ICSRs were: other antidiabetics (biguanide, insulin, DPP-4 inhibitors, GLP-1 receptor agonists, and sulphonylurea), diuretics and antihypertensive drugs. We found an important number of patients using diuretics (n = 125), ACE inhibitors and ARB blockers (n = 163), and NSAIDs (n = 43) who had ARF (**Table 2**) The most frequent comorbidities of the patients with ARF were hypertension, cardiac disorders, depression and anxiety, hyperlipidemia, and pain. Associated ketoacidosis was frequently reported (27.87% of reports with ARF reactions), followed by different types of infections. If we cumulate the number of infections, these become the most frequently reported PTs (30.84% of reports with ARF reactions) (**Table 2**) Regarding associated conditions with ARF that induce plasmatic volume depletion, we found dehydration, diarrhea, and vomiting (n = 437 associated PTs), cardiac failure (n = 86 associated diseases), hypovolemia (n = 25 associated PTs), or concomitant use of diuretics (n = 124).

For nephrolithiasis, the majority of reports were also serious (79%) and 50% of the cases with this information available had a favorable outcome. No fatal cases were reported. We found 46 nephrolithiasis reactions with positive de-challenge (58.22%

**TABLE 1 |** Characteristics of ARF and nephrolithiasis cases/reactions.

| Characteristic | ARF n (%) | Nephrolithiasis n (%) |
|---|---|---|
| Total reports (ICSRs) | 3.751 | 227 |
| Total number of reactions | 3.972 | 231 |
| **Patients** | | |
| **Age group** | | |
| 0–27 days | 1 (0.03%) | 0 |
| 28 days–23 months | 1 (0.03%) | 0 |
| 2–18 years | 0 (0%) | 0 (0%) |
| 18–44 years | 344 (12.69%) | 9 (7.08%) |
| 45–64 years | 1590 (58.67%) | 76 (59.84%) |
| 65–74 years | 548 (20.24%) | 32 (25.19%) |
| >75 years | 226 (8.33%) | 10 (7.87%) |
| Unknown | 1041 | 100 |
| **Gender** | | |
| Female | 1397 (42.99%) | 90 (44.11%) |
| Male | 1852 (56.94%) | 114 (55.88%) |
| Unknown | 502 | 4 |
| **Reports** | | |
| **Reporting year** | | |
| 2011 | 1 (0.02%) | 0 |
| 2012 | 1 (0.02%) | 1 (0.44%) |
| 2013 | 8 (0.21%) | 0 |
| 2014 | 67 (1.78%) | 10 (4.40%) |
| 2015 | 341 (9.09%) | 53 (23.34%) |
| 2016 | 372 (9.91%) | 32 (14.09%) |
| 2017 | 681 (18.15%) | 36 (15.85%) |
| 2018 | 1156 (30.81%) | 34 (14.95%) |
| 2019 | 737 (19.64%) | 27 (11.89%) |
| 2020 | 218 (5.81%) | 20 (8.81%) |
| 2021 | 169 (4.5%) | 14 (6.16%) |
| **WHO region of report** | | |
| Europe | 448 (11.94%) | 24 (11%) |
| Eastern Mediterranean region | 2 (0.05%) | 1 (0.45%) |
| America | 3057 (81.49%) | 184 (84.4%) |
| Western Pacific | 229 (6.1%) | 9 (4.12%) |
| South-East Asia | 9 (0.23%) | 0 |
| Africa | 6 (0.15%) | 0 |
| ***Report source (N)** | 3755 | 227 |
| Spontaneous | 3605 (96.08%) | 206 (90.74%) |
| Study | 139 (3.7%) | 21 (9.25%) |
| Other | 4 (0.10%) | 0 |
| PMS | 2 (0.05%) | 0 |
| Other | 2 (0.05%) | 0 |
| Unknown | 3 | 0 |
| ***Notifier type (N)** | 3827 | 258 |
| Physician | 996 (26.04%) | 68 (58.62%) |
| Pharmacist | 179 (4.86%) | 2 (1.72%) |
| Other health professional | 265 (7.19%) | 14 (12.05%) |
| Consumer/non-health professional | 2235 (60.86%) | 32 (27.58%) |
| Lawyer | 8 (2.17%) | 0 |
| Unknown | 144 | 142 |
| **Drugs** | | |
| **Canagliflozin** | **2640 (66.81%)** | **109 (47.18%)** |
| 10 mg | 1 | 0 |
| 50 mg | 2 | 0 |
| 90 mg | 1 | 0 |
| 100 mg | 514 | 29 |
| 150 mg | 6 | 0 |
| 200 mg | 12 | 1 |
| 300 mg | 567 | 18 |
| Unknown | 1412 | 55 |
| Canagliflozin + metformin | 121 | 6 |
| Canagliflozin + teneligliptin | 4 | 0 |
| **Dapagliflozin** | 622 (15.74%) | 55 (23.80%) |
| 5 mg | 87 | 12 |
| 10 mg | 205 | 17 |
| 15 mg | 1 | 0 |
| 20 mg | 1 | 1 |
| 25 mg | 1 | - |
| Unknown | 238 | 18 |
| Dapagliflozin + metformin | 88 | 7 |
| Dapagliflozin + saxagliptin | 1 | 0 |
| **Empagliflozin** | 606 (15.33%) | 65 (28.13%) |
| 5 mg | 0 | 0 |
| 10 mg | 179 | 19 |
| 12.5 mg | 17 | 1 |
| 20 mg | 1 | 0 |
| 25 mg | 114 | 9 |
| 50 mg | 1 | 0 |
| Unknown | 239 | 29 |
| Empagliflozin + metformin | 36 | 2 |
| Empagliflozin + linagliptin | 18 | 5 |
| Empagliflozin + linagliptin + metformin | 1 | 0 |
| **Ertugliflozin** | 15 (0.37%) | 1 (0.43%) |
| Ertugliflozin | 11 | 0 |
| Ertugliflozin + metformin | 2 | 0 |
| Ertugliflozin + sitagliptin | 2 | 1 |
| **Ipragliflozin** | 52 (1.26%) | 0 |
| 25 mg | 2 | 0 |
| 50 mg | 42 | 0 |
| 75 mg | 1 | 0 |
| 100 mg | 1 | 0 |
| Unknown | 6 | 0 |
| **Luseogliflozin** | 16 (0.40%) | 1 (0.43%) |
| 2.5 mg | 14 | 1 |
| 5 mg | 2 | 0 |
| **Events** | 3972 | 231 |
| **ARF PT** | n (%) | |
| Acute kidney injury | 2487 (62.61%) | |
| Acute phosphate nephropathy | 0 | |
| Anuria | 16 (0.40%) | |
| Azotemia | 6 (0.15%) | |
| Continuous hemodiafiltration | 0 | |
| Dialysis | 23 (0.57%) | |
| Fetal renal impairment | 0 | |
| Hemodialysis | 5 (0.12%) | |
| Hemofiltration | 1 (0.02%) | |
| Neonatal anuria | 0 | |
| Nephropathy toxic | 2 (0.05%) | |
| Oliguria | 8 (0.20%) | |
| Peritoneal dialysis | 1 (0.02%) | |
| Prerenal failure | 15 (0.37%) | |
| Renal failure | 907 (22.83%) | |
| Renal failure neonatal | 0 | |
| Renal impairment | 501(12.61%) | |
| Renal impairment neonatal | 0 | |
| Subacute kidney injury | 0 | |
| **Serious** | | |
| Serious | 3761(95.79%) | 182 (79.13%) |
| Non-serious | 165 (4.2%) | 48(20.86%) |
| Unknown | 46 | 1 |

(Continued in next column)

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**TABLE 1 |** (*Continued*) Characteristics of ARF and nephrolithiasis cases/reactions.

| Characteristic | ARF n (%) | Nephrolithiasis n (%) |
|---|---|---|
| **Seriousness** | | |
| Death | 134 (3.7%) | 1 (0.55%) |
| Life threatening | 344 (9.4%) | 6 (3.35%) |
| Caused/prolonged hospitalization | 2102 (57.7%) | 79 (44.13%) |
| Disabling/incapacitating | 8 (0.2%) | 3 (1.67%) |
| Other | 1054 (28.9%) | 90 (50.27%) |
| Unknown | 330 | 52 |
| **Time to onset** | | |
| <1 week | 59 (18.32%) | 5 (21.73%) |
| 1–2 weeks | 25 (7.76%) | 0 |
| 0.5–1 month | 33 (10.24%) | 1 (4.34%) |
| 1–2 months | 47 (14.59%) | 3 (13.04%) |
| 2–3 months | 36 (11.18%) | 3(13.04%) |
| 3–6 months | 43 (13.35%) | 0 |
| 6–12 months | 33 (10.24%) | 6 (26.08%) |
| 12–24 months | 32 (9.93%) | 3(13.04%) |
| >24 months | 14 (4.34%) | 2(8,69%) |
| Unknown | 280 | 204 |
| **Reaction (event) duration (total known n)** | 141 | 8 |
| <1 week | 64 (45.39%) | 3(37.5%) |
| 1–2 weeks | 32(22.69%) | 0 |
| 0.5–1 month | 19(13.47%) | 0 |
| 1–2 months | 12(8.51%) | 3(37.5%) |
| 2–3 months | 5(3.54%) | 0 |
| 3–6 months | 5(3.54%) | 0 |
| 6–12 months | 10.70) | 2(25%) |
| 12–24 months | 3(2.12%) | 0 |
| Unknown | 3827 | 219 |
| **Outcome (total known n)** | **n =1882** | **n = 80** |
| Fatal | 51 (2.70%) | 0 |
| Not recovered/not resolved | 152 (8.07%) | 31 (38.75%) |
| Recovered/resolved with sequelae | 19 (1%) | 0 |
| Recovering/resolving | 801 (42.56%) | 9 (11.25%) |
| Recovered/resolved | 859 (45.64%) | 40 (50%) |
| Unknown + data not available | 1865 | 146 |
| **De-challenge performed, n (%)** | | |
| Dose reduced | 13 (0.64%) | 1 (0.73%) |
| Drug withdrawn | 1843 (91.32%) | 85 (62.5%) |
| Drug increased | 6 (2.99%) | 2 (1.47%) |
| Drug not changed | 143 (7.13%) | 48 (35.29%) |
| Unknown | 1579 | 62 |
| Not applicable | 92 | 0 |
| **De-challenge outcome (Total known n)** | **n =1865** | **n = 79** |
| Reaction abated | 1724 (92.43%) | 46 (58.22%) |
| No effect observed | 141 (7.56%) | 33 (41.77%) |
| Not applicable | 10 | 1 |
| Effect unknown | 1740 | 117 |
| **Rechallenge action** | | |
| No rechallenge | 1 | 0 |
| Rechallenge | 2793 | 116 |
| **Rechallenge outcome** | | |
| Reaction recurred | 3 | 0 |
| No recurrence | 942 | 42 |
| Effect unknown | 1848 | 74 |

*ARF, acute renal failure; PT, preferred term; WHO, World Health Organization; N, total number of cases; n, number of cases in a given category; % is calculated of N or of the total known number in a given category; ICSR, individual case safety report; AE, adverse event; *, one AE may have one or more reporters; one ICSR may include more than one AE reported; one ICSR may have as suspect or interacting drugs more than one gliflozins—this led to a higher number of notifiers and report types than the total number of ICSRs; de-challenge, reports where dose of gliflozin was decreased/drug withdrawn; if two or more values of time-to-onset were reported in one ICSR, the most decreased value was chosen; serious, seriousness counted per reaction; outcome, the worse reported outcome in a chosen report.*

of the available data), but no cases with positive re-challenge were reported (**Table 1**). Urinary/renal infections were the most frequent associated adverse event with nephrolithiasis (52 reports, 22.51%).

No dose–response pattern was observed for ARF and nephrolithiasis (**Table 1**).

## 3.3 Fatal Outcome Analysis

Of the total of 3972 ARF ICSRs, 134 (3.7%) deaths were reported as seriousness criteria and a fatal outcome due to ARF reaction was reported for 51 patients (1.35%).

The characteristics of reports, patients, and reactions are shown in **Table 3**. Most of the reports came from spontaneous reporting and half from healthcare professionals. Therefore, half of the fatal ARF cases were considered medically confirmed.

In 32 fatal ARF reports (62.74%), the only suspect drug was one of the gliflozins. Most of the ARF cases were reported as AKI (n = 30) followed by renal failure (n = 20), renal impairment (n = 2), hemofiltration (n = 1), and dialysis (n = 1). In 16 (31%) cases, the only fatal reaction reported was as an ARF PT: AKI (n = 9), renal failure (n = 6), or renal impairment (n = 1).

In the majority of the reports (n = 35, 68%), other associated conditions were also considered responsible for this fatal outcome along with ARF. The most frequent associated causes of death were metabolic acidosis (including ketoacidosis) in 11 patients (21.56%) and sepsis in 10 patients (19.60%) (**Table 4**).

## 3.4 Disproportionality Analysis

### 3.4.1 ARF

A PRR of *4.68* (95% CI 4.53–4.83) for the association ARF narrow SMQ–gliflozins (all) as compared to ARF–other drugs was found. When we used all database as reference, we found 28 significant associations between different gliflozins use and acute kidney injury, renal failure, renal impairment, dialysis, anuria, and prerenal failure PTs (**Figure 2**).

In the sensitivity analysis, the significance (as defined by PRR≥1, associated with≥5 cases) of these association was kept for most of the pairs 27) when taking into account only ARF cases where gliflozins were the single suspected drug. When reference was set as all reactions reported to antidiabetics instead of the entire database, 20 of the aforementioned associations were significant in terms of PRR. Narrowing further the analysis to gliflozins as single suspected drugs versus the reports to antidiabetics, we found significant PRRs in 18 pairs (**Figure 2**).

### 3.4.2 Nephrolithiasis

For nephrolithiasis, we found a PRR of 3.44 (95% CI 3.00–3.95) for all gliflozins calculated versus the entire database. When we took into account all reports where gliflozins were deemed suspected/interacting drugs, we found six pairs of gliflozins–nephrolithiasis with significant PRRs (against both the

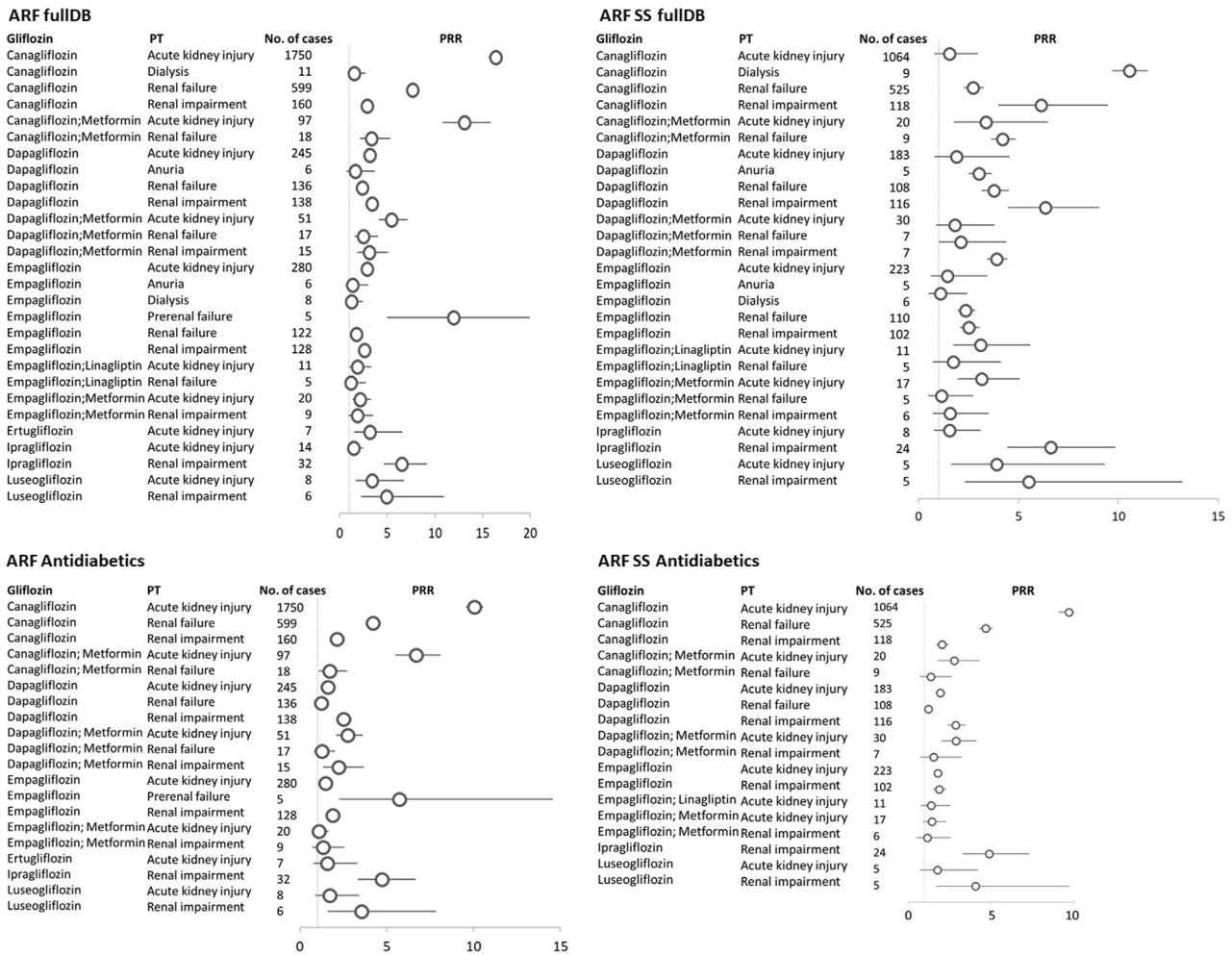


**FIGURE 2 |** Gliflozins-ARF narrow SMQ reactions with the proportional reporting ratio (PRR) greater than 1 and minimum 5 reactions were reported. ARF fullDB, acute renal failure narrow SMQ reactions with PRR calculated against all reports in VigiBase; ARF SS fullDB, acute renal failure narrow SMQ reactions with PRR calculated against all reports in VigiBase where gliflozins are the only suspect in the respective reaction; ARF Antidiabetics, acute renal failure narrow SMQ reactions with PRR calculated against all reports to antidiabetics in VigiBase; ARF SS Antidiabetics, acute renal failure narrow SMQ reactions with PRR calculated against all reports to antidiabetics in VigiBase where gliflozins are the only suspect in the respective reaction; PT, MedDRA preferred term; circles represent PRR, and horizontal lines represent 95% confidence interval.

entire database and reports to antidiabetics). When narrowing to reports where gliflozins were the only suspected drug, we found significant PRRs only for dapagliflozin + metformin and empagliflozin + linagliptin combinations (**Figure 3**).

## 4 DISCUSSION

Renal safety of SGLTi is much debated in the medical literature. While the benefits of gliflozins in the chronic mild or moderate kidney disease are widely recognized, they are also suspected of inducing adverse renal effects, like acute kidney injury and nephrolithiasis.

Our research focused on the association of gliflozins and ARF and nephrolithiasis in the world's largest pharmacovigilance database (VigiBase), with the aim to characterize the patients, reports, and drugs involved and also to look into the disproportionality analysis.

Most of both the ARF and nephrolithiasis reactions were reported in patients within the 45–64 years of age group and slightly more in males. This is in line with results of Perlman et al. (2017) who reported a mean age of 59 years and 49% females in their FDA adverse event report system (FAERS) database for the ARF broad SMQ.

Some articles reported that SGLT2 inhibitors were not observed to be associated with increased risk for AKI. The JADER database study (Katsuhara and Ogawa, 2020) did not find a significant association between SGLT2 inhibitors and ARF, but 1) the database is smaller (only 126 ARF cases reported to SGLT2) and also 2) they used ARF broad definition and included 50 PTs, which may have affected their ROR. One network meta-analysis (Zhao et al., 2020) only included clinical trials on patients with established

**TABLE 2 |** Concomitant medication (co-suspect and interacting) and associated conditions in ARF and nephrolithiasis reports.

| | ARF N | Nephrolithiasis N |
|---|---|---|
| **Concomitant medication** | | |
| Biguanide | 690 | 10 |
| Insulin | 209 | 0 |
| DPP-4 inhibitors | 134 | 0 |
| *Diuretics | 125 | 0 |
| *ACE inhibitors | 110 | 0 |
| GLP-1 receptor agonist | 60 | 3 |
| *ARB | 53 | 0 |
| Sulfonylurea | 47 | 0 |
| *NSAIDS | 43 | 0 |
| Statin | 15 | 0 |
| Acetylsalicylic acid | 9 | 0 |
| **Allopurinol | 2 | 1 |
| **Associated diseases** | **N** | **N** |
| Hypertension | 379 | 20 |
| Blood cholesterol increased | 173 | 5 |
| Pain | 164 | 12 |
| Cardiac disorder | 119 | 2 |
| Cardiac failure | 86 | 1 |
| Thyroid disorder | 77 | 1 |
| Depression | 71 | 4 |
| Infection | 45 | 0 |
| Anxiety | 42 | 2 |
| Gastroesophageal reflux disease | 42 | 6 |
| Renal disorders and chronic kidney disease | 20 | 2 |
| Urinary tract infection | 16 | 0 |
| Blood pressure decreased | 16 | 0 |
| Fluid retention | 15 | 2 |
| Diarrhea | 4 | 1 |
| Vomiting | 4 | 0 |
| Gout | 16 | 3 |
| Vitamin D deficiency | 11 | 3 |
| Obesity | 4 | 2 |
| Prostatic hypertrophy | 12 | 1 |
| Colitis ulcerative | 2 | 1 |
| Sepsis | 2 | 0 |
| **Associated reported PTs** | **N** | **N** |
| Diabetic ketoacidosis, ketoacidosis, euglycemic diabetic ketoacidosis | 1107 | 15 |
| Infection (including UTI) | 428 | 60 |
| Dehydration, vomiting, and diarrhea | 437 | 11 |
| Sepsis, urosepsis, *Escherichia* sepsis, staphylococcal sepsis, bacterial sepsis, streptococcal sepsis, wound sepsis, pulmonary sepsis, and *Candida* sepsis | 308 | 18 |
| Osteomyelitis and acute osteomyelitis | 214 | 0 |
| Metabolic acidosis and lactic acidosis | 228 | 2 |
| Urinary tract infection, kidney infection, and pyelonephritis | 275 | 45 |
| Toe/leg/foot/limb amputation and amputation | 319 | 1 |
| Cellulitis | 89 | 0 |
| Gangrene | 81 | 0 |
| Encephalopathy and metabolic Encephalopathy | 71 | 0 |
| Hyperkalemia | 69 | 1 |
| Septic shock | 66 | 1 |
| Myocardial infarction | 61 | 1 |
| Fournier's gangrene | 45 | 0 |
| Hypotension | 45 | 1 |
| Pancreatitis acute | 28 | 0 |
| Hypovolemia | 25 | 0 |
| Cerebrovascular accident | 24 | 0 |
| Urinary tract obstruction | 5 | 2 |

(Continued in next column)

**TABLE 2 |** (*Continued*) Concomitant medication (co-suspect and interacting) and associated conditions in ARF and nephrolithiasis reports.

*ARF, acute renal failure; PTs, preferred terms; ICSR, individual case safety report; N, total number of cases; n, number of cases in a given category; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; NSAID, nonsteroidal antiinflammatory drugs; UTI, urinary tract infection; *, drugs that may induce acute kidney injury (Perazella and Rosner, 2022b); **, drugs that may induce nephrolithiasis (Daudon et al., 2018); drug indication was not mentioned in all reports. One ICSR may include more than one ARF PT reported, and one ICSR may have as suspect or interacting drugs more than one gliflozins, and this may lead to a discrepancy between the number of cases and number of drugs.*

or at risk of cardiovascular disease or CKD, limiting its generalizability to other patient populations without these risks, and since the renal risk was not the primary objective, the AKI events were more likely to be underreported. Also, the definitions of ARF may differ between the trials included. On the other hand, case reports of ARF due to SGLT2i with proper documentation are published, and ADR reports continue to be submitted to VigiBase, despite the FDA strengthening the warning on the risk of AKI in October 2015, so its effect should be faded.

The FDA warning on the risk of AKI associated with gliflozins was issued in June 2016 and probably impacted the reporting of ARF in the VigiBase. The number of ARF reports doubled from 2015 to 2017 (341–720), but the highest number of ARF cases was in 2018 (1186 reports). Perlman et al. (2017) found a rise of 1 in ROR after the FDA warning and by September 2016 (a period of approximately 2 months. Interestingly, for ARF, a lot of the reports came from the consumers only (59.57% of the notifiers with available information), although typically this is not a reaction that can be recognized by consumers. We could not identify the reason for this reporting and how much this impacted the disproportionality analysis. A dose–response relationship could not be established, as variation in the number of cases *per* dose was probably due to the patterns of the gliflozins' use (e.g., approximately the same number of cases for canagliflozin 100 and 300 mg, more case for dapagliflozin 10 versus 5 mg, but also more cases for empagliflozin 10 versus 25 mg). This is consistent with the dose trend of reports from another analysis that looked at the gliflozins reactions in VigiBase during the same period (Frent et al., 2021).

The exact mechanism for gliflozins induced AKI is not fully understood. Decreased glomerular pressure is a likely potential explanation, but development of osmotic nephropathy may be also an alternative explanation at least in some reports. Some case reports with biopsy evidence of osmotic nephropathy were published (Sia et al., 2021; Perazella and Juncos, 2022). A possible explanation is that proximal tubules are exposed to significant amounts of filtered glucose, as there are some experimental studies and in humans exposed to glucose 10% solutions that leads to osmotic nephropathy. Probably, the excessive amount of urinary glucose undergoes tubular cell pinocytosis. Most of the AKI cases occurring in clinical

**TABLE 3 |** Characteristics of fatal ARF.

| Characteristic | ARF n (%) |
|---|---|
| Total reports (ICSRs) | 51 |
| Total number of reactions | 54 |
| **Patients** | |
| **Age group** | |
| 18–44 | 2 (4.54%) |
| 45–64 | 15 (34.09%) |
| 65–74 | 15 (34.09%) |
| >75 | 12 (27.27%) |
| Unknown | 7 |
| **Gender** | |
| Female | 20 (40.81%) |
| Male | 29 (59.18%) |
| Unknown | 2 |
| **Reports** | |
| Reporting year | |
| 2011 | 0 |
| 2012 | 0 |
| 2013 | 0 |
| 2014 | 1 (1.96%) |
| 2015 | 7 (13.72%) |
| 2016 | 5 (9.80%) |
| 2017 | 5 (9.80%) |
| 2018 | 21 (41.17%) |
| 2019 | 4 (7.84%) |
| 2020 | 4 (7.84%) |
| 2021 | 4 (7.84%) |
| **WHO region of report** | |
| Europe | 11 (21.56%) |
| America | 32 (62.74%) |
| Western Pacific | 7 (13.72%) |
| Africa | 1 (1.96%) |
| **Report source (N)** | |
| Spontaneous | 48 (94.11%) |
| Study | 3 (5.88%) |
| ***Notifier type (N)** | |
| Physician | 22 (43.13%) |
| Other health professional | 4 (7.84%) |
| Consumer/non-health professional | 25 (49.01%) |
| **Drugs** | |
| Canagliflozin | 26 (50.98%) |
| 100 mg | 10 (62.5%) |
| 300 mg | 6 (37.5%) |
| Dapagliflozin | 16 (31.37%) |
| 5 mg | 3 (23.07%) |
| 10 mg | 10 (76.92%) |
| Dapagliflozin + metformin | 4 (7.84%) |
| Empagliflozin | 9 (17.64%) |
| 10 mg | 4 (57.14%) |
| 25 mg | 3 (42.85%) |
| Empagliflozin + metformin | 1 (1.96%) |
| **Events** | |
| **ARF PT** | 54 |
| Acute kidney injury | 30 (55.55%) |
| Dialysis | 1 (1.85%) |
| Hemofiltration | 1 (1.85%) |
| Renal failure | 20 (37.03%) |
| Renal impairment | 2 (3.73%) |
| Acute phosphate nephropathy, anuria, azotemia, continuous hemodiafiltration, fetal renal impairment, hemodialysis, neonatal anuria, nephropathy toxic, oliguria, peritoneal dialysis, prerenal failure, renal failure neonatal, renal impairment neonatal, and subacute kidney injury | 0 |
| **Time to onset** | |
| <1 week | 3 (30%) |
| 1–2 weeks | 0 |
| 0.5–1 month | 2 (20%) |
| 1–2 months | 0 |
| 2–3 months | 2 (20%) |
| 3–6 months | 1 (10%) |
| 6–12 months | 0 |
| 12–24 months | 1 (10%) |
| >24 months | 1 (10%) |
| **De-challenge performed, n** | — |
| Drug withdrawn | 13 (86.66%) |
| Drug not changed | 2 (13.33%) |

*ARF, acute renal failure; PT, preferred term; AE, adverse event; ICSR, individual case safety report; WHO, World Health Organization; N, total number of cases; n, number of cases in a given category; % is calculated of N or of the total known number in a given category; *, one AE may have one or more reporters; one ICSR may include more than one AE reported; one ICSR may have as suspect or interacting drugs more than one gliflozins. This led to a higher number of notifiers than the total number of ICSRs; de-challenge, reports where dose of gliflozin was decreased/drug withdrawn; if two or more values of time to onset were reported in one ICSR, the most decreased value was chosen; serious, seriousness counted per reaction; outcome, the worse reported outcome in a chosen report.*

practice were not biopsied; therefore, drug-induced osmotic nephropathy as a possible mechanism for AKI induced by SGLT2i is probably under-recognized (Perazella and Juncos, 2022). A possible approach mentioned in the literature is to undertake a kidney biopsy in patients with prolonged AKI (>5 days) or dialysis-dependent AKI that persists despite withdrawing SGLT2i, as such a clinical presentation is unlikely only due to a reduction in glomerular pressure or water and sodium depletion (Phadke et al., 2020). In our analysis, in 92.43% % of patients with ARF where gliflozin was discontinued, the reaction abated and most patients improved after stopping the drug. This is in line with the strengthening warning of the FDA (U.S. Food and Drug Administration, 2016).

The FDA warning was based on the analysis of 101 cases of AKI reported during March 2013–October 2015 with approximately half of the AKI occurring within 1 month of starting the drug (U.S. Food and Drug Administration, 2016). In our analysis, only 36.32% of the cases with available information occurred within 1 month and another 14.59% occurred during 1–2 months of starting therapy. It is well known that the initiation of SGLT2i may cause an increase in serum creatinine and decrease in eGFR during the first 6 weeks of therapy. In patients with moderate renal impairment, the increase in serum creatinine generally does not exceed 0.2 mg/dl, occurs within the first 6 weeks of starting therapy, and then stabilizes. Increases that do not fit this pattern should prompt further evaluation to exclude the possibility of acute kidney injury

**TABLE 4 |** Concomitant medication (co-suspect, interacting, and concomitant) and associated conditions in fatal ARF reports.

| **Concomitant medication** | **N** |
|---|---|
| Biguanide | 22 |
| Insulin | 14 |
| DPP-4 inhibitors | 11 |
| *Diuretics | 11 |
| *ACE inhibitors | 5 |
| GLP-1 receptor agonist | 4 |
| *ARB | 6 |
| Sulfonylurea | 9 |
| *NSAIDS | 4 |
| Statin | 10 |
| Acetylsalicylic acid | 5 |
| **Associated diseases** | |
| Type 2 diabetes mellitus | 22 |
| Hypertension | 5 |
| Pain | 4 |
| Blood cholesterol increased | 1 |
| Depression | 1 |
| Cardiac failure | 4 |
| Thyroid disorder | 3 |
| Gastroesophageal reflux disease | 1 |
| **Associated PTs** | N |
| Diabetic ketoacidosis, ketoacidosis, and euglycemic diabetic ketoacidosis | 15 |
| Dehydration, vomiting, and diarrhea | 13 |
| Sepsis, septic shock, and urosepsis | 12 |
| Osteomyelitis and acute osteomyelitis | 1 |
| Metabolic acidosis and lactic acidosis | 10 |
| Urinary tract infection | 8 |
| Leg/foot amputation | 2 |
| Gangrene | 1 |
| Hyperkalemia | 2 |
| Myocardial infarction | 6 |
| Encephalopathy and metabolic encephalopathy | 4 |
| Fournier's gangrene | 1 |
| Hypotension | 3 |
| Pancreatitis | 3 |
| Cerebrovascular accident | 2 |
| Cardiogenic shock | 2 |

*ARF, acute renal failure; ICSR, individual case safety report; N, total number of cases; n, number of cases in a given category; DPP-4, dipeptidyl peptidase-4; GLP-1, glucagon-like peptide-1; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; NSAIDS, nonsteroidal antiinflammatory drugs; PT, preferred term; *, drugs that may induce acute kidney injury (AKI) (Perazella and Rosner, 2022b); drug indication was not mentioned in all reports;one ICSR may include more than one ARF PT reported, and one ICSR may have as suspect or interacting drugs more than one gliflozins, and this may lead to a discrepancy between the number of cases and number of drugs.*

*[1]Introductory Guide for Standardised MedDRA Queries (SMQs) Version 24.1*

*ACKNOWLEDGEMENTS (2021)*

(AstraZeneca Pharmaceuticals, 2021; Janssen Pharmaceuticals, 2021; Boehringer Ingelheim Pharmaceuticals, 2022). However, in VigiBase almost half of the cases (49%) with available data occurred after 2 months of SGLT2i therapy. A descriptive study of clinical spectrum and mechanism of AKI in patients with diabetes mellitus on SGLT2i found a wide interval of 7–365 days period after initiation of SGLT2i for AKI (Pearlman et al., 2018).

There are some known risk factors that may predispose patients with SGLT2i treatment to AKI, like decreased blood volume, chronic kidney insufficiency, congestive heart failure, and concomitant medications such as diuretics, ACE inhibitors, ARBs, and NSAIDs (U.S. Food and Drug Administration, 2016).

Since the cause of AKI due to gliflozins is generally attributed to osmotic diuresis that induce plasmatic volume depletion (AstraZeneca Pharmaceuticals, 2021; Janssen Pharmaceuticals, 2021; Boehringer Ingelheim Pharmaceuticals, 2022), we looked at the associated conditions of the patients like dehydration, diarrhea and vomiting, cardiac failure, hypovolemia, or concomitant use of diuretics. Regarding other medication that can cause/contribute to ARF, we found a significant number of patients with diuretics, ACE inhibitors, ARB blockers, and NSAIDs. This is still far from the findings of Pearlman et al. (2018), where all patients with gliflozins-associated AKI had been prescribed RAAS blockers and most had also injection of contrast-product or NSAIDs).

The most associated reaction in ARF cases was ketoacidosis in 27.87% of patients. Diabetic ketoacidosis (DKA) is a known rare but potentially life-threatening condition also related to SGLT2i (AstraZeneca Pharmaceuticals, 2021; Janssen Pharmaceuticals, 2021; Boehringer Ingelheim Pharmaceuticals, 2022); Plewa et al., 2022). Due to glucose-induced osmotic polyuria and even emesis, volume depletion is a major cause of AKI in DKA patients. AKI is a complication of diabetic ketoacidosis and an independent risk factor for poor long-term renal outcomes and mortality in DKA patients (Orban et al., 2014; Chen et al., 2020; Janssen Pharmaceuticals, 2021).

Sepsis and septic shock were the second most common reactions reported together with ARF in our analysis (n = 366 reactions reported). Sepsis is a known complication of diabetes mellitus and a major cause of AKI. Diabetes was also identified as an independent risk factor for AKI. Moreover, the risk of AKI during sepsis is increased in patients with diabetes. AKI develops in one-fourth of patients with sepsis and half of the patients with shock and is associated with high-mortality (up to 70%) (Venot et al., 2015) ARF with fatal outcome.

In our study, the reported data for time-to-onset was limited, only 10 cases out of 54 cases of fatal ARF, with 5 cases reported within 6 weeks of treatment with gliflozin. Fatal ARF may occur also within 6 weeks of the treatment with gliflozin, when an acute reversible decrease in eGFR is expected. AKI that may lead to hospitalization or dialysis was previously reported in SGLT2i US Prescribing Information (US PI), but AKI with fatal outcome was not considered as expected with gliflozins (fatalities were not mentioned in the FDA strengthened warning or in the SGLT2i US PI) (U.S. Food and Drug Administration, 2016; Janssen Pharmaceuticals, 2021; AstraZeneca Pharmaceuticals, 2021; Boehringer Ingelheim Pharmaceuticals, 2022). Medical literature presents though scattered reports suggesting that the risk for AKI may occasionally be fatal or might require renal replacement therapy (Szalat et al., 2018) and we provide in our analysis additional evidence showing that fatal ARF associated with the use of gliflozins is possible, and even more, this may also occur within first 6 weeks of gliflozin treatment.

## 4.1 Nephrolithiasis

SGLT2i treatment could lower the risk for incident and recurrent kidney stones in people with type 2 diabetes, as recent evidence

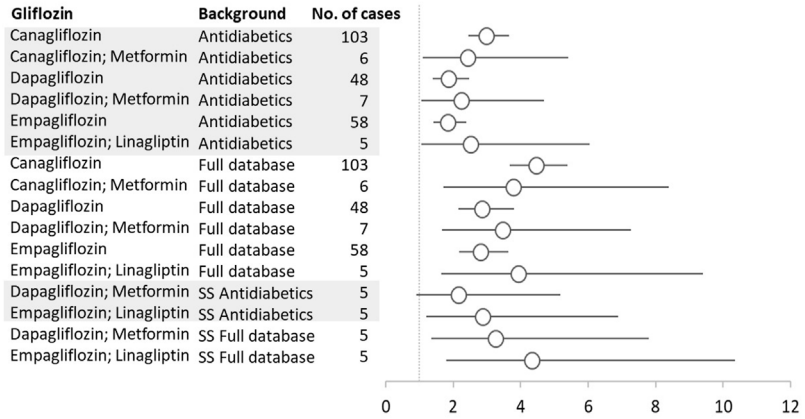


**FIGURE 3 |** Gliflozins–Nephrolithiasis reactions with the proportional reporting ratio (PRR) greater than 1 and minimum five reactions were reported. SS, single suspect; circles represent PRR, and vertical lines represent 95% confidence.

suggests (Kristensen et al., 2021; Balasubramanian et al., 2022). However, it was also suggested that SGLT2i can cause hyperuricosuria (Chino et al., 2014; Novikov et al., 2019), which may confer a greater risk for specific types of kidney stones. Moreover, a recent study of pooled analysis of data from clinical studies found that in 19% of patients, treatment with luseogliflozin resulted in increased serum uric acid, which may be due to reduced glomerular filtration of uric acid via the tubuloglomerular feedback (Chino et al., 2022). Yet, another meta-analysis found no association of SGLT-2 inhibitors with nephrolithiasis (Cosentino et al., 2019).

In 2017, a potential signal of nephrolithiasis in patients using SGLT2 inhibitors was detected by the FDA, but the decision was not to update the product information based on available information at that time (U.S. Food and Drug Administration, 2017). Our analysis does not contradict previous studies with conflicting results; it only adds the global perspective from VigiBase, the largest database of spontaneous reported ADRs and we included data until September 2021; therefore, data reported from four additional years were included. In fact, the highest evidence till present is the one the meta-analyses of randomized controlled trials like, where no association has been observed (Cosentino et al., 2019). In VigiBase, fewer nephrolithiasis reactions (231) were reported than ARF reactions (3,972), and these did not seem to have been impacted by the FDA potential signal from beginning of 2017. Positive de-challenge was noticed in 20% from the total of 231 reactions, but no cases with positive re-challenge were reported. The most frequently associated adverse event with nephrolithiasis was urinary/renal infection (52 reports, 22.51%). Kidney stone formers are at increased risk of developing urinary tract infections. Some potential mechanisms have been postulated, like bacteria, which increase aggregation of crystals or increase expression of a stone matrix (Brain et al., 2021).

Although we found disproportionality for gliflozins–nephrolithiasis reactions, the low number of reactions reported and the fact that most of them come from the USA, where all adverse events are reported, whether or not implying a causality relationship, firm conclusions regarding SGLT2i-induced nephrolithiasis are still debatable.

## 4.2 Disproportionality Analysis

The disproportionality analysis showed an increased risk of ARF and gliflozins (PRR = 4.67). From the total of 28 gliflozin-ARF PTs associations found significant in the general analysis, 20 kept their significance when the background was restricted to antidiabetics' events (considering only reactions to antidiabetics as background). This analysis was done in order to take into account the increased baseline risk of ARF in diabetes patients. In the scope of eliminating alternative causes' risk, we calculated the PRRs for reactions where only gliflozins were suspected and we found that almost all pairs from the general analysis kept their significance. We can therefore say that our findings for the ARF SMQ narrow are consistent with the ones from the 2016 study (Perlman et al., 2017). Likewise, for nephrolithiasis, our case–non case analysis showed a significant disproportionality (PRR = 3.44) in the general analysis and the same pairs kept significance with antidiabetics as the background. However, it is important to notice that only fixed combinations of gliflozins and metformin/linagliptin kept their significant PRR when excluding nephrolithiasis reports with other suspected drugs. More research is needed to investigate these associations.

Our analysis adds to the current knowledge the description of the gliflozins-related ARF cases from VigiBase and the description of fatal cases. We would like to emphasize here the judicious usage of gliflozins in patients with factors that may predispose patients to ARF. Treating physicians should be aware that AKI is a serious adverse event with potential fatalities when gliflozin class is used. Fatal ARF may occur also within 6 weeks of the treatment with gliflozin, when an acute reversible decrease in eGFR is expected; however, our observation is based on limited time-to-onset data. A high prevalence of severe infections (sepsis) was found in the patients with ARF, and this finding strengthens the link between sepsis and ARF.

### 4.3 Limitations

1. Another study on ARF reports related to gliflozins was published and contained data from the FDA adverse event report system, FAERS database, until September 2016 (Perlman et al., 2017). We are adding a global perspective, as the information is from VigiBase, the largest database of spontaneous reported ADRs and for an extended reporting period, until 31 August 2021.
2. Most of the ARF reports came from spontaneous reporting, the majority from consumers followed by healthcare professionals (60.86% and 38.09% from available data, respectively with 59.57% coming from consumers only). Therefore, almost 60% of the cases were not medically confirmed. Meanwhile, half of the fatal ARF cases were considered medically confirmed.
3. The disproportionality method: The real risk of ADRs cannot be measured, but only the difference in the rate of notifications by calculating the PRR. However, this method is useful for detecting health risks that need further investigation.
4. Underreporting, lack of reported clinical details, including laboratory results, and reporting bias (more likely to report severe cases).
5. The information contained in the VigiBase comes from a variety of sources, the amount of information in each report varies between reports, and the probability that the suspected adverse effect is drug-related is not the same in all cases. Variation in the causality relation between the drug and the ADR may have affected our analysis since approximately 80% of ARF reports and 84% of nephrolithiasis reports come from the regions of America of which the United States of America (United States) may have a great contribution. The United States collects any adverse event associated with the use of a drug in humans, whether or not considered drug-related (eCFR—Code of Federal Regulations, 2020), while other countries collect only suspected ADRs with at least a possibility of a causal relationship between the drug and reported (Vigiaccess, 2022) Also, the frequency of reporting to VigiBase may vary over time and between countries. This could be the case for increased reporting of AKI following the FDA warning (U.S. Food and Drug Administration, 2016), which could have resulted in increased recognition and reporting of AKI (notoriety bias).

## 5 CONCLUSION

SGLT2i are considered safe and provide multiple benefits for patients with type 2 diabetes mellitus. Exposure of patients to SGLT2i is expected to increase due to the recent evidence of cardiovascular and renal protection that led to extension of their indications. ARF cases are rarely reported and the benefit–risk balance of these antidiabetics remains favorable. Nevertheless, healthcare professionals and patients should be aware that: 1) AKI may occur following the use of SGLT2i and may produce serious and even life-threatening consequences, 2) especially in the context of concomitant diseases or medications affecting the renal mechanisms, and 3) also fatal ARF may occur within the first 6 weeks (however, our observation is based on limited time-to-onset data) of treatment with gliflozin, when an acute reversible decrease in eGFR is expected. The observational nature of this study precludes firm statements, but the importance of the findings demands future in-depth analyses to explore the relation with the fatal outcome.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the WHO Uppsala Monitoring Center, but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Requests to access these datasets should be directed to: CustomSearches@who-umc.org.

## AUTHOR CONTRIBUTIONS

CB, IF and CM conceived the study. All authors (IF, CB, DL, AF, FC, and CM) were involved substantially in the design and planning of the study. IF, DL, and CB were involved in data analysis. IF and CB prepared the manuscript. All authors interpreted the results, contributed to later drafts of the manuscript, and approved the final manuscript.

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## SUPPLEMENTARY MATERIAL

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# Safety of biological therapy in patients with rheumatoid arthritis in administrative health databases: A systematic review and meta-analysis

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**Background:** Rheumatoid arthritis (RA) is a systemic inflammatory disease that affects the synovial fluid of joints, tendons, and some extra-articular sites. Biologic agents have been highly effective and are comparable in reducing RA symptoms, slowing disease progression, and improving physical function; however, concerns have been raised about the risks of several potential adverse effects. Thus, this study aimed to assess the safety of biological therapy in patients with rheumatoid arthritis in observational studies using administrative health databases.

**Methods:** PubMed, Embase, Lilacs, Ovid, Scopus, and Web of Science were searched from inception to 21 October 2021. The analysis was divided into five groups: tumor necrosis factor inhibitors (TNFi) versus non-TNFi; TNFi versus csDMARDs; bDMARDs versus csDMARDs; abatacept versus bDMARDs; and TNFi versus Janus kinase inhibitors (JAKi). The adverse events were cancer, cardiovascular events, infection, herpes zoster, tuberculosis, and death. The methodological quality of the studies was assessed by the Newcastle-Ottawa Scale. A random-effects model estimated risk ratios with 95% confidence intervals.

**Results:** Thirty-one studies were eligible for inclusion in the present systematic review, published from 2014 to 2021. A total of 1,039,398 RA patients were assessed. The 31 studies evaluated eleven different biological drugs. No significant differences were found regarding safety between TNFi versus non-TNFi (RR 1.08; 95% CI 0.92–1.28; $p < 0.01$; $I^2 = 93.0\%$), TNFi versus csDMARDs (RR 0.91; 95% CI 0.75–1.10; $p < 0.01$; $I^2 = 87.0\%$), bDMARDs

versus csDMARDs (RR 0.99; 95% CI 0.82–1.20; $p < 0.01$; $I^2 = 93.0\%$), abatacept versus bDMARDs (RR 0.80; 95% CI 0.54–1.18; $p < 0.01$; $I^2 = 90.0\%$), and TNFi versus JAKi (RR 3.54; 95% CI 0.30–42.09; $p = 0.01$; $I^2 = 81.0\%$). In the subgroup analysis, among studies comparing abatacept to TNFi, a lower risk of cardiovascular events was associated with abatacept (RR 0.37; 95% CI 0.24–0.55).

**Conclusion:** Our results do not suggest an increased risk of adverse events associated with biological therapy in treating RA patients, indicating a lower risk of cardiovascular events with abatacept than TNFi. However, these findings must be interpreted with caution given the limitations of this study and the low/very low certainty of the evidence.

**Systematic Review Registration:** https://www.crd.york.ac.uk/prospero/display_record.php?, identifier [CRD42020190838].

KEYWORDS

**rheumatoid arthritis, biological therapy, systematic review, meta-analysis, drug safety**

## 1 Introduction

Rheumatoid arthritis (RA) is a systemic inflammatory disease that affects the synovial fluid of joints, tendons, and some extra-articular sites (Tundia et al., 2016). Its estimated prevalence is 0.45% worldwide (Almutairi et al., 2021). The etiology of the disease is still unknown, but some studies point to the existence of an antigen that causes the synovial inflammatory process. In addition, there are risk factors such as genetics, heredity, hormones, environment, and habits and customs (Andrade and Dias, 2019).

Clinical Protocols and Therapeutic Guidelines indicate disease-modifying drugs (DMARD), starting with monotherapy with conventional synthetic DMARDs (csDMARDs) in first-line treatment, such as methotrexate. The use of biological DMARDs (bDMARDs) may be necessary in case of therapeutic failure or toxicity. This second class of drugs entails exceptionally high costs for patients, families, and healthcare systems (Coimbra De Oliveira, 2018).

The biologic agents have been highly effective and are comparable in reducing RA symptoms, slowing disease progression, and improving physical function (Donahue et al., 2008; Yun et al., 2016). However, because of the different immune-modulatory properties of specific drugs and drug classes, concerns have been raised about the risks of several potential adverse effects, including hospitalized infection, malignancy, congestive heart failure, and mortality, which could place a significant burden on patients and health care systems (Yun et al., 2016).

Administrative health databases are massive repositories of data collected in healthcare for various purposes, maintained in hospitals, health maintenance organizations, and health insurance organizations. Administrative databases may contain a variety of information such as medical claims for reimbursement, records of health services, medical procedures, prescriptions, diagnoses, and socioeconomic and demographic information. Therefore, data from administrative health databases may provide a sufficiently large and representative sample of subjects, contributing to meaningful, valid, and generalizable findings (Gavrielov-Yusim and Friger, 2014).

All over the world, there are databases of health information systems that have provided valuable information on rheumatic diseases and the use of biological medicines. Such data are used in pharmacovigilance and academic research, enabling the improvement of knowledge about the use of biological drugs. The constant improvement, referenced by a solid scientific framework, is built through multiple bases, increasing heterogeneity and size samples, hence the power of statistical analyses.

Despite the wide use of such databases along with clinical research, questions remain about possible risks associated with the use of medications, as well as the dimension of their adverse events (Donahue et al., 2008), requiring permanent surveillance of their use, especially in the treatment of RA (Desai et al., 2016; Harada et al., 2017; Dreyer et al., 2018). Therefore, this systematic review and meta-analysis aimed to assess the safety of biological therapy in patients with rheumatoid arthritis in observational studies using administrative health databases.

## 2 Methods

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) Statement (Page et al., 2021). Before starting the literature search, the protocol for this systematic review was registered in the International Prospective Register of Systematic Review (PROSPERO) database (CRD42020190838).

## 2.1 Eligibility criteria

The PICOS structure was adopted to define the eligibility criteria. The population of interest (P) was patients with rheumatoid arthritis, the intervention (I) was the use of biological drugs (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, abatacept, rituximab, and tocilizumab), the comparator (C) was patients with rheumatoid arthritis unexposed to biological drugs or exposed to different drug classes, and the outcomes of interest (O) were adverse events and/or serious adverse events, and death.

Observational studies with administrative databases were eligible for inclusion. No language or date restrictions were applied. Clinical trials, review articles, case reports, case series, and animal studies were excluded.

## 2.2 Outcomes

The safety outcomes considered for inclusion in this systematic review and meta-analysis included adverse events (AEs) and/or serious adverse events (SAEs) such as infections (fungal, bacterial, and viral), tumors and cancer, cardiovascular events, and death.

## 2.3 Search strategy

Searches were performed in Embase, Lilacs (Virtual Health Library), MEDLINE (PubMed), MEDLINE and Epub Ahead of Print (Ovid), Scopus, and Web of Science Core Collection to identify studies that assessed the safety of biological therapy in patients with rheumatoid arthritis from inception to 21 October 2021. Moreover, gray literature sources (Catálogo de Teses e Dissertações da CAPES and specialized journals) were searched to identify studies that were not indexed in the databases but might be appropriate for inclusion in this systematic review.

Published articles and conference papers registered in these databases were identified using the terms "rheumatoid arthritis," "adalimumab," "certolizumab pegol," "golimumab," "infliximab," "abatacept," "rituximab," "tocilizumab," "biosimilar agent," "hydroxychloroquine," "methotrexate," "salazosulfapyridine," "administrative personnel," "observational study," and "cohort analysis" in Embase; "rheumatoid arthritis," "adalimumab," "certolizumab pegol," "golimumab," "infliximab," "abatacept," "rituximab," "tocilizumab," "antirheumatic agents," "methotrexate," "hydroxychloroquine," "sulfasalazine," "biosimilar pharmaceuticals," "administrative personnel," and "cohort studies" in Virtual Health Library; "rheumatoid arthritis," "adalimumab," "certolizumab pegol," "golimumab," "infliximab," "abatacept," "rituximab," "tocilizumab," "antirheumatic agents," "methotrexate," "hydroxychloroquine," "sulfasalazine," "biosimilar pharmaceuticals," "administrative personnel," and "cohort studies" in Pubmed; "rheumatoid arthritis," "adalimumab," "certolizumab pegol," "golimumab," "infliximab," "abatacept," "rituximab," "tocilizumab," "antirheumatic agents," "methotrexate," "hydroxychloroquine," "sulfasalazine," "biosimilar pharmaceuticals," "administrative personnel," and "cohort stud*" in Ovid, Scopus, and Web of Science. Search process details are presented in Supplementary Table S1.

## 2.4 Study selection and data extraction

Two reviewers (CCB and LG) independently screened articles' titles and abstracts for potentially relevant articles using Rayyan (Ouzzani et al., 2016). Studies that met the inclusion criteria in the first screening had their eligibility confirmed by full reading. Articles that met all the inclusion criteria were included in the final review. A third reviewer (DBS) was referred to in cases of disagreement.

Two reviewers extracted the included studies' details (MJQ and FCA). The extracted data include information related to authors, journal, publication year, country, sample size, safety outcomes, statistical analysis method (including statistical tests and measure of association with confidence intervals), and adjustment variables (confounders).

## 2.5 Methodological quality assessment

Two reviewers (CTC and MJQ) assessed the methodological quality of the included studies using the Newcastle-Ottawa Scale (NOS) (Wells et al., 2012). This tool has three domains with a score based on a star system, ranging from zero to nine stars: selection (four stars), comparability (two stars), and exposure or outcome of interest (three stars). Studies with a score of 0–3 stars were considered low-quality, those with a score of 4–6 stars were evaluated as moderate quality, and those which scored seven or more stars were classified as high-quality (Neal et al., 2019).

## 2.6 Statistical analysis

Data were extracted from eligible studies and arranged in a 2 × 2 table. The fixed or random-effects model was used to calculate risk ratios (RR) and 95% confidence intervals (95% CI), depending on the heterogeneity between the studies. Heterogeneity and consistency were evaluated by the $I^2$ statistic and Cochran's Q test (Higgins, 2003). A random-effects model was adopted when heterogeneity was verified ($I^2 > 50\%$; $p < 0.10$). The analysis was divided into five groups: tumor necrosis factor inhibitors (TNFi) versus non-TNFi; TNFi versus csDMARDs; bDMARDs versus csDMARDs; abatacept versus bDMARDs; and TNFi versus Janus kinase inhibitors (JAKi). A subgroup analysis by adverse event was conducted. Publication bias was assessed by visual

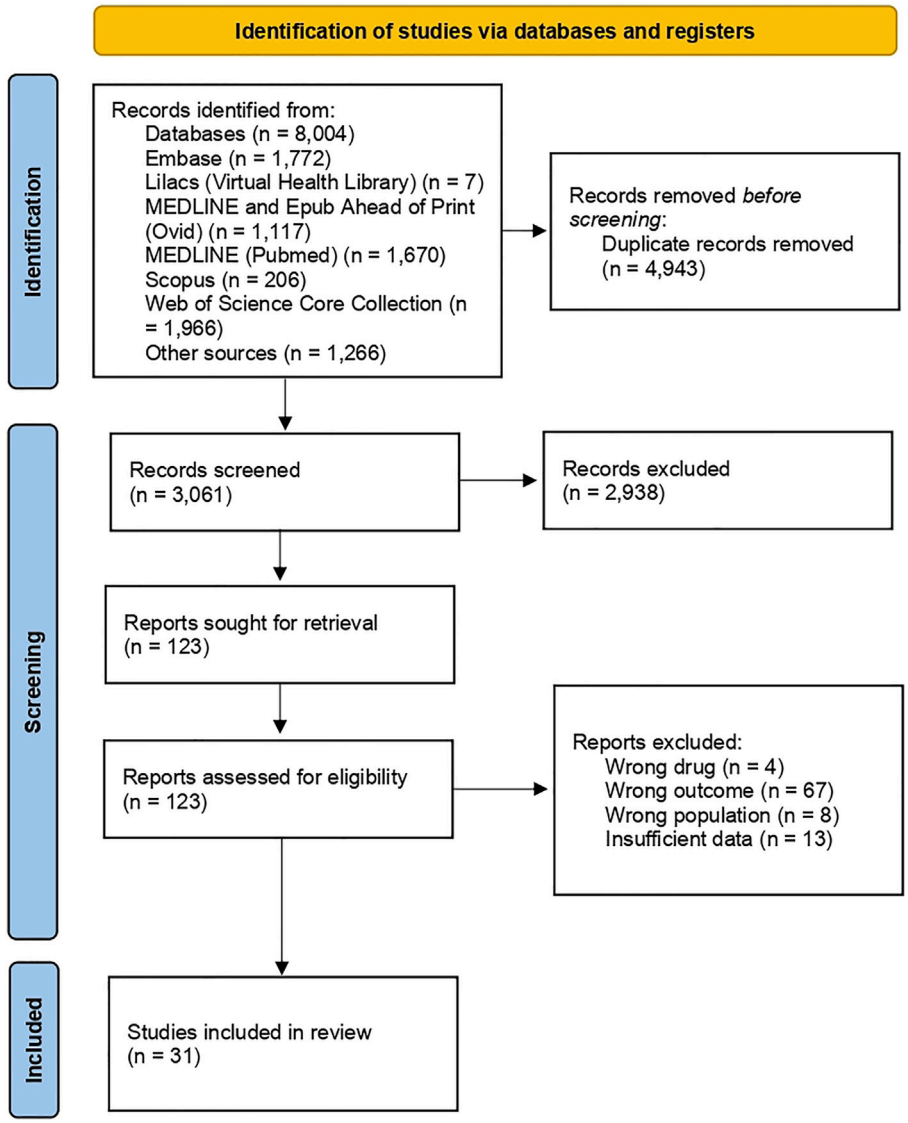


FIGURE 1
Flow chart of search results.

inspection of the funnel plot and statistically using Egger's tests. Analyses were carried out using R version 4.1.2 and the "meta" package version 4.13-0 (Balduzzi et al., 2019).

## 2.7 Assessment of the certainty of the evidence

The certainty of the evidence was rated using GRADEpro software (Grading of Recommendations, Assessment, Development and Evaluation). This system grades the quality of evidence at four levels—high, moderate, low, or very low—according to study design limitations, indirect evidence, inconsistency of results, inaccuracy of results, and the significant likelihood of publication bias (Schünemann et al., 2013).

# 3 Results

## 3.1 Selected studies

The initial search returned 8,004 studies, of which 4,943 were duplicates. After screening titles and abstracts, 123 studies were analyzed regarding inclusion criteria, and 92 were excluded. Subsequently, references of the included studies were

TABLE 1 Characteristics of the included studies.

| Study | Year | Country | Patients | Person-years | Number of events | Female (%) | Mean disease duration (years) | Mean disease activity | Outcome |
|---|---|---|---|---|---|---|---|---|---|
| Arkema | 2014 | Sweden | 48,782 | 271,889 | 50 | 71.4 to 75.6 | NR | NR | Tuberculosis |
| Chen | 2020 | United States | 65,734 | 15,840 | 619 | 83.0 to 84.0 | NR | NR | Hospitalized infection |
| Chen | 2021 | Taiwan | 197,935 | 519,971 | 7,580 | 63.1 | 3.4 | NR | Cardiovascular diseases |
| Curtis | 2016 | United States | 63,102 | 40,507.4 | 2,264 | 79.7 to 83.7 | NR | NR | Herpes zoster |
| Desai | 2017 | United States | 7,222 | 9,918 | 370 | 75.0 to 79.0 | NR | NR | Hypertension |
| Dreyer | 2017 | Denmark | 1,678 | 3,686 | 108 | 70.3 | 10.0 to 16.0 | DAS28: 3.4 to 5.1 | Second malignant neoplasm |
| de Germay | 2020 | United States | 15,846 | NR | 16,192 | 80.6 to 82.8 | NR | NR | Cancer |
| Grøn | 2019 | Denmark and Sweden | 8,987 | 10,873 | 639 | 76.0 to 81.0 | 7.0 to 11.0 | DAS28: 4.7 to 5.1 | Serious infection |
| Grøn | 2020 | Denmark | 3,696 | 2,720 | 2,060 | 78.0 | NR | NR | Infection |
| Harada | 2017 | Japan | 1,987 | 6,753.5 | 43 | 81.5 | 6.0 | DAS28: 4.2 | Herpes zoster |
| Hellgren | 2020 | Sweden | 71,645 | 450,828 | 392 | NR | 6.7 | DAS28: 4.8 | Lymphoma |
| Kim | 2017 | United States | 40,119 | 22,046 | 125 | 81.7 to 84.7 | NR | NR | Cardiovascular diseases |
| Kim | 2020 | Korea | 996 | NR | 62 | 87.1 | NR | DAS28 to ESR: 4.7 | Hypertension |
| Listing | 2015 | Germany | 8,908 | 31,378 | 463 | 77.3 | 10.3 | DAS28: 5.3 | Death |
| Low | 2017 | United Kingdom | 14,258 | 65,973 | 252 | 59.5 to 78.0 | 6.0 to 11.0 | DAS28: 5.3 to 6.6 | Myocardial infarction |
| Meissner | 2017 | Germany | 489 | NR | 166 | 74.8 | 9.7 | DAS28: 5.1 | Stroke |
| Mercer | 2015 | United Kingdom | 15,016 | 64,221 | 563 | 73.0 to 76.0 | NR | NR | Solid cancer |
| Mercer | 2017 | United Kingdom | 15,298 | 114,599 | 114 | 74.0 to 76.0 | NR | NR | Lymphoma |
| Ozen | 2021 | United States | 18,754 | 94,781 | 1,801 | 79.4 | 14.2 | NR | Cardiovascular diseases |
| Patel | 2021 | United States | 30,439 | NR | 8,046 | 81.2 to 85.7 | NR | NR | Infection |
| Pawar | 2019 | United States | 141,869 | 42,148 | 1,773 | 81.7 to 83.1 | NR | NR | Serious infection |
| Pawar | 2020 | United States | 130,718 | 100,790 | 3,140 | 78.0 | NR | NR | Serious infection |
| Pettipher and Benitha | 2019 | South Africa | 4,830 | 8,205 | 96 | 67.0 to 71.0 | NR | SDAI: 40.9 to 45.4 | Tuberculosis |
| Raaschou | 2014 | Sweden | 11,343 | 1,142 | 18 | 100.0 | NR | NR | Recurrence of breast cancer |
| Rahman | 2020 | Canada | 1,577 | 4,048 | 126 | 77.0 to 86.6 | 6.5 to 9.8 | DAS28 to ESR: 4.4 to 5.7 | Cancer, serious infections, herpes zoster, tuberculosis, and opportunistic infections |
| Richter | 2016 | Germany | 917 | NR | 1,017 | 64.2 to 73.5 | 14.5 to 16.5 | DAS28: 4.3 to 4.6 | Serious infection, sepsis, and death |
| Rutherford | 2018 | United Kingdom | 19,282 | 46,772 | 2,606 | 76.1 to 79.6 | 11.0 to 16.0 | DAS28: 5.9 to 6.6 | Serious infection |
| Sakai | 2018 | Japan | 164 | 82,176 | 760 | 81.5 | NR | NR | Herpes zoster |
| Yun | 2015 | United States | 10,183 | 7,807 | 2,666 | 78.8 to 84.6 | NR | NR | Hospitalized infection |
| Yun | 2016 | United States | 23,784 | 16,576 | 2,530 | 83.9 to 88.7 | NR | NR | Hospitalized infection |
| Zhang | 2016 | United States | 47,193 | 74,662 | 585 | 85.0 | NR | NR | Acute myocardial infarction |

NR: not reported.

manually searched to detect relevant articles, but none were identified. Studies were excluded due to the analysis of the wrong drug, outcome and population, and insufficient data (Figure 1). Details on the reasons and references excluded after the full reading are available in the Supplementary Material (Supplementary Table S2).

## 3.2 Study characteristics

Thirty-one studies were eligible for inclusion in the present systematic review; eleven population-based cohorts (Arkema et al., 2015; Raaschou et al., 2015; Mercer et al., 2015; Mercer et al., 2017; Desai et al., 2016; Low et al., 2017; Dreyer et al., 2018; Chen et al., 2020; Kim et al., 2020; Pettipher and Benitha, 2020; Hellgren et al., 2021), eight prospective (Listing et al., 2015; Richter et al., 2016; Meissner et al., 2017; Rutherford et al., 2018; Grøn et al., 2019; Grøn et al., 2020; Rahman et al., 2020; Ozen et al., 2021) and eight retrospective cohorts (Yun et al., 2014; 2016; Curtis et al., 2016; Zhang et al., 2016; Kim et al., 2017; Pawar et al., 2019; 2020; Patel et al., 2021), and four case-control studies (Harada et al., 2017; Sakai et al., 2018; de Germay et al., 2020; Chen et al., 2021), published from 2014 to 2021 (Supplementary Table S3).

A total of 1,039,398 rheumatoid arthritis patients were assessed. The mean age ranged between 46 and 78 years and most were women (60–100%). Mean disease duration was reported by thirteen studies and ranged between 3.4 and 16.5 years (Listing et al., 2015; Raaschou et al., 2015; Richter et al., 2016; Harada et al., 2017; Low et al., 2017; Meissner et al., 2017; Dreyer et al., 2018; Rutherford et al., 2018; Grøn et al., 2019; Rahman et al., 2020; Chen et al., 2021; Hellgren et al., 2021; Ozen et al., 2021). Among the thirteen studies which described mean disease activity, RA patients had moderate to high disease activity (Listing et al., 2015; Raaschou et al., 2015; Richter et al., 2016; Harada et al., 2017; Low et al., 2017; Meissner et al., 2017; Dreyer et al., 2018; Rutherford et al., 2018; Grøn et al., 2019; Kim et al., 2020; Pettipher and Benitha, 2020; Rahman et al., 2020; Hellgren et al., 2021) (Table 1).

The 31 studies evaluated eleven different biological drugs, among them TNFi (etanercept, infliximab, adalimumab, certolizumab pegol, and golimumab), non-TNFi (rituximab, abatacept, tocilizumab, and anakinra), JAKi (tofacitinib), and csDMARDs (mainly methotrexate). Furthermore, the adverse events evaluated by the studies were cancer (solid cancer and lymphoma), cardiovascular events, infection, herpes zoster, tuberculosis, and death (Supplementary Table S3).

## 3.3 Quality of the included studies

According to the NOS, 27 studies were classified as high quality, of which seven were "nine stars" (Mercer et al., 2015, 2017; Zhang et al., 2016; Meissner et al., 2017; Pawar et al., 2019; Chen et al., 2020; Hellgren et al., 2021), fifteen were "eight stars" (Yun et al., 2014, 2016; Arkema et al., 2015; Listing et al., 2015; Richter et al., 2016; Desai et al., 2016; Kim et al., 2017; Low et al., 2017; Rutherford et al., 2018; Dreyer et al., 2018; Grøn et al., 2019; Grøn et al., 2020; Pawar et al., 2020; Chen et al., 2021; Ozen et al., 2021), and five were "seven stars" (Raaschou et al., 2015; Curtis et al., 2016; de Germay et al., 2020; Kim et al., 2020; Patel et al., 2021). Four studies were considered moderate quality, of which two scored "six stars" (Harada et al., 2017; Sakai et al., 2018), one "five stars" (Rahman et al., 2020), and one "four stars" (Pettipher and Benitha, 2020) (Supplementary Table S4).

## 3.4 Meta-analysis

### 3.4.1 TNFi versus non-TNFi

The safety of TNFi versus non-TNFi was assessed by 19 studies (Yun et al., 2014, 2016; Listing et al., 2015; Curtis et al., 2016; Richter et al., 2016; Zhang et al., 2016; Harada et al., 2017; Kim et al., 2017, 2020; Meissner et al., 2017; Rutherford et al., 2018; Sakai et al., 2018; Pawar et al., 2019, 2020; Chen et al., 2020, 2021; Pettipher and Benitha, 2020; Ozen et al., 2021; Patel et al., 2021). The meta-analysis revealed no significant differences in the safety of TNFi compared to non-TNFi (RR 1.08; 95% CI 0.92–1.28; $p < 0.01$; $I^2 = 93.0\%$). In the subgroup analysis, the risk of herpes zoster events was lower in the TNFi group (RR 0.92; 95% CI 0.72–1.17). In addition, subgroup analysis by safety outcome did not show a statistically significant higher risk of any outcomes among the TNFi (Figure 2), except for the tuberculosis event, which had a higher risk among TNFi; however, only one study was included. Visual inspection of the funnel plot indicated asymmetry, suggesting publication bias (Supplementary Figure S1). However, Egger's test did not indicate publication bias (intercept = 2.44, $p = 0.07$).

### 3.4.2 TNFi versus csDMARDs

Eleven studies evaluated the safety of TNFi compared to csDMARDs (Listing et al., 2015; Mercer et al., 2015; 2017; Raaschou et al., 2015; Desai et al., 2016; Harada et al., 2017; Low et al., 2017; Meissner et al., 2017; Sakai et al., 2018; Kim et al., 2020; Ozen et al., 2021). Overall, there was no significant difference in the safety of TNFi versus csDMARDs; however, a lower risk of events was found among TNFi (RR 0.91; 95% CI < 0.75–1.10; $p < 0.01$; $I^2 = 87.0\%$). Similarly, there were no significant differences between TNFi and csDMARDs by safety outcome (Figure 3). Funnel plot visual inspection suggested asymmetry (Supplementary Figure S2), and Egger's test confirmed publication bias (intercept = 3.54, $p = 0.02$).

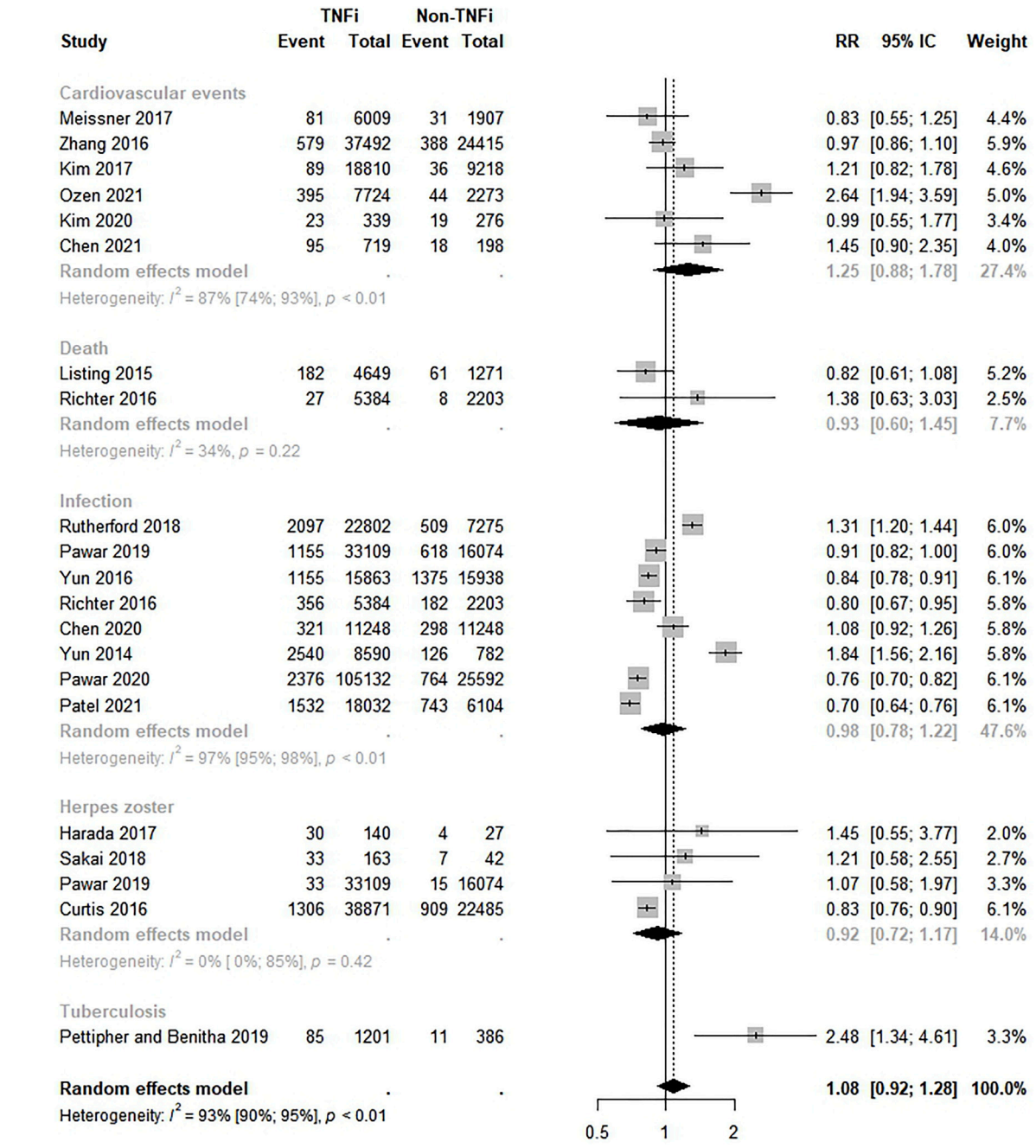


FIGURE 2
Comparative safety of TNF inhibitions and non-TNF inhibitions. TNFi: TNF inhibitions; non-TNFi: non-TNF inhibitions.

### 3.4.3 bDMARDS versus csDMARDs

Thirteen studies estimated the safety of bDMARDs compared to csDMARDs (Arkema et al., 2015; Mercer et al., 2017; Listing et al., 2015; Mercer et al., 2015; Desai et al., 2016; Harada et al., 2017; Low et al., 2017; Meissner et al., 2017; Sakai et al., 2018; Dreyer et al., 2018; Kim et al., 2020; Ozen et al., 2021; Hellgren et al., 2021). No significant difference in the safety of these therapies was found (RR 0.99; 95% CI 0.82–1.20; $p$ < 0.01; $I^2$ = 93.0%). In the analysis by safety outcome, no statistically significant risk of any of the outcomes was observed (Figure 4). Funnel plot visualization suggests asymmetry (Supplementary Figure S3).

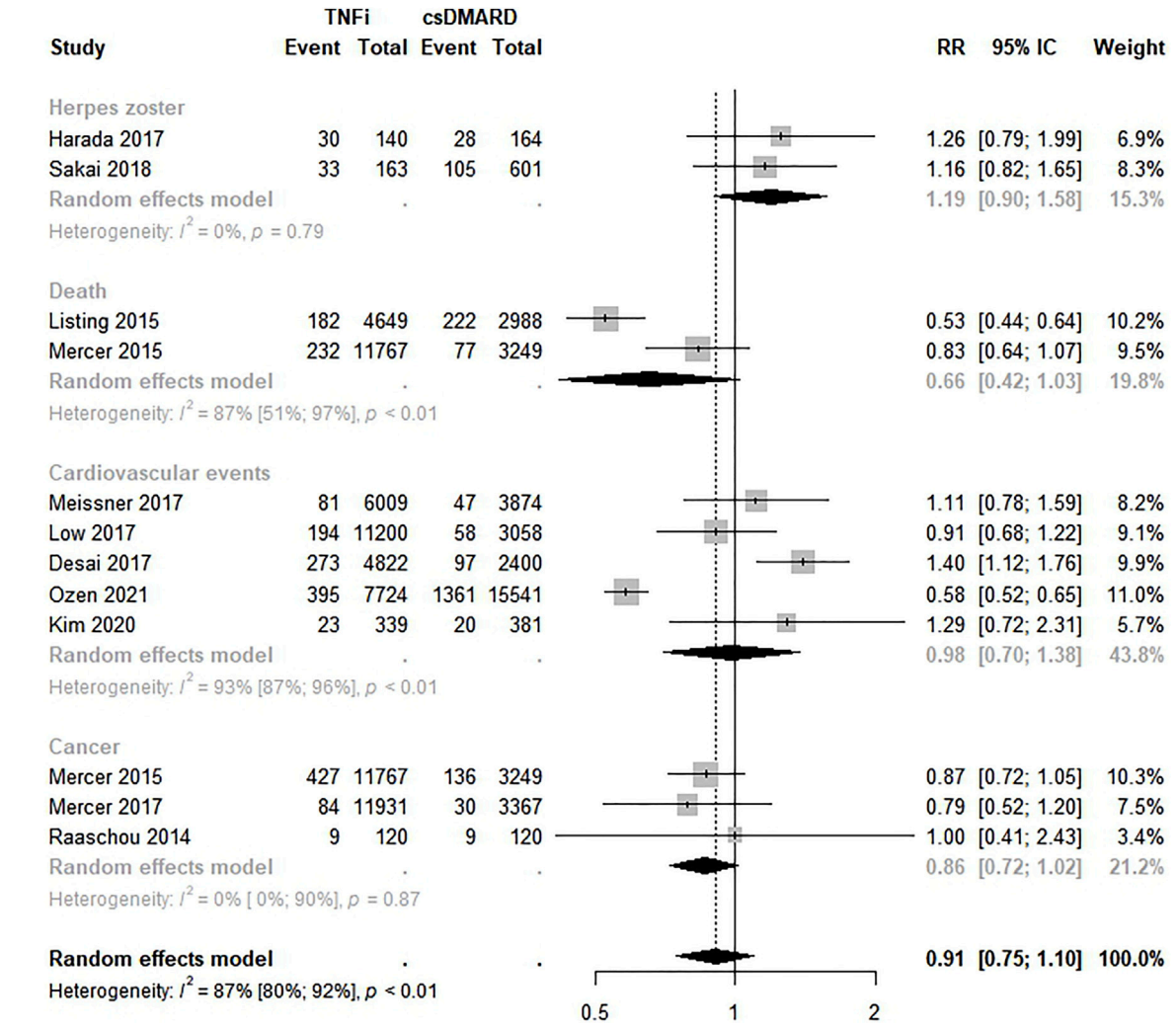


FIGURE 3
Comparative safety of TNF inhibitions and conventional disease-modifying anti-rheumatic drugs. TNFi: TNF inhibitions; cDMARD: conventional disease-modifying anti-rheumatic drugs.

The Egger's test confirmed publication bias (intercept = 5.53, $p$ = 0.01).

### 3.4.4 Abatacept versus TNFi

The safety between abatacept and TNFi was evaluated by six studies (Chen et al., 2020, 2021; Kim et al., 2020; Pawar et al., 2020; Ozen et al., 2021; Patel et al., 2021). The meta-analysis showed a lower risk of adverse events, but there were no significant differences in the safety of abatacept compared to TNFi (RR 0.80; 95% CI 0.54–1.18; $p$ < 0.01; $I^2$ = 90.0%). However, a lower risk of cardiovascular events was found among RA patients who used abatacept rather than TNFi in the analysis by outcome measure (RR 0.37; 95% CI 0.24–0.55) (Figure 5).

### 3.4.5 TNFi versus JAKi

Only two studies evaluated the safety of TNFi versus JAKi (Curtis et al., 2016; Ozen et al., 2021). The meta-analysis revealed a higher risk of adverse events with no significant differences in the safety of TNFi compared to JAKi (RR 3.54; 95% CI 0.30–42.09; $p$ = 0.01; $I^2$ = 81.0%) (Figure 6).

## 3.5 Certainty of the evidence

The certainty of the evidence that contributed to the meta-analyses was low and very low due to the design of the studies, risk of bias, high heterogeneity between studies, low number of studies included in the analysis, and publication bias detected in

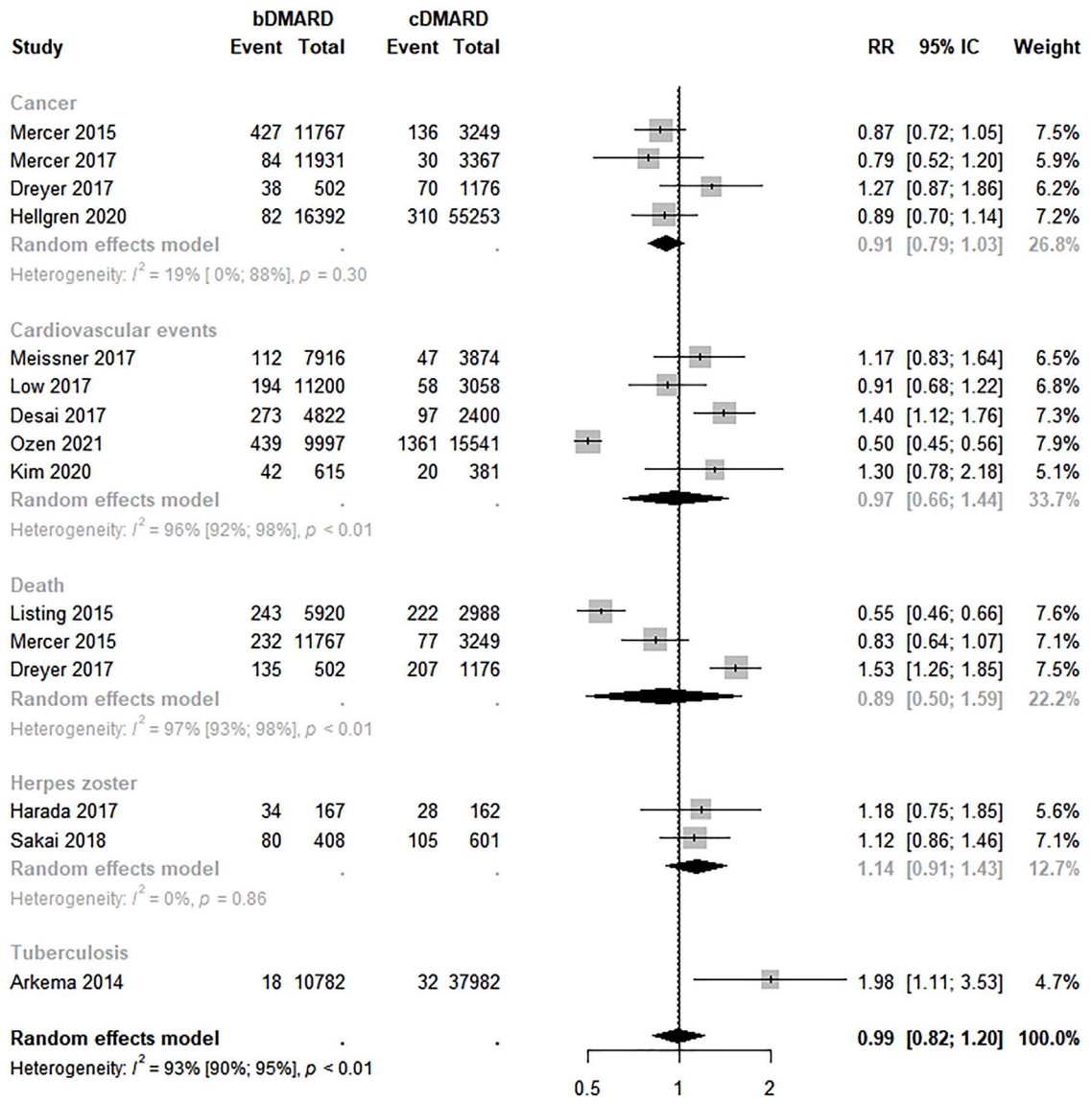


FIGURE 4
Comparative safety of biological disease-modifying anti-rheumatic drugs and conventional disease-modifying anti-rheumatic drugs. bDMARD: biological disease-modifying anti-rheumatic drugs; cDMARD: conventional disease-modifying anti-rheumatic drugs.

some of the analyses (Supplementary Figures S4–S8). Therefore, this systematic review and meta-analysis results must be interpreted with caution.

## 4 Discussion

Our study estimated the safety of different drug classes of DMARDs in patients with rheumatoid arthritis based on observational studies with data from administrative databases. For studies with this type of data, it is important to confirm and expand the results obtained in clinical trials, as their homogeneity, the limited number of subjects, and relatively short follow-up time may limit the extrapolation of results. In addition, the increasing number of therapeutic alternatives require careful long-term follow-up to assess effectiveness and safety, which is only viable through observational studies, especially those from administrative health databases, taking into account the greatest amount of available data about patients' medication and care (Suissa and Garbe, 2007; Ziemssen et al., 2017).

Our meta-analysis did not show significant differences in safety between TNFi versus non-TNFi, TNFi versus csDMARDs,

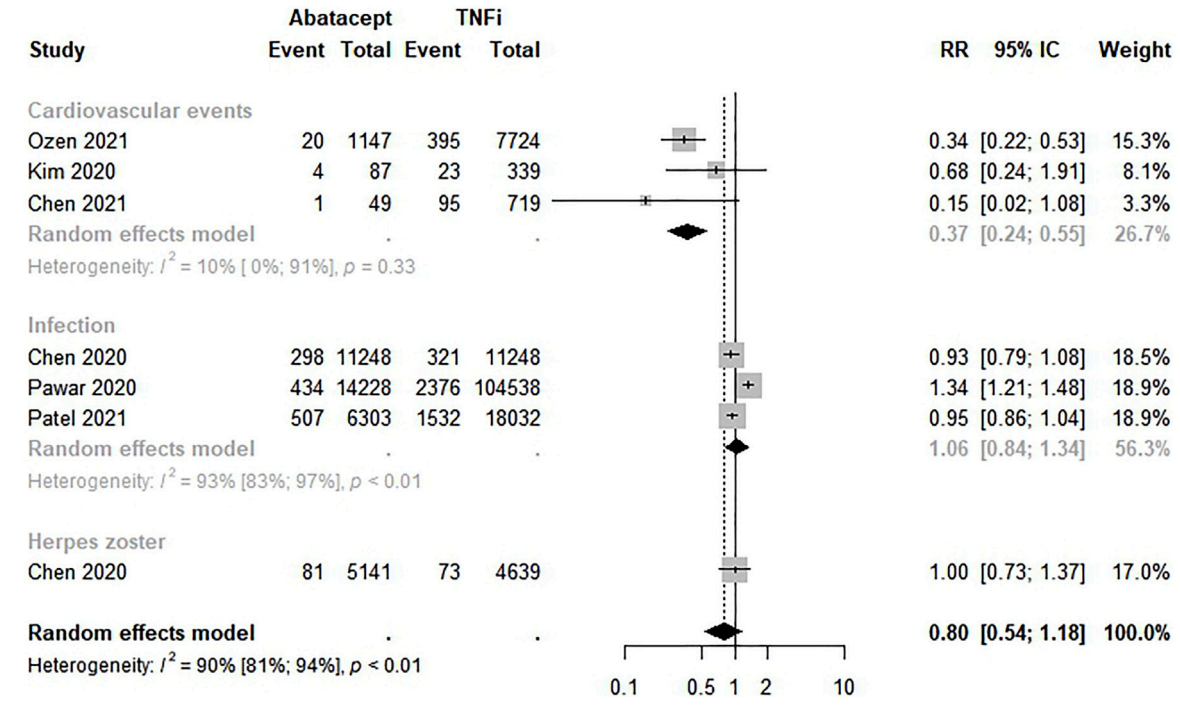


FIGURE 5
Comparative safety of abatacept and biological disease-modifying anti-rheumatic drugs. bDMARD: biological disease-modifying anti-rheumatic drugs.

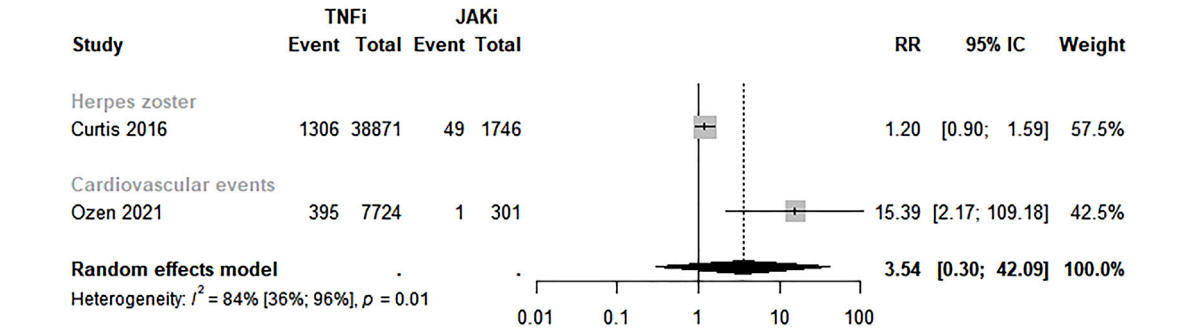


FIGURE 6
Comparative safety of TNF inhibitors and JAK inhibitors. TNFi: TNF inhibitors; JAKi: Janus Kinase inhibitors.

bDMARDs versus csDMARDs, and TNFi versus JAKi for different safety outcomes, as cardiovascular events, death, infections, herpes zoster, cancer, and tuberculosis. However, a lower risk of cardiovascular events was found among RA patients who used abatacept in the analysis by outcome measure (RR 0.37; 95% CI 0.24–0.55) compared to TNFi.

RA and other inflammatory autoimmune rheumatic diseases are characterized by systemic inflammation, which contributes to atherosclerosis, endothelial dysfunction, plaque vulnerability, and atherothrombotic events, increasing the risk of cardiovascular disease in RA patients (Mackey et al., 2018). Nevertheless, cardiovascular disease is the leading cause of death and hospitalization among RA patients (Ozen et al., 2021).

Previous studies have reported a cardiovascular disease risk reduction in RA patients using DMARDs as hydroxychloroquine (Sharma et al., 2016), methotrexate (Micha et al., 2011), and TNFi

(Low et al., 2017; Ozen et al., 2021). Nonetheless, despite several years and a considerable number of studies on cardiovascular events in patients with RA, there are still discrepant results. Even methotrexate, the most studied DMARD in the last 20 years, has not yet confirmed its cardioprotective action, hovering over the hypotheses of better control of disease activity or direct cardiovascular effect associated with the use of higher doses of the drug (Ozen et al., 2021). Therefore, our findings suggesting a 63% lower risk of these diseases among patients using abatacept compared to TNFi indicate a possible benefit for RA patients using this drug and must be further investigated.

Furthermore, evidence has shown an increased risk of certain types of solid cancers and lymphomas in people diagnosed with RA, with a strong association between the intensity of disease activity and inflammatory activity (Mercer et al., 2015; Hellgren et al., 2021). Although most patients from the studies included in the present systematic review had severe rheumatoid arthritis and poor prognosis, a higher risk of cancer was not observed in any of our meta-analyses. However, a systematic review and meta-analysis of 10 observational studies found an increased overall cancer (RR 1.13; 95% CI 1.02–1.24) and non-melanoma skin cancer risk (RR 1.26; 95% CI 1.09–1.45) among abatacept compared to csDMARDs or TNFi RA patients. Therefore, it is essential to closely monitor patients exposed to abatacept (Xie et al., 2020).

While high disease activity is a risk factor for infections in people with RA (Au et al., 2011; Mehta et al., 2019), biological therapy may increase the risk of serious infections due to its potent immunosuppressive effects. Furthermore, as biological drugs act on different cellular targets and cytokines, it can be hypothesized that the risk of infection may be different between them (Pawar et al., 2019), which brings concerns about clustered analysis of bDMARDs.

Our meta-analyses observed opposite effects between TNFi and non-TNFi regarding infection risk. Studies that used data from the Medicare, United States health insurances (Yun et al., 2016; Pawar et al., 2019, 2020; Patel et al., 2021), and the German biologics register RABBIT (Richter et al., 2016) presented a lower risk of infection in patients exposed to TNFi, while studies using data from the Medicare and Medicaid (Yun et al., 2014) and the British Society for Rheumatology Biologics Register (BSRBR-RA) (Rutherford et al., 2018) pointed to a higher risk of the outcome among TNFi-exposed subjects. These divergences may be related to differences in some patients' characteristics, such as disease activity, previous exposure to biologic drugs, disease duration, comorbidities, age, and differences in follow-up time from baseline. Although the mechanisms of any risks remain unclear, the meta-analysis results showed no association between the comparative risk of TNFi drugs versus non-TNFi.

As stated before, RA is associated with an increased prevalence of several comorbidities, as cardiovascular disease, infection, malignancy, lung disease, and neuropsychiatric disease (Jeong et al., 2017). Nonetheless, it has also been observed that some comorbidities and external factors such as age, obesity, smoking, and dyslipidemia strongly influence the course of RA (Kłodziński and Wisłowska, 2018; Ozen et al., 2021). Therefore, these factors may affect this and other meta-analyses results since the studies adopted different techniques for adjusting those confounders and imputation of missing data.

In addition, the differences in the drugs selected to represent each class and the number of individuals taking them in each study should be highlighted. The individual effects observed for each drug may differ according to the number of individuals included in each study and the comparison with drugs or pharmacological groups that present different mechanisms of action. Still, some studies did not specify the number of individuals separately in the analysis by drug class, and some did not list the drugs in each category. We also highlight the underrepresentativeness of some biological medicines in the included studies, such as anakinra. This medicine was evaluated by only four of the included studies in this systematic review (Listing et al., 2015; de Germay et al., 2020; Hellgren et al., 2021; Ozen et al., 2021).

The concomitant use of other drugs not included in the analysis, such as glucocorticoids and immunosuppressive agents, may also interfere with our results. Unfortunately, however, most of the articles did not provide such information. Nevertheless, it is impossible to quantify its contribution to the observed effects even with this information due to the lack of supplementary data on dosage, time of exposure, and individual response to each medication or therapeutic regimen.

Furthermore, the use of prior biologics is widespread, and only a few studies verify the differences in the safety outcomes among biological-naïve and exposed (Arkema et al., 2015; Raaschou et al., 2015; Pettipher and Benitha, 2020). A population-based cohort with 48,782 RA patients from the Swedish Rheumatology Quality Register between 2002 and 2011 observed a higher risk of tuberculosis among biological-exposed compared with biological-naïve patients (HR 4.4; 95% CI 2.3–8.5) (Arkema et al., 2015). Pettipher and Benitha (2020), in a population-based cohort with data from 4,830 subjects from the South African Biologics Registry (SABIO) between 2008 and 2017, found a tuberculosis rate of 1,240 per 100,000 person-years for biologic users compared to 0 per 100,000 person-years among the biologic-naive cohort.

Moreover, TNFi-treated RA patients did not have a significantly higher risk of recurrent breast cancer than biologic-naïve patients (HR 1.1; 95% CI 0.4–2.8) in a population-based cohort with 11,343 subjects from the Swedish biologics register (ARTIS) between 2001 and 2010 (Raaschou et al., 2015).

Taking the disability-adjusted life years (DALYs) WHO indicator into account, which combines years of life lost to premature mortality (YLLs) and years of healthy life lost due to disability (YLDs), the systematic analysis of the Global Burden of Disease Study from 2017 showed almost 20 million prevalent cases

of RA in that year, accounting for 1.2 million incident cases that resulted in 3.4 million disability-adjusted life years (DALYs) (Safiri et al., 2020). Based on the available evidence, it would not be reckless to say that the adverse effects associated with the medications can count as an adjuvant on time of healthy life lost due to disability.

Our results reassure the need for further post-market long-term studies for biological drugs. In this way, the best therapeutic choices can be ensured for patients with RA, given the severity of adverse effects of the drug therapy, aiming to improve their quality of life and prevent premature mortality related to RA.

## 4.1 Strengths and limitations

Our study has important strengths and limitations. Strengths include using a validated scale to assess individual studies' methodological quality, evaluating the evidence's certainty, and using random-effects meta-analysis to deal with the heterogeneity between studies. Furthermore, we contacted some authors to obtain sufficient data to perform the meta-analysis.

The high heterogeneity between studies, which persisted after subgroup analysis, was a limitation of the present study. Several factors could justify this, such as RA severity and prognosis differences, and some population characteristics.

Furthermore, the type of analysis used cannot treat confounders such as age, gender, ethnicity, level of education, work, type of health insurance, BMI, smoking, comorbidity, hypertension, diabetes, and use of drugs that can influence the outcome, such as statins, aspirin, NSAIDs, and the imputations made in several studies.

An important limitation is that some studies differ in the moment of drug exposure for the outcome. Therefore, experienced and naïve, prevalent, and incident individuals were included in the meta-analysis. Also, as the included studies followed patients with different pharmacological treatments at different times, a follow-up time bias cannot be discarded. These differences may influence the development of adverse events, such as cancer. Also, RA patients in non-TNFi therapy usually have a longer disease duration than those using TNFi and csDMARDs, which may impact and confound these meta-analyses results.

It is important to state that nowadays, RA patients tend to be exposed to more biological agents, relying on cumulative exposure to biologics, making it impossible to differentiate the results of current therapy from those of previous therapies. Besides, we could not analyze the safety outcomes by comparing biological-naïve and biologic-experienced patients due to the lack of studies making such comparisons. Also, some studies presented short baseline periods, which may introduce a misclassification bias in these studies.

There is the possibility of overlapping in some of the cohorts included, mainly those using data from Medicare. Overlap is a problem of precision related to sampling, so overlapping cohorts in systematic reviews may overstate sample size and the number of events, falsely leading to greater precision in the analysis (Lunny et al., 2021). Nonetheless, these cohort studies generally compared different drugs and outcomes, which probably reduced this effect in the present systematic review and meta-analysis.

Even though the prevalence of RA is considerably higher in older people, there are studies with only individuals over 65, such as those based on Medicare data (Yun et al., 2016; Zhang et al., 2016; Patel et al., 2021), which may influence our results. In addition, the use of health insurance databases can unbalance the results by selecting patients with higher earnings and better access to care.

Also, a low number of studies were included in the meta-analyses of abatacept versus TNFi and TNFi versus JAKi, which may be related to our search strategies when we chose to specify the name of each drug instead of including direct terms. Furthermore, the inclusion of low number of studies in meta-analysis may result in findings by chance. Nonetheless, meta-analyses with a small number of studies present valid results (Herbison et al., 2011). Finally, a small number of studies for these analyses excluded the possibility of publication bias analysis. However, it should be noted that the interpretation of graph asymmetry is subjective and interpretation errors may occur (Sterne et al., 2004).

The publication bias found in studies that evaluated TNFi versus csDMARDs and bDMARDS versus csDMARDs is probably associated with the eligibility criteria adopted, including only observational studies with administrative databases. Also, the inclusion of mesh terms related to the study design on the search strategy may have an impact on its sensitivity.

In summary, the present study suggests a decreased risk of cardiovascular events among abatacept users compared to TNFi users. In contrast, no significant differences in cardiovascular events, death, infections, herpes zoster, cancer, and tuberculosis were found between TNFi compared to non-TNFi, TNFi compared to csDMARDs, bDMARDs compared to csDMARDs, and TNFi compared to JAKi. Nonetheless, these data should be interpreted with caution given the limitations previously stated and the low/very low certainty of the evidence according to the GRADE. Therefore, further studies using administrative databases and longer follow-up times are needed to confirm our findings.

# Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material; further inquiries can be directed to the corresponding author.

## Author contributions

DS, RC, MJ, CC, and FA conceived the study. MJ, CC, FA, and DS contributed to the study design, data analysis, and data interpretation. MJ, CC, FA, CB, LG, and DS contributed to the study selection, data extraction, and interpretation of data. MJ, CC, FA, CB, LG, DP, SB, WA, EB, JA, RC, MB, and DS were involved in drafting the manuscript and revised it critically.

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## Conflict of interest

The authors declare that the research was conducted without any commercial or financial relationships that may result in a potential conflict of interest.

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## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2022.928471/full#supplementary-material

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# Real-world effectiveness of biological therapy in patients with rheumatoid arthritis: Systematic review and meta-analysis

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**Background:** The treatment of rheumatoid arthritis (RA), a chronic systemic inflammatory autoimmune disease, is based on disease-modifying anti-rheumatic drugs (DMARDs). Typically, it starts with conventional synthetic DMARDs (csDMARDs), and depending on the patient's response to the treatment and the adverse events experienced, biological DMARDs (bDMARDs) are initiated. bDMARDs are more specific to inflammatory factors than csDMARDs and more efficient in inducing remission and low disease activity. Thus, this study aimed to assess the effectiveness of biological therapy in patients with rheumatoid arthritis in administrative health databases.

**Methods:** PubMed, Embase, Lilacs, Ovid, Scopus, and Web of Science databases were searched from inception to 21 October 2021, to identify observational studies that evaluated the effectiveness of biological therapy in patients with rheumatoid arthritis using administrative databases and real-world data. The methodological quality was assessed by the methodological index for non-randomized studies (MINORS). A fixed or random-effects model estimated risk ratios with 95% confidence intervals. The analysis was divided into four groups: tumor necrosis factor inhibitors (TNFi) versus non-TNFi; TNFi versus TNFi (adalimumab, etanercept, and golimumab versus infliximab); bDMARDs versus Janus kinase inhibitors (JAKi); and bDMARDs monotherapy versus combination therapy (bDMARDs and MTX).

**Results:** Twenty-one records were eligible for inclusion in this systematic review and meta-analysis; seven population-based cohorts, eight

prospective, and six retrospective cohort studies. Overall, 182,098 rheumatoid arthritis patients were evaluated. In the meta-analysis, lower effectiveness was observed among TNFi users than in non-TNFi (RR: 0.88; 95% CI: 0.81–0.95; $p < 0.01$; $I^2 = 94.0\%$) and bDMARDs than in JAKi (RR: 0.86; 95% CI: 0.79–0.94; $p < 0.01$; $I^2 = 93.0\%$). Higher effectiveness among adalimumab, etanercept, and golimumab than in infliximab (RR: 1.19; 95% CI: 1.05–1.36; $p < 0.01$; $I^2 = 96.0\%$) was found. No significant differences in the effectiveness of bDMARD monotherapy compared to combination therapy (RR: 0.83; 95% CI: 0.68–1.00; $p < 0.01$; $I^2 = 81.0\%$) was observed. E-value analysis indicated that the estimates were not robust against unmeasured confounding.

**Conclusion:** According to the available real-world data, our results suggest that biological therapy effectively treats patients with rheumatoid arthritis, indicating higher effectiveness with non-TNFi and JAKi than with TNFi.

**Systematic Review Registration:** https://www.crd.york.ac.uk/prospero/display_record.php?ID#CRD42020190838, identifier CRD42020190838.

KEYWORDS

**rheumatoid arthritis, biological therapy, meta-analysis, effectiveness, administrative health databases**

## 1 Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory autoimmune disease that affects the synovial fluid of joints, tendons, and some extra-articular sites, leading to deformity and destruction of joints by bone erosion and cartilage destruction (Guo et al., 2018; Lin et al., 2020). It is estimated that 0.4–1.3% of the world population is affected by the disease, which is two to four times more frequent in women. The age at onset is commonly situated around 30 years, with a peak in the fifth decade of life (Amaya-Amaya et al., 2013; Lin et al., 2020).

Treatment for RA aims to reduce disease activity state, through clinical remission or at least achievement of low disease activity, especially for patients with previous treatment failure. RA treatment is based on disease-modifying anti-rheumatic drugs (DMARDs), typically starting with conventional synthetic DMARDs (csDMARDs) as methotrexate (MTX), hydroxychloroquine, and sulfasalazine, and depending on the patient's response to the treatment and the adverse events experienced, biological DMARDs (bDMARDs) are initiated to reduce RA symptoms, slow disease progression, and improve physical function (Smolen et al., 2020).

Several bDMARDs have recently emerged in RA management, including TNF-α inhibitors (TNFi) as adalimumab, etanercept, and infliximab; IL-6 receptor antibody, such as tocilizumab; and JAK inhibitors (JAKi) as tofacitinib (Guo et al., 2018; Smolen et al., 2020). However, despite the wide range of biological medicines available, their real-world effectiveness is still under discussion.

There is uncertainty about the effectiveness of TNFi with the first and subsequent uses. In many observational studies, slightly better retention rates and effectiveness have been reported for etanercept than for adalimumab and infliximab, but there is some uncertainty about whether this superiority reflects channeling bias or an actual difference (Lee et al., 2008; Hetland et al., 2010). Consequently, direct evidence of the effectiveness of TNFi is needed to inform clinical and drug reimbursement decision-makers.

Previous systematic reviews and meta-analyses of randomized clinical trials (RCTs) have shown improvement in the remission rates of RA patients with first-line TNFi versus placebo (with or without MTX) (Gulácsi et al., 2019), and better response rates in subjects are exposed to tocilizumab and sarilumab than to adalimumab (Sung and Lee, 2021). Nonetheless, a systematic review and network meta-analysis of 28 RCTs compared the efficacy of csDMARDs, TNFi, non-TNFi, and JAKi with abatacept and found no significant differences between these drugs (Paul et al., 2020).

Although RCTs evaluate the efficacy of treatments in selected groups of patients defined by strict inclusion criteria, the value of these trials in predicting therapeutic effectiveness in "real-world" patients is limited. This systematic review and meta-analysis were designed to complement the knowledge obtained in RCTs and observational studies with primary data by evaluating the real-world effectiveness of TNFi in patients with RA in observational studies with administrative health databases.

Therefore, this systematic review and meta-analysis aimed to assess the real-world effectiveness of biological therapy in patients with rheumatoid arthritis in observational studies with administrative health databases.

# 2 Methods

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement (Page et al., 2021). The protocol for this systematic review was registered in the International Prospective Register of Systematic Review (PROSPERO) database before starting the literature search (CRD42020190838).

## 2.1 Eligibility criteria and outcome measures

The PECOS structure was adopted to define the eligibility criteria. Therefore, the population of interest (P) was patients with rheumatoid arthritis, the exposure (E) was the use of biological drugs (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, abatacept, rituximab, and tocilizumab), the comparator (C) was patients with rheumatoid arthritis unexposed to biological drugs or exposed to different drug classes, the outcome of interest (O) was therapeutic effectiveness, and the study design (S) was observational studies.

Effectiveness was the main outcome of interest for this study. Effectiveness was considered as remission or improvement of disease activity, measured by the Disease Activity Score 28 (DAS28), European Alliance of Associations for Rheumatology (EULAR), Clinical Disease Activity Index (CDAI), or The Simplified Disease Activity Index (SDAI); improvement in functional capacity, measured by the Health Assessment Questionnaire (HAQ); persistence in therapy; or other measures adopted by the studies.

Other outcomes associated with effectiveness explored in this systematic review and meta-analysis were: the reduction of clinical disease activity assessed by ACR70 (70% reduction criteria of the American College of Rheumatology), ACR50 (50% reduction criteria of the American College of Rheumatology), drug withdrawal, and maintenance of remission after withdrawal of the drug.

Observational studies (prospective cohort, retrospective cohort, and case-control) with administrative databases and real-world data were eligible for inclusion. No language or date restrictions were applied. Clinical trials, review articles, case reports, case series, and animal studies were excluded.

## 2.2 Search strategy

Searches were conducted in Embase, Lilacs, Ovid, PubMed, Scopus, and Web of Science databases to identify studies that assessed the effectiveness of biological therapy in patients with rheumatoid arthritis from inception to 21 October 2021. In addition, grey literature sources were searched (Catálogo de Teses e Dissertações da CAPES and specialized journals) to identify any studies that were not indexed in the databases but might be relevant for inclusion in the present systematic review. Search process details are presented in Supplementary Table S1.

## 2.3 Study selection and data extraction

Articles' titles and abstracts were independently evaluated by two reviewers (CCB and LG) for potentially relevant articles using Rayyan (Ouzzani et al., 2016). The studies that met the inclusion criteria in the first stage had their eligibility confirmed by reading the full article. The qualitative and quantitative synthesis included those that met all the inclusion criteria. A third reviewer (DBS) was consulted when the reviewers disagreed on whether an article should be included.

Two reviewers independently extracted the included studies' details (MJQ and FCA). The extracted data include authors, journal, publication year, country, sample size, effectiveness outcomes, statistical analysis method (including statistical tests and measure of association with confidence intervals), and adjustment variables (confounders).

## 2.4 Methodological quality assessment

Two reviewers (CTC and MJQ) assessed the methodological quality of the included studies using the methodological index for non-randomized studies (MINORS) (Slim et al., 2003), a validated index to assess the quality of observational studies. This tool contains 12 questions, with a global ideal score for comparative studies of 24 points. The quality assessment of the included studies was measured as follows: 0 to 6 points, very low quality; 7 to 12 points, low quality; 13 to 18 points, moderate quality; and 19 to 24 points, high quality (Pithon et al., 2019).

## 2.5 Statistical analysis

Data were extracted from eligible studies and arranged in 2 × 2 tables. Risk ratios (RRs) and 95% confidence intervals (95% CI) were calculated by the fixed or the random-effects model, depending on the heterogeneity between the studies. The $I^2$ statistic and Cochran's Q test were adopted to evaluate heterogeneity and consistency (Higgins, 2003). The random-effects model was applied when heterogeneity was verified ($I^2 > 50\%$; $p < 0.05$). The analysis was divided into four groups: TNFi

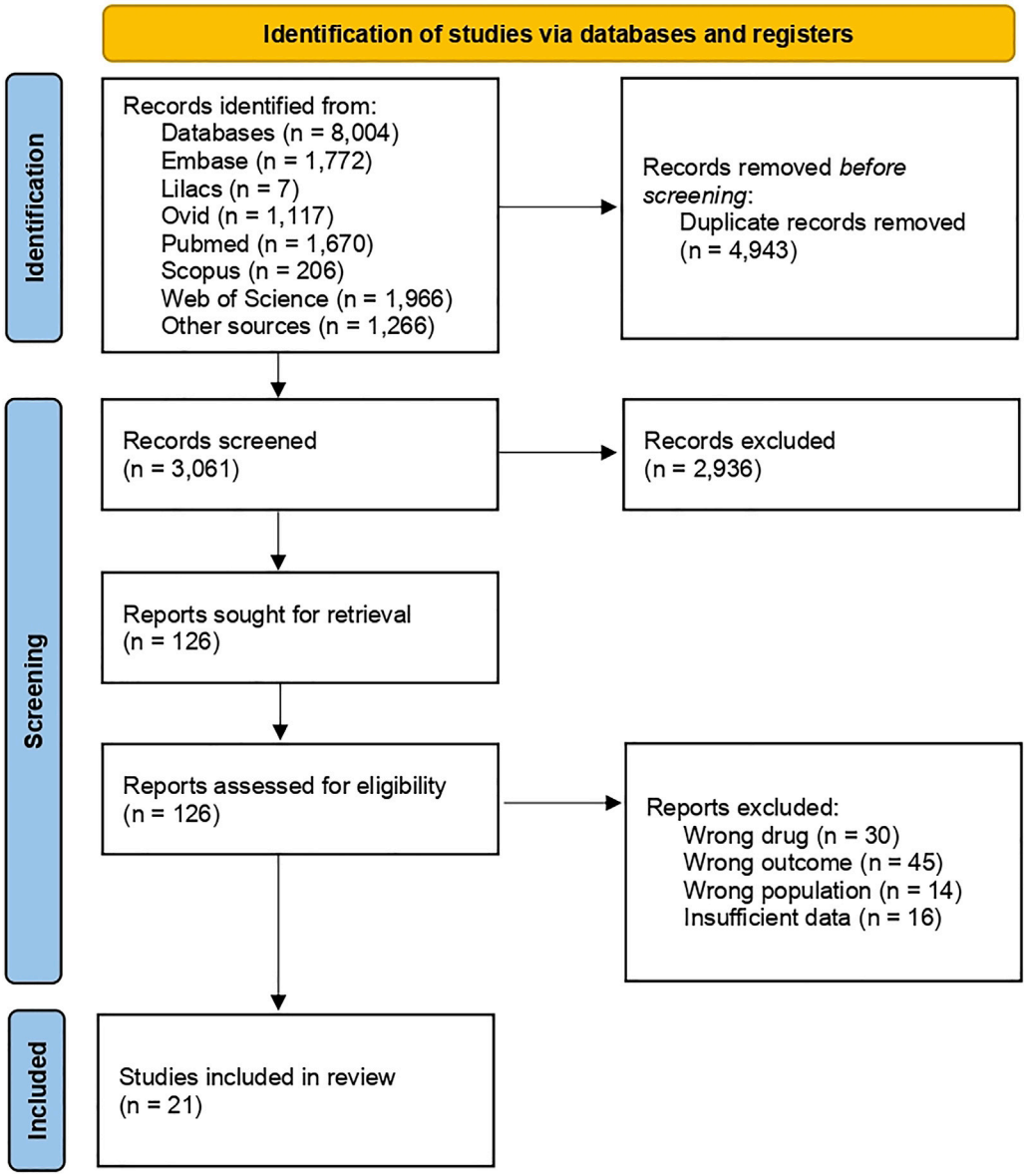


FIGURE 1
Flow chart of search results.

versus non-TNFi; TNFi versus TNFi (adalimumab, etanercept, and golimumab versus infliximab); bDMARDs versus JAKi; and bDMARD monotherapy versus combination therapy (bDMARDs and MTX). A subgroup analysis by effectiveness measure was conducted. Publication bias was assessed by visual inspection of the funnel plot and statistically using Egger's tests. A minimum of ten studies were considered to elaborate on this graph and judge the risk of bias associated with missing data (Page et al., 2020). Analyses were carried out with R version 4.1.2 and the "meta" package version 4.13-0 (Balduzzi et al., 2019).

## 2.6 Sensitivity analysis

Sensitivity analyses were performed, stratifying the analysis by prior use of bDMARDs and no prior use of bDMARDs since bDMARD-naïve patients have a greater response to bDMARDs than those with previous exposure to bDMARDs (Wakabayashi et al., 2011; Mori et al., 2018).

Additionally, an evaluation of how sensitive the estimates from each study were to the effects of unmeasured confounders was performed through the E-value. This measure represents an unmeasured confounder's strength to make a reported exposure-

TABLE 1 Characteristics of the included studies.

| Study | Year | Country | Patients | Mean disease duration (years) | Mean disease activity | Prior use of bDMARDs | Current use of steroids | Outcome |
|---|---|---|---|---|---|---|---|---|
| Acurcio | 2016 | Brazil | 76,351 | NR | NR | NR | NR | Medication persistence in the 1st and 2nd year |
| Bird | 2020 | Australia | 1,950 | 8.9–10.0 | NR | No | NR | Medication persistence and improvement and remission in DAS28, CDAI, and SDAI |
| Chatzidionysio | 2014 | Sweden | 7,052 | 8.4–9.9 | DAS28: 4.7–5.1 | Yes | Yes | Improvement, remission, and change in DAS28 and therapy discontinuation in 6 months |
| Choi | 2021 | South Korea | 8,018 | NR | NR | Yes | NR | Drug failure and medication persistence |
| Curtis | 2015 | United States of America | 5,474 | NR | NR | NR | Yes | Effectiveness (high adherence, no increase in biologic dose, no biologic switch, no new DMARD, no new/increased oral glucocorticoid, and ≤1 glucocorticoid injection) |
| Curtis | 2021 | United States of America | 1,270 | 7.3–9.2 | CDAI: 31.5–33.2 | Yes | NR | Change in CDAI at months 6 and 12 |
| Ebina | 2020 (a) | Japan | 3,897 | 4.7–9.2 | DAS28-ESR: 4.1–4.6 | Yes | Yes | Treatment discontinuation |
| Ebina | 2020 (b) | Japan | 221 | 7.8–11.6 | DAS28-CRP: 3.2–3.9 | Yes | Yes | Treatment discontinuation |
| Gharaibeh | 2020 | United States of America | 14,775 | NR | NR | No | Yes | Nonadherence, increased index medication dose, addition of a conventional DMARD, switch of biologic medications, addition of glucocorticoid or increased glucocorticoid dose, and receipt of ≥2 intra-articular injections in 1 year |
| Harrold | 2015 | United States of America | 1,398 | 11.5–13.4 | CDAI: 21.4–22.9 | Yes | Yes | Responsiveness to medication treatment based on improvement in CDAI, modified ACR20 (mACR20), modified ACR50 (mACR50), and modified ACR70 (mACR70) responses at 6th and 12th month |
| Kihara | 2017 | United Kingdom | 2,636 | 4.0–5.0 | DAS28: 6.0–6.2 | Yes | Yes | Change in DAS28, EULAR response, DAS28 remission, change in HAQ score, and proportion of patients who achieved the minimal clinically important difference in HAQ at the 6th month |

(Continued on following page)

TABLE 1 (*Continued*) Characteristics of the included studies.

| Study | Year | Country | Patients | Mean disease duration (years) | Mean disease activity | Prior use of bDMARDs | Current use of steroids | Outcome |
|---|---|---|---|---|---|---|---|---|
| Lauper | 2018 | Czech Republic, Finland, Italy, Norway, Portugal, Romania, Russia, Slovenia, Spain, and Switzerland | 8,308 | 7.9–10.2 | DAS28: 4.0–4.6 | Yes | Yes | Medication persistence, change in CDAI, and DAS28-ESR in 1 year |
| Li | 2021 | Taiwan | 8,663 | NR | NR | No | NR | Treatment discontinuation and switching |
| Neovius | 2015 | Sweden | 9,139 | 12–13 | DAS28: 5.1–5.2 | No | NR | Therapy discontinuation due to any cause (except for pregnancy and remission) and remission in 5 years |
| Østergaard | 2007 | Denmark | 300 | NR | DAS28-CRP: 5.9 | No | NR | DAS28 and EULAR response rates at week 26 and 52 |
| Pappas | 2021 (a) | United States of America | 617 | 8.8 | CDAI: 3.5–3.7 | No | Yes | Medication persistence, discontinuation, and switching |
| Pappas | 2021 (b) | United States of America | 4,816 | 7.1–8.6 | CDAI: 20.4 | No | Yes | Improvement in CDAI and DAS28, remission based on CDAI and DAS28, and change in CDAI, HAQ, and EQ-5D |
| Rahman | 2020 | Canada | 1,577 | 6.5–9.8 | DAS28-CRP: 4.1–5.3 | Yes | Yes | Medication discontinuation, improvement in DAS28 and HAQ-DI, SDAI remission, and low disease activity |
| Silvagni | 2018 | Italy | 4,478 | 5.0 | NR | No | Yes | Medication persistence |
| Youssef | 2020 | Australia | 6,914 | 10.0 | NR | Yes | Yes | Medication persistence |
| Yun | 2015 | United States of America | 14,244 | NR | NR | No | Yes | No switch to a different biologic, high adherence to the index drug, no addition of a new non-biologic DMARD, no biologic dose increase compared with starting, no initiation of glucocorticoids/no increase in dose, and no more than one joint injection on unique days after 3 months of new treatments |

ACR, American College of Rheumatology; CDAI, Clinical Disease Activity Index; DAS28, Disease Activity Score-28; DAS28-CRP, DAS-28C-reactive protein; DAS28-ESR, DAS-28 erythrocyte sedimentation rate; DMARD, disease-modifying anti-rheumatic drug; EULAR, European Alliance of Associations for Rheumatology; HAQ, Health Assessment Questionnaire; HAQ-DI, HAQ Disability Index; NR, not reported; SDAI, Simplified Disease Activity Index.

outcome association statistically non-significant (Mathur and VanderWeele, 2020). Thus, the size of unobserved confounding able to nullify the mean risk ratio was quantified, and the unmeasured confounding strengths sufficient to allow 10% of studies with true RR above or below a threshold to remain statistically significant were calculated for each one of the four groups analyzed.

# 3 Results

## 3.1 Selected studies

The initial search returned 8,004 records, of which 4,943 were duplicates. After screening titles and abstracts, 126 studies were analyzed regarding inclusion criteria, and 105 were excluded.

Afterward, references to the included studies were manually searched to detect relevant articles, but none was identified. Therefore, articles were excluded from analyzing the wrong drug, outcome, and population and from having insufficient data (Figure 1).

## 3.2 Study characteristics

Twenty-one records were eligible for inclusion in this systematic review; seven population-based cohorts (Østergaard et al., 2007; Chatzidionysiou et al., 2015; Neovius et al., 2015; Acurcio et al., 2016; Kihara et al., 2017; Choi et al., 2021; Li et al., 2021), eight prospective (Harrold et al., 2015; Lauper et al., 2018; Ebina et al., 2020a, 2020b; Rahman et al., 2020; Curtis et al., 2021; Pappas et al., 2021a, 2021b), and six retrospective cohort studies (Curtis et al., 2015; Yun et al., 2015; Silvagni et al., 2018; Bird et al., 2020; Gharaibeh et al., 2020; Youssef et al., 2020), which are published from 2007 to 2021 (Supplementary Table S2).

Overall, 182,098 rheumatoid arthritis patients were evaluated; the majority were women (67–88%), and the mean age ranged between 48 and 70 years (Supplementary Table S2). Disease duration was between 4 and 13 years. Most studies included patients with moderate to high disease activity, indicating severe rheumatoid arthritis and poor prognosis (Table 1).

Ten studies compromised RA patients in second-line therapy (Chatzidionysiou et al., 2015; Harrold et al., 2015; Kihara et al., 2017; Lauper et al., 2018; Ebina et al., 2020a, 2020b; Rahman et al., 2020; Youssef et al., 2020; Choi et al., 2021; Curtis et al., 2021), nine in first-line therapy (Østergaard et al., 2007; Neovius et al., 2015; Yun et al., 2015; Silvagni et al., 2018; Bird et al., 2020; Gharaibeh et al., 2020; Li et al., 2021; Pappas et al., 2021b, 2021a), and two did not report this information (Curtis et al., 2015; Acurcio et al., 2016) (Table 1).

Studies evaluated second-line therapy with tocilizumab versus TNFi (monotherapy or combination therapy with csDMARDs) after the use of at least one bDMARD (Lauper et al., 2018); second-line treatment with bDMARDs and tsDMARD after the use of other bDMARDs and tsDMARD (Youssef et al., 2020); and second and third-line bDMARDs and tsDMARD (Choi et al., 2021). One research included patients with previous therapy with bDMARDs and concurrent DMARDs (Curtis et al., 2021). Another study indicated a proportion of biologic-experienced RA patients of 6.3–19.7% (Rahman et al., 2020).

Five reports evaluated therapy switching, of which one analyzed switching from first TNFi to second TNFi (Chatzidionysiou et al., 2015); one from TNFi to abatacept and other TNFi (Harrold et al., 2015); one from any bDMARD to tocilizumab (Kihara et al., 2017); one from any bDMARD to another bDMARD or tofacitinib (Ebina et al., 2020a); and one from tocilizumab or abatacept after failure to bDMARDs or JAKi (Ebina et al., 2020b). The first four studies did not report the duration of the first therapy. The last one observed mean therapy duration between 16.4 and 26.7 months for tocilizumab and 10.9 and 11.0 months for abatacept.

Furthermore, fourteen records described the proportion of RA patients in current use of steroids (Chatzidionysiou et al., 2015; Curtis et al., 2015; Yun et al., 2015; Harrold et al., 2015; Kihara et al., 2017; Silvagni et al., 2018; Lauper et al., 2018; Ebina et al., 2020a, 2020b; Rahman et al., 2020; Youssef et al., 2020; Gharaibeh et al., 2020; Pappas et al., 2021a, 2021b), which ranged from 9.9 to 78.0%; however, none of these studies did a separate analysis for patients who are currently exposed to steroids and unexposed to steroids.

The 21 studies investigated nine different biological drugs, among them TNFi (etanercept, infliximab, adalimumab, certolizumab pegol, golimumab, and tocilizumab), non-TNFi (rituximab and abatacept), and JAKi (tofacitinib). Additionally, three studies compared bDMARD monotherapy and combination therapy (bDMARDs and MTX).

Regarding the outcomes, most articles analyzed medication persistence, remission, and improvement in disease activity. The studies' remission and disease activity measures encompassed DAS28, EULAR, CDAI, SDAI, and HAQ.

## 3.3 Quality of the included studies

According to the MINORS, twenty studies were classified as high quality (Chatzidionysiou et al., 2015; Curtis et al., 2015, 2021; Harrold et al., 2015; Neovius et al., 2015; Yun et al., 2015; Acurcio et al., 2016; Kihara et al., 2017; Lauper et al., 2018; Silvagni et al., 2018; Bird et al., 2020; Ebina et al., 2020a, 2020b; Gharaibeh et al., 2020; Rahman et al., 2020; Youssef et al., 2020; Choi et al., 2021; Li et al., 2021; Pappas et al., 2021a, 2021b) and one as moderate quality (Østergaard et al., 2007). Overall, studies scored between 14 and 24 points (Supplementary Table S3).

## 3.4 Meta-analysis

### 3.4.1 TNFi versus non-TNFi

Twelve studies assessed the effectiveness between TNFi and non-TNFi (Curtis et al., 2015; Harrold et al., 2015; Yun et al., 2015; Kihara et al., 2017; Lauper et al., 2018; Ebina et al., 2020a, 2020b; Gharaibeh et al., 2020; Youssef et al., 2020; Choi et al., 2021; Li et al., 2021; Pappas et al., 2021b). A statistically significant lower effectiveness was observed among TNFi users than in non-TNFi users (RR: 0.88; 95% CI: 0.81–0.95; $p < 0.01$; $I^2 = 94.0\%$). The analysis by effectiveness measure revealed lower therapy persistence (RR: 0.82; 95% CI: 0.72–0.92) with TNFi than with non-TNFi drugs (Figure 2). Visual inspection of the funnel plot did not suggest asymmetry

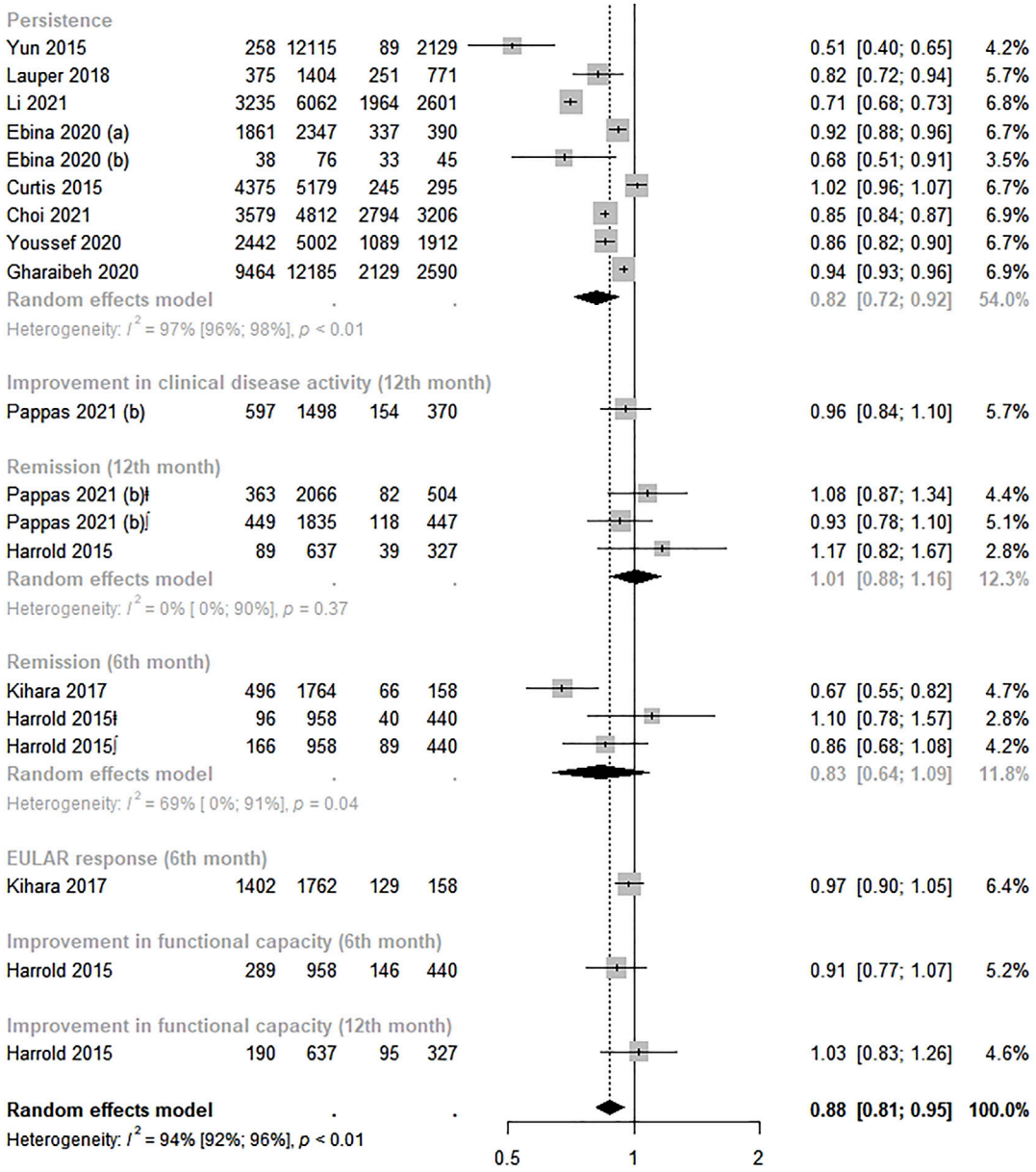


FIGURE 2
Effectiveness of TNF inhibitors compared to non-TNF inhibitors. TNFi, TNF inhibitors; non-TNFi, non-TNF inhibitors; ǂ, remission based in CDAI; ∫, remission based in DAS28.

(Supplementary Figure S1), and Egger's test did not indicate publication bias (intercept = −0.01, $p$ = 0.99).

### 3.4.2 Adalimumab, etanercept, and golimumab versus infliximab

Ten studies evaluated the effectiveness of adalimumab, etanercept, and golimumab versus infliximab (Østergaard et al., 2007; Curtis et al., 2015, 2021; Neovius et al., 2015; Ebina et al., 2020a, 2020b; Gharaibeh et al., 2020; Rahman et al., 2020; Youssef et al., 2020; Choi et al., 2021). Overall, adalimumab, etanercept, and golimumab were 19.0% more effective for rheumatoid arthritis than infliximab (RR: 1.19; 95% CI: 1.05–1.36; $p$ < 0.01; $I^2$ = 96.0%). Higher therapy persistence (RR: 1.09; 95% CI: 1.01–1.19) and remission in the 12th month (RR: 2.09; 95% CI: 1.74–2.51) were pointed out in

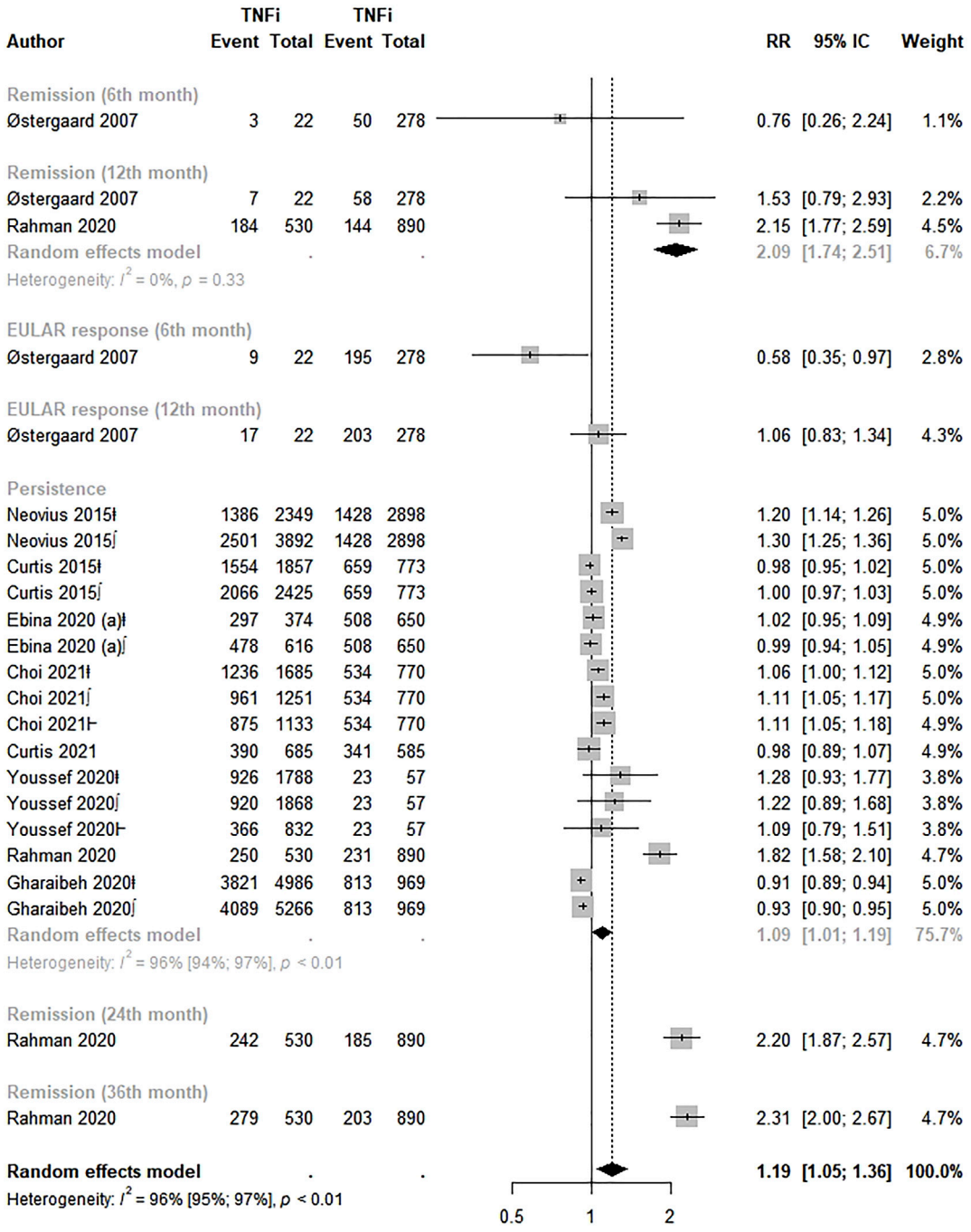


FIGURE 3
Effectiveness of Adalimumab, Etanercept and Golimumab compared to Infliximab. TNFi, TNF inhibitors; ł, adalimumab; ∫, etanercept; Ⱶ, golimumab.

the analysis by effectiveness measure (Figure 3). Visual inspection of the funnel plot indicated asymmetry, suggesting publication bias (Supplementary Figure S2). Egger's test indicated publication bias (intercept = 3.97, $p$ = 0.02).

The analysis by drug showed a significant higher effectiveness of golimumab (RR: 1.57; 95% CI: 1.19–2.08; $p$ < 0.01; $I^2$ = 97.0%) over infliximab. However, the subgroup analysis by effectiveness measure did not reveal statistically significant results for

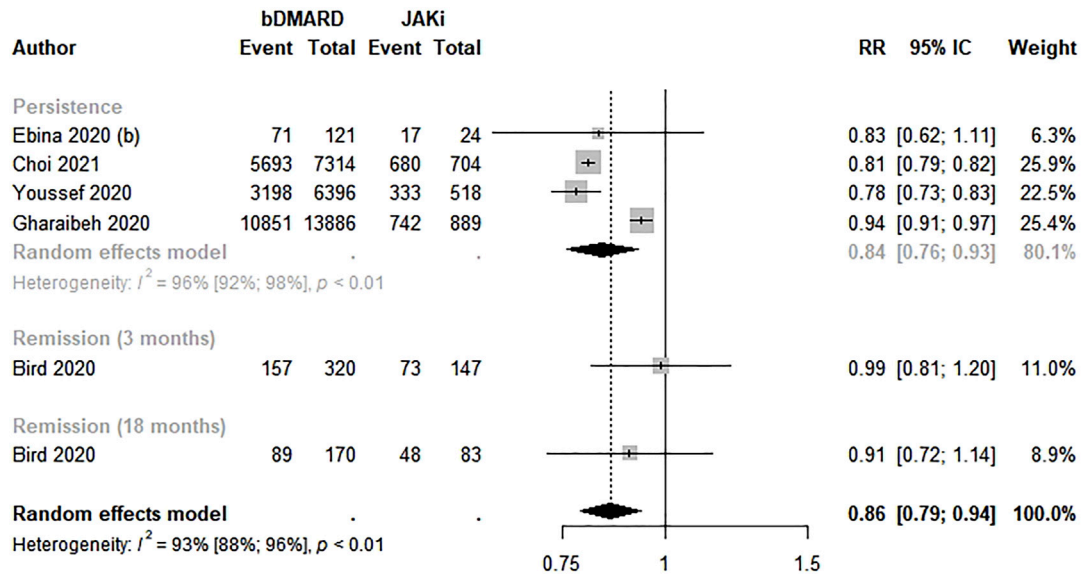


FIGURE 4
Effectiveness of biological disease-modifying anti-rheumatic drugs compared to Janus kinase inhibitors. bDMARD: biological disease-modifying anti-rheumatic drug; JAKi: Janus kinase inhibitors.

adalimumab, etanercept, or golimumab over infliximab (Supplementary Figure S3).

### 3.4.3 bDMARDs versus JAKi

Five studies estimated the effectiveness of bDMARDs compared to JAKi (Bird et al., 2020; Ebina et al., 2020b; Gharaibeh et al., 2020; Youssef et al., 2020; Choi et al., 2021). bDMARDs were 14.0% less effective for rheumatoid arthritis than JAKi (RR: 0.86; 95% CI: 0.79–0.94; $p$ < 0.01; $I^2$ = 93.0%). Regarding the analysis by effectiveness measure, a lower persistence in bDMARD therapy was observed (RR 0.84; 95% CI 0.76–0.93) (Figure 4).

### 3.4.4 bDMARD monotherapy versus combination therapy

The effectiveness between bDMARD monotherapy and combination therapy was evaluated by three studies (Østergaard et al., 2007; Kihara et al., 2017; Lauper et al., 2018). The meta-analysis revealed a lower effectiveness of bDMARD monotherapy than of combination therapy with borderline statistical significance (RR: 0.83; 95% CI: 0.68–1.00; $p$ < 0.01; $I^2$ = 81.0%). However, a lower EULAR response in the 6th month with statistical significance was observed in bDMARD monotherapy (RR: 0.85; 95% CI: 0.74–0.99) (Figure 5).

## 3.5 Sensitivity analysis

In analyses by prior use of bDMARDs, a statistically significant lower effectiveness was observed among TNFi users than in non-TNFi users who had never been exposed to biological therapy (RR: 0.86; 95% CI: 0.78–0.95; $p$ < 0.01; $I^2$ = 96.0%), while non-significant differences were observed among biologic-experienced patients (Supplementary Figure S4).

In contrast, a 50.0% higher effectiveness was presented by biologic-experienced subjects exposed to adalimumab, etanercept, and golimumab than to infliximab (RR: 1.50; 95% CI: 1.15–1.95; $p$ < 0.01; $I^2$ = 96.0%). Regarding biologic-naïve patients, there were no significant differences between the drugs (RR: 1.05; 95% CI: 1.00–1.11; $p$ < 0.01; $I^2$ = 94.0%) (Supplementary Figure S5).

In the sensitivity analysis of bDMARDs compared to JAKi, bDMARDs had lower effectiveness than JAKi in biologic-naïve patients (RR: 0.86; 95% CI: 0.79–0.95; $p$ < 0.01; $I^2$ = 95.0%), and non-statistical significance was found among patients with prior use of biologics (Supplementary Figure S6).

Non-significant differences on effectiveness were observed in sensitivity analysis of bDMARD monotherapy compared to combination therapy among patients who had previously been exposed to biologic drugs (RR: 0.87; 95% CI: 0.66–1.14; $p$ < 0.01; $I^2$ = 94.0%) and those who had never been exposed to biologic drugs (RR: 0.89; 95% CI: 0.76–1.04; $p$ < 0.01; $I^2$ = 85.0%) (Supplementary Figure S7).

The sensitivity analysis for unmeasured confounding showed that an unobserved confounder needed to be associated with both TNFi use and effectiveness with a risk ratio of at least 1.65 (95% CI: 1.00–2.82) to reduce to less than 10% the percentage of meaningfully strong true causal effects. For adalimumab, etanercept, and golimumab and the outcome, a risk ratio of at least 1.97 (95% CI: 1.00–3.52) would be necessary to reduce to

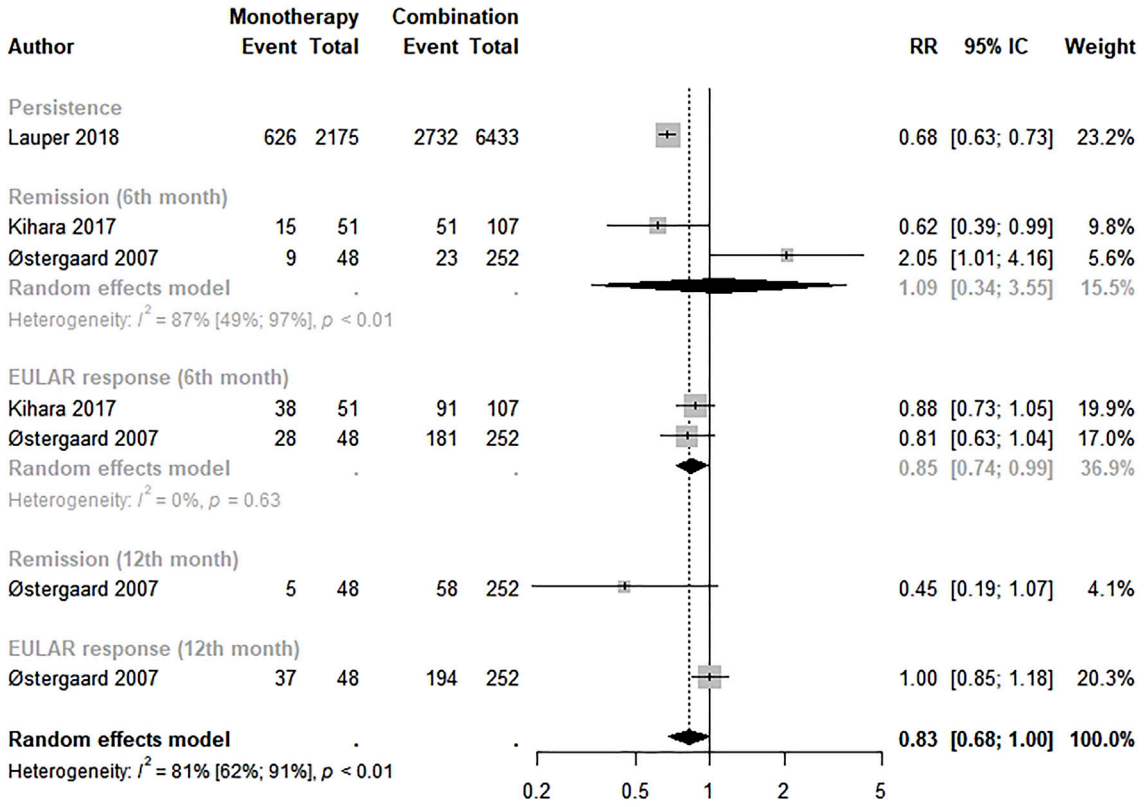


FIGURE 5
Effectiveness of biological disease-modifying anti-rheumatic drugs monotherapy compared to combination therapy. Monotherapy: biological disease-modifying anti-rheumatic drugs monotherapy; combination: biological disease-modifying anti-rheumatic drugs + methotrexate.

less than 10% the percentage of meaningfully strong true causal effects, while for bDMARDs and bDMARD monotherapy, the necessary risk ratios should be 1.61 (95% CI: 1.00–2.85) and 2.06 (95% CI: 1.00–4.08), respectively.

## 4 Discussion

This systematic review and meta-analysis provide a quantitative estimate of the real-world effectiveness of different biological therapies in patients with rheumatoid arthritis in studies using administrative health databases. Real-world effectiveness data provide valuable evidence to support the efficacy findings from randomized controlled trials (RCTs) (Blonde et al., 2018) once trial patients may not represent the real-world RA population.

Overall, this meta-analysis showed statistically significant differences in effectiveness between the biological medicines analyzed. For example, TNFi showed less effectiveness in RA patients than non-TNFi drugs, as well as bDMARDs compared to JAKi, and bDMARD monotherapy compared to combination therapy. In contrast, golimumab showed higher effectiveness than infliximab. However, it is important to highlight the low number of studies included in some analyses.

These findings are similar to the results of efficacy from previous RCTs. The ADACT and AMPLE trials compared the efficacy of tocilizumab versus adalimumab and abatacept versus adalimumab, respectively, and indicated greater effectiveness of non-TNFi over the TNFi analyzed (Gabay et al., 2013; Weinblatt et al., 2013). Regarding JAKi, RCT findings are controversial, pointing to the greater effectiveness of baricitinib over adalimumab (Keystone et al., 2017; Taylor et al., 2017) and lower effectiveness of tofacitinib than of adalimumab (Fleischmann et al., 2017).

The development of drugs to target TNF-α has been one of the most impressive advances in treating inflammatory diseases in the past decade. However, some patients do not tolerate or respond adequately to available TNFi. In these cases, other biologically derived drugs with different action mechanisms may be used, such as abatacept, which is a T-cell co-stimulation inhibitor, and JAKi, which are oral drugs counteracting the activation of cytosolic enzymes presiding over many biologic functions (JAKs) (Smolen et al., 2009; Angelini et al., 2020).

TNF-α is an important cytokine that mediates inflammation and bone degradation in RA through local inflammation and pannus formation, eventually leading to further cartilage erosion and bone destruction. The introduction of TNFi has revolutionized RA treatment options, resulting in the development of further biologic DMARDs (Ma and Xu, 2013). TNFi drugs act by reducing TNF-α levels in RA, restoring the balance in the cytokine system. Many TNFi drugs are available nowadays, including infliximab, adalimumab, etanercept, and golimumab. The first TNFi drug for RA was infliximab, a chimeric human-murine monoclonal antibody that binds with high affinity to soluble and transmembrane forms of TNF-α but not to lymphotoxin. Since the advent of infliximab, genetically engineered molecules employing a slightly different compositional and pharmacodynamic approach have been marketed (Pelechas et al., 2019).

Unlike the present results, where significant effectiveness of adalimumab over infliximab was not observed, ATTEST and AMPLE trials found higher efficacy of adalimumab than infliximab, with a statistically significant odds ratio of ACR20 (OR: 1.73; 95% CI: 1.04–2.87), ACR50 (OR: 1.49; 95% CI: 1.02–2.19), and low disease activity (DAS28) (OR: 2.12; 95% CI: 1.19–3.78) were observed among patients treated with adalimumab (Christensen et al., 2013). However, results from these RCTs reflect a limited population of RA patients, leading to limitations related to small sample size and exclusion criteria that limit generalizability to real-world subjects. So, these differences highlight real-world studies' importance in investigating drug effects in clinical practice since the effectiveness of drug therapy depends on factors such as adherence to the medication and the outcomes associated with the drug use in different patient populations.

Although significantly higher effectiveness of etanercept over infliximab was not found in the meta-analysis, a retrospective cohort study with data from the CORRONA registry pointed out that patients on etanercept monotherapy experience greater therapy persistence in the 6th and 12th month and are less likely to reintroduce a csDMARD than patients on other TNFi monotherapies. The authors stated that the development of neutralizing anti-drug antibodies to TNFi other than etanercept might contribute to these findings (Pappas et al., 2021a).

Similar to the findings of this systematic review and meta-analysis, a systematic review of sixteen RCTs compared the efficacy of TNFi using Bayesian mixed treatment comparison models and found greater efficacy of golimumab than infliximab by the Health Assessment Questionnaire (HAQ) score (Schmitz et al., 2012). Golimumab is a human anti-TNF-α monoclonal antibody generated and matured in an *in vivo* system, with high affinity and specificity for human TNF-α, and effectively neutralizes TNF-α bioactivity (Ma and Xu, 2013). Furthermore, this biological drug presents low levels of immunogenicity and a more attractive dosage scheme (every 4 weeks) (Pelechas et al., 2019), which may influence its greater effectiveness than infliximab.

According to previous studies, using combination therapy (bDMARDs and MTX) contributes to a higher persistence of biological therapy in RA patients (Lauper et al., 2018). Similarly, patients treated with higher MTX doses tend to persist in treatment for a longer time (Soliman et al., 2011; Aaltonen et al., 2017). However, in the meta-analysis comparing bDMARD monotherapy to combination therapy, a borderline statistically significant lower effectiveness was found among patients treated exclusively with bDMARDs. This finding may be related to the evaluation of different biological medicines by each study, such as tocilizumab or TNFi (Lauper et al., 2018), tocilizumab (Kihara et al., 2017), and infliximab and etanercept (Østergaard et al., 2007).

Furthermore, the sensitivity analysis revealed lower effectiveness of TNFi versus non-TNFi and bDMARDs versus JAKi in biologic-naïve patients, indicating a possible benefit from non-TNFi and JAKi pharmacotherapy in these subjects. Regarding biologic-experienced subjects, higher effectiveness was observed with adalimumab, etanercept, and golimumab than with infliximab. Given the present findings, adalimumab, etanercept, and golimumab may be effective treatment options for patients with inadequate response to infliximab.

Most of the included studies evaluated as effectiveness measure therapy persistence, remission, and improvement in disease activity. Persistence in therapy is an excellent indirect and composite measure of effectiveness, safety, and tolerability, reflecting the long-term impact on the course of the disease (Silvagni et al., 2018). Twelve studies evaluated the therapy persistence in this systematic review (Curtis et al., 2015; Neovius et al., 2015; Yun et al., 2015; Lauper et al., 2018; Ebina et al., 2020a, 2020b; Gharaibeh et al., 2020; Rahman et al., 2020; Youssef et al., 2020; Choi et al., 2021; Curtis et al., 2021; Li et al., 2021). In addition, the majority of the studies that evaluated the therapy persistence of TNFi in comparison to non-TNFi found significant differences among the therapies, favoring non-TNFi over TNFi (Curtis et al., 2015; Yun et al., 2015; Lauper et al., 2018; Ebina et al., 2020a; Youssef et al., 2020; Choi et al., 2021; Li et al., 2021). The same pattern was observed among articles that assessed persistence among bDMARD and JAKi, showing lower persistence in bDMARD RA patients (Gharaibeh et al., 2020; Youssef et al., 2020; Choi et al., 2021). In contrast, only two articles found significant differences between adalimumab, etanercept, and golimumab versus infliximab, pointing to a higher persistence among RA patients exposed to adalimumab and etanercept than infliximab (Neovius et al., 2015; Rahman et al., 2020).

According to Yun et al. (2014), one in every three patients interrupts their treatments with the first bDMARD in the first year of use due to lack of efficacy and/or adverse events. Nonetheless, treating autoimmune diseases that cause systemic inflammation is vital since there is evidence that the persistence of systemic inflammation leads to a higher risk of death (Listing

et al., 2015). Furthermore, RA patients present a higher risk of death due to cardiovascular events when compared to the general population (Zhang et al., 2016).

A critical treatment goal in managing RA patients is the achievement of clinical remission (Ajeganova and Huizinga, 2017). However, only six studies used this outcome as an effectiveness measure (Østergaard et al., 2007; Harrold et al., 2015; Kihara et al., 2017; Bird et al., 2020; Rahman et al., 2020; Pappas et al., 2021b). Furthermore, only one of the included studies observed significant differences among the biological therapies evaluated in clinical remission (Rahman et al., 2020). The prospective cohort used data from the Biologic Treatment Registry Across Canada (BioTRAC) between 2002 and 2017 and evaluated the effectiveness of golimumab and infliximab. The authors observed higher SDAI clinical remission at 12, 24, and 36 months in patients treated with golimumab (34.7, 47.5, and 52.7%, respectively) than in those treated with infliximab (of 16.2, 20.8, and 22.8%, respectively) (Rahman et al., 2020).

The expressive variation in the remission and disease activity measures adopted by the studies included in the present systematic review and meta-analysis, encompassing DAS28, EULAR, CDAI, SDAI, and HAQ, must be highlighted. A treat-to-target strategy is recommended in RA, and for this purpose, regular RA disease activity assessments must be made during routine care. Many RA disease activity measures are available that incorporate data gathered from a combination of sources, including patient-reported measures, provider assessments, laboratory values, and/or imaging modalities; nevertheless, these measures may vary in performance and feasibility (England et al., 2019). Considering these, the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) recommend a variety of RA disease activity measures, such as CDAI, DAS28-ESR/CRP, and SDAI, for regular use (England et al., 2019; Smolen et al., 2020).

It is important to emphasize that because of the different immune-modulatory properties of specific drugs and drug classes, biological therapy may be related to several potential adverse events, such as hospitalized infection, solid cancers and lymphoma, cardiovascular diseases, and mortality (Yun et al., 2016). Therefore, the pharmacotherapy selection must consider not only the medicine's efficacy but also its associated risk.

RA treatment has progressively improved over the last decades due to the contribution of biological therapies and treat-to-target strategies, which aim at the achievement of clinical remission by slowing or stopping the progression of joint destruction and deformity. This process improved therapeutic results and quality of life and reduced patient morbidity and mortality (Bullock et al., 2018; Ho et al., 2019). Furthermore, therapy choice depends on disease severity, the patient's clinical response, and previously experienced side effects. Although biological medicines improve the likelihood of reaching the treatment target in many RA patients, they are costly, limiting their widespread use and contributing to the inequity of access across countries. Thus, they should be used in an evidence-based manner that accounts for availability and affordability within the local healthcare system (Ho et al., 2019; Smolen et al., 2020).

## 4.1 Strengths and limitations

This systematic review and meta-analysis present strengths and limitations. This is a comprehensive assessment of the evidence, incorporating all available published studies on the real-world effectiveness of biological therapies in patients with rheumatoid arthritis. Strengths also encompass studies with administrative health databases as inclusion criteria, random-effects meta-analysis to deal with the heterogeneity, and the conduction of sensitivity analysis stratified by prior use of bDMARDs and no prior use of bDMARDs.

A significant limitation is the possibility of findings by chance in the meta-analyses comparing bDMARDS versus JAKi and bDMARD monotherapy versus combination therapy due to the low number of studies included. Meta-analyses of small numbers of studies have limitations that can impact their findings, although they present valid results (Herbison et al., 2011). Also, it was not possible to analyze bDMARDs compared to csDMARDs since only one of the included studies evaluated this (Acurcio et al., 2016).

Also, it was not possible to perform sensitivity analyses by the duration of previous drugs because the included studies did not have this information and by RA patients currently exposed to steroids versus those unexposed to these medicines since none of the included studies reported patients unexposed to steroids.

Another limitation is the high heterogeneity between studies, which persisted after subgroup and sensitivity analyses. This could be justified by several factors such as differences in measures of effectiveness adopted, differences in RA severity and prognosis, and differences in some population characteristics.

The publication bias found in studies that evaluated TNFi compared to TNFi (infliximab) is probably associated with the eligibility criteria adopted, including only observational studies with administrative databases, usually resulting in more extensive studies.

Moreover, raw data were used to perform meta-analyses instead of adjusted measures, considering the variety of association measures and the several combinations of covariates submitted to the adjustment procedures by the studies. So, the type of analysis performed cannot control confounders such as age, gender, ethnicity, education, work, type of health insurance, body mass index (BMI), smoking, comorbidities, and use of drugs that can influence drugs' effectiveness, such as steroids and NSAIDs.

Although real-world data may not be as rigorous as RCT data because of the string inclusion criteria, data collection, and quality control, it may lead to a better understanding of the effectiveness of biological therapy in a more complex and heterogeneous RA population, which is more representative of clinical practice.

## Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material; further inquiries can be directed to the corresponding author.

## Author contributions

CC, MQ, FA, and DS contributed to the study design, data analysis, and data interpretation. CC, MQ, FA, CB, LG, and DS contributed to the study selection, data extraction, and interpretation of data. CC, MQ, FA, CB, LG, DP, SB, WA, EB, JA, RC, MB, and DS were involved in drafting the manuscript and revised it critically.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## Supplementary material

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# Potential safety signals for antibacterial agents from the Brazilian national pharmacovigilance database (Vigimed/VigiFlow)

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Antibacterial drugs are a widely used drug class due to the frequency of infectious diseases globally. Risks knowledge should ground these medicines' selection. Data mining in large databases is essential to identify early safety signals and to support pharmacovigilance systems. We conducted a cross-sectional study to assess adverse drug events related to antibiotics reporting between December 2018 and December 2021 in the Brazilian database (Vigimed/VigiFlow). We used the Reporting Odds Ratio (ROR) disproportionality analysis method to identify disproportionate reporting signals (SDR), referring to statistical combinations between drugs and adverse events. Vancomycin was the most reported antibiotic ($n$ = 1,733), followed by ceftriaxone ($n$ = 1,277) and piperacillin and tazobactam ($n$ = 1,024). We detected 294 safety signals related to antibacterials. We identified azithromycin leading in the number of safety signals ($n$ = 49), followed by polymyxin B ($n$ = 25). Of these, 95 were not provided for in the drug label and had little or no reports in the medical literature. Three serious events are associated with ceftazidime and avibactam, a new drug in the Brazilian market. We also found suicide attempts as a sign associated with amoxicillin/clavulanate. Gait disturbance, a worrying event, especially in the elderly, was associated with azithromycin. Our findings may help guide further pharmacoepidemiologic studies and monitoring safety signals in pharmacovigilance.

KEYWORDS

**pharmacovigilance, adverse drug reaction reporting systems, anti-bacterial agents, drug-related side effects and adverse reactions, safety signals, spontaneous reports**

## Introduction

Individual case safety reports (ICSRs) from the spontaneous reporting system provide an essential information source for studying adverse drug events (ADEs) (Li et al., 2022). The database screening may be used to discover unknown drug-event pairs associated with signals of disproportionate reporting (Dijkstra et al., 2020). The evaluation of a signal encompasses quantitative and qualitative aspects (Meyboom et al., 1997; Hauben and Aronson, 2009). Meyboom and collaborators define a signal is more than just a statistical association, it consists of a hypothesis based on data and arguments (Meyboom et al., 1997) According to the World Health Organization (WHO), a safety signal is an information on a new or known ADE that may be caused by a medicine and is typically generated from more than a single report of a suspected event. A signal does not imply a direct causal relationship between an event and a drug but added with more information (consistent data, biological plausibility, association strength, for example) raises a hypothesis that requires further assessment (World Health Organization, 2022a). Regarding the quantitative aspect, statistical techniques (cluster analysis, link analysis, deviation detection, and disproportionality assessment) can be used to determine and assess the strength of ADE signals by the disproportional analysis (Montastruc et al., 2011).

Several measures of disproportionality reporting are available, and some studies propose direct comparisons of methods using synthetic, noise-free data (Zorych et al., 2013; Dijkstra et al., 2020). The reporting odds ratio (ROR) is the disproportionality method used by Eudravigilance e UMC Uppsala (World Health Organization, 2022a; European Medicines Agency, 2022) and performs well in most cases.

Low and middle-income countries (LMIC) face challenges in establishing efficient pharmacovigilance systems capable of generating data to inform health policies and practices (Kiguba et al., 2021). In Brazil, the largest country in South America, a new ADE notification system was deployed in 2018 (Vogler et al., 2020) by the National Health Surveillance Agency (ANVISA). Vigimed was the name given in Brazil to Vigiflow, a web-based ICSR management system developed by UMC, which replaced Notivisa due to system instability, an inability to import data series or export the database for analysis, and a lack of analytical and statistical tools (Vogler et al., 2020).

Data mining in pharmacovigilance databases may guide 1) additional analytical studies in specific populations that may be more susceptible to ADE occurrence and 2) epidemiologic studies for risk quantification and risk-minimization activities (Emanuel Raschi, 2016). Previous studies from our group found relevant signals of disproportionate reporting in pediatric and oncologic care from the former Brazilian database (Notivisa) (Barcelos et al., 2019; Vieira et al., 2020).

Antibacterials are a strategic drug class for pharmacoepidemiologic studies due to the frequency and their use consequences. These medicines have been associated with ADEs, microbial resistance, morbidity, and mortality worldwide (Tamma et al., 2017; Montastruc et al., 2021; Li et al., 2022). In addition, cultural factors can influence antibiotic use (Touboul-Lundgren et al., 2015). Brazil is one of the countries with the highest consumption of these drugs (World Health Organization, 2018) which raised on COVID-19 disease pandemic (Silva et al., 2021; Ul Mustafa et al., 2021).

We aimed to identify and analyze potential safety signals related to antibacterial agents for systemic use from the Brazilian electronic system for the spontaneous report (Vigimed/VigiFlow) from 2018 to 2021. This study is the first to analyze signals of disproportionate reporting involving antibacterials based on data obtained from the new Brazilian electronic reporting system.

## Materials and methods

We conducted a registry-based cross-sectional study (European Medicines Agency, 2021). We collected data from the ADE spontaneous reports Brazilian database (Vigimed/Vigiflow) between January and March 2022. The Vigimed platform is currently available in the ANVISA database (Agência Nacional de Vigilância Sanitária, 2022c). We included all reports of antibacterials for systemic according to Anatomical Therapeutic Chemical Classification System - ATC J01) related to 1 December 2018, and 31 December 2021 period (World Health Organization, 2020).

Antibacterials were classified by the fifth level of the Anatomical Therapeutic Chemical (ATC) Code (World Health Organization, 2020). We also considered AWaRe Classification to compare ADE reports by antibiotics with different levels (three groups) of microbial resistance (Habarugira et al., 2021). The Access group includes antibiotics with a lower potential for resistance than the other groups. They are first or second-choice empirical treatments for infectious syndromes. Watch group antibiotics should be prioritized as critical targets of administration and monitoring programs. The Watch group has 11 antibiotics in the WHO Model List of Essential Medicines. Antibiotics in the Reserve group should be treated as a "last resort". These drugs are vital points of antimicrobial stewardship programs. Seven antibiotics from the reserve group make up the WHO Model List of Essential Medicines (World Health Organization, 2019, 2021).

We compared case/non-case where cases were ICSR with ADE. We created a database containing 1) drug names, 2) reported ADE, and 3) the number of notifications of each ADE for each target drug. According to the European Medicines Agency, we did not consider drug-event pairs with less than three notifications and notifications dealing with medication errors (Aronson, 2009; European Medicines Agency, 2018b).

Concerning statistical analyses, we used the Reporting Odds Ratio (ROR) disproportionality analysis method, as implemented by the EudraVigilance Data Analysis System (EVDAS) used by the European Medicines Agency (European Medicines Agency, 2018a). We used the ROR measure to identify disproportionate reporting signals (SDR), referring to statistical combinations between drugs and ADEs. This method assumes that when a signal (involving a specific ADE) is associated with a drug, it indicates that the ADEs reported more frequently in association with this drug than other drugs (European Medicines Agency, 2006). The ROR calculation considers its 95% confidence interval and the number of individual cases (Van Puijenbroek et al., 2002).

The ROR measure is defined by the formula [(a.d)/(c.b)], where:

- "a" indicates the number of reports that list the target drug P and the target ADE R;
- "b" indicates the number of reports that list the target drug P but not the target ADE R;
- "c" indicates the number of reports that list the target ADE R but not the drug P;
- Finally, "d" indicates the number of reports that do not list the target ADE R or drug P.

When the inferior limit of the ROR's 95% confidence interval is greater than 1, the association between ADE and the target drug is considered statistically significant (Rothman et al., 2004). Therefore, we consider it an SDR. A situation occurs when c = 0 or all database reports containing a target ADE are associated with only one drug. In this case, there is a division by zero, and it is not possible to calculate the ROR. In this situation, the ROR value is arbitrarily set at 99.9 to reflect the presence of a possible SDR. We also differentiate in the following analysis the cases where $3 \leq a < 5$ and $a \geq 5$.

We assess previous information about safety signals found in the drug labels (summary of product characteristics - SPC) available on the ANVISA website (Agência Nacional de Vigilância Sanitária, 2022b). All safety signals not mentioned in SPCs were tabulated. Additionally, we investigated the existence of any complementary data that could reinforce the suspicion of a causal relationship between the antibiotic and the observed event in studies published in the following databases: UpToDate, Pubmed, Embase, Web of Science, and Medline. The search was performed using the drug name according to ATC and Preferred Terms (PT) (International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use, 2020).

## Results

We found 12,665 ADE reports involving 53 antibacterials for systemic use (Group J01) between 1 December 2018, and 31 December 2021, in the Vigimed/VigiFlow database (Brazil). The most reported antibiotics were: vancomycin ($n$ = 1,733), ceftriaxone ($n$ = 1,274), piperacillin/tazobactam ($n$ = 1,024), ciprofloxacin ($n$ = 936), and azithromycin ($n$ = 870) (Figure 1).

We obtained 294 safety signals. Azithromycin ($n$ = 49) and polymyxin B ($n$ = 25) were the main antibiotics involved in these signals, as shown by the bar color density in Figure 1. For 67.7% of pairs, the event reported was already described in the label of the respective antibiotic. Table 1 presents the 95 signals, few or not reported in the literature.

Concerning serious safety signals, we found eight involving antibiotics classified as Reserve. Polymyxin B had five serious ADE (depressed level of consciousness, dyspnea, acute respiratory failure, oxygen saturation decreased, and cardio-respiratory arrest) not previously described. Death, depression level of consciousness, and sepsis with ceftazidime/avibactam, an antibiotic recently introduced in the Brazilian market, were also identified in our study (Table 1).

In watch antibiotics, gait disturbance, a worrying event, especially in the elderly, was associated with azithromycin. Suicide attempts with amoxicillin also is a serious and unprecedented potential safety signal. Ineffectiveness, described in other countries, was obtained for azithromycin, cefuroxime, amoxicillin, and amoxicillin/clavulanate (Table 1).

In the access class, we highlight hyperthermia as an event previously described for oxacillin (Table 1).

## Discussion

This first study involving the new Brazilian electronic notification system (Vigimed/VigiFlow) found 294 safety signals associated with disproportionate reporting for antibacterials of the three AWaRe classes. Some signals.

Ceftazidime/avibactam is a new antibiotic that began to be marketed in Brazil in 2018 and that seemed to be well tolerated (Cheng et al., 2020). This drug is restricted to infections with no other therapeutic option and is expected to have a lower frequency of use than other agents (Watch and Access) (World Health Organization, 2019). A study that analyzed adverse events from two phases II and III clinical trials did not report any serious adverse events (Cheng et al., 2020). In the report issued by the EMA in 2021, ceftazidime/avibactam was not related to any safety signal (European Medicines Agency, 2018c). However, we found three potentially serious signals related to ceftazidime-avibactam (Table 1). Other pharmacovigilance databases also received reports of the same ADE for this same drug. Eudravigilance and Vigiaccess contain eight and 19 reports of sepsis associated with the same drug, respectively (European Medicines Agency, 2018c; World Health Organization, 2022b). Five reports for the depressed level of consciousness and 82 for death were described in VigiAccess (World Health Organization, 2022b). Ceftazidime/avibactam was the suspicion drug for

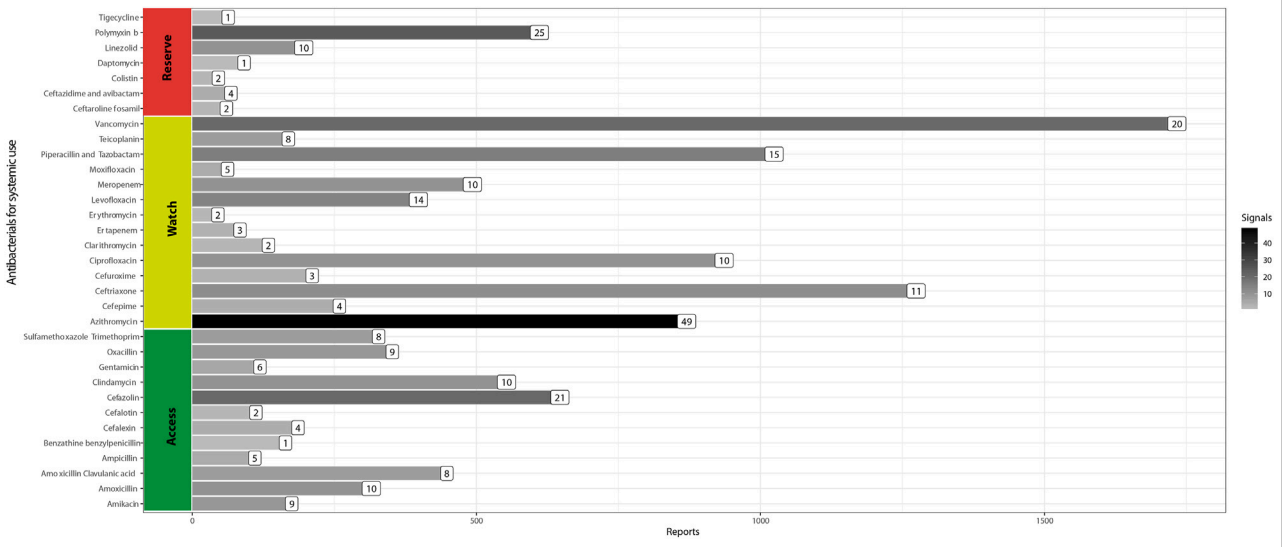


FIGURE 1
Adverse drug event reports and safety signals involving systemic antibacterials (Brazil, 2018–2021).

123 deaths in the FDA Adverse Event Reporting System (FAERS) (Food and Drug Administration, 2021). Nevertheless, data that support the causality for these ADEs are not yet available.

We found many signals of azithromycin associated with infections and immune system disorders. The possible causal relationship between azithromycin and the reported infections has biological plausibility. The pathophysiological mechanism for this adverse effect refers to local microbiota modification by the azithromycin, eliminating bacteria commensals and allowing the growth and proliferation of fungi and opportunistic microorganisms (Seelig, 1966). For example, there is a risk of candidiasis caused by azithromycin (Wilton et al., 2003). Similarly, microbiological imbalance generated by the previous use of antibiotics might cause broad immunity and metabolism changes, leading to the recurrence of infections, such as pneumonia (Francino, 2015). Withal gait disorders contribute to reduced mobility, fall risk, diminished quality of life, and serious injuries, including significant fractures and head trauma (Pirker and Katzenschlager, 2017). Eventually, drugs cause gait disturbance (Kanao-Kanda et al., 2016), but we did not find gait disturbances as an adverse event associated with azithromycin in the medical literature. Nevertheless, a study reported akathisia (ADE typically attributed to antipsychotics) after exposure to azithromycin (Riesselman and El-Mallakh, 2015). Accumulating azithromycin in brain tissue can prove unpredictable effects (Jaruratanasirikul et al., 1996), a possible mechanism by which azithromycin causes gait disturbance. The pandemic caused by COVID-19 increased azithromycin consumption in Brazil (Del Fiol et al., 2022). This scenario may have contributed to the emergence of safety signals not previously observed (Meyboom et al., 1997) (Figure 1).

Our study showed ineffectiveness signals for two antibacterials classified as Watch (cefuroxime and azithromycin) and amoxicillin, azithromycin, and amoxicillin/clavulanate. The preferred terms “ineffective drug,” “therapeutic product effects decreased,” and “pathogen resistance” are triggers for monitoring microbial resistance in pharmacovigilance databases (Habarugira et al., 2021). We expect the investigation of these specific signals in observational studies in the Brazilian population.

We found five previously unreported signals associated with polymyxin B. Depressed level of consciousness and cardiorespiratory arrest may be secondary to hyponatremia, an adverse event associated with polymyxin B previously (Rodriguez et al., 1970). Drug interactions of polymyxin B with other drugs might cause respiratory symptoms, such as neuromuscular blockers and aminoglycosides (Pohlmann, 1966). Furthermore, in 1964, a report on respiratory arrest associated with polymyxin B infusion was published (Small, 1964). To our knowledge, there have been no other similar reports.

We described suicide attempts and amoxicillin as a signal in our analysis. We found no previous report of amoxicillin-related suicidal behavior in the medical literature. However, in the FAERS database, suicide attempt events associated with amoxicillin also were reported ($n$ = 73) (Food and Drug Administration, 2021). Suicidal behavior is heterogeneous and multifactorial, influenced by complex interactions between

TABLE 1 Signals not reported on drug labels or post marketing (Brazil, 2022).

| ATC Code | Drug | ADE | ROR | SDR Intensity | Previous description |
|---|---|---|---|---|---|
| Reserve | | | | | |
| J01DD52 | Ceftazidime/avibactam | Death | 144.77 | a ≥3 a <5 | not described |
| | | Depressed Level of Consciousness | 23.12 | | not described |
| | | Sepsis | 392.15 | | not described |
| J01DF01 | Aztreonam | Tremor | | a>=3 e c = 0 | not described |
| J01XB02 | Polymyxin b | Depressed Level of Consciousness | 6.62 | a ≥5 | not described |
| | | Dyspnoea | 2.69 | | not described |
| | | Acute Respiratory Failure | 16.53 | | not described |
| | | Oxygen Saturation Decreased | 2.51 | | not described |
| | | Cardio-Respiratory Arrest | 4.94 | a ≥3 a <5 | not described |
| J01DI02 | Ceftaroline fosamil | Flushing | 6.47 | a ≥3 a <5 | not described |
| Watch | | | | | |
| J01FA10 | Azithromycin | Oropharyngeal pain | 23.81 | a ≥5 | not described |
| | | Decreased Immune Responsiveness | 5.08 | | not described |
| | | Covid-19 | 16.18 | | not described |
| | | Asthmatic Crisis | 19.5 | | not described |
| | | Immunodeficiency | 81.58 | | not described |
| | | Peripheral Swelling | 81.58 | | not described |
| | | Influenza | 17.53 | | not described |
| | | Drug Ineffective | 2.41 | | Literature[1] |
| | | Gait Disturbance | 10.19 | | not described |
| | | Pneumonia | 7.32 | | not described |
| | | Dysaesthesia | 20.39 | | not described |
| | | Asthma | 18.08 | a ≥3 a <5 | not described |
| | | Depression | 18.08 | | not described |
| | | Dysphonia | 9.04 | | not described |
| | | Dyspepsia | 4.51 | | not described |
| | | Pharyngitis | 20.32 | | not described |
| | | Depressed Mood | 27.12 | | not described |
| | | Urinary Tract Infection | 3.87 | | not described |
| | | Osteoarthritis | 40.65 | | not described |
| | | Weight Decreased | 4.51 | | not described |
| | | Blood Pressure Increased | 8.12 | | not described |
| | | Condition Aggravated | 4.06 | | not described |
| | | Rhinitis | 8.13 | | not described |
| | | Rhinorrhoea | 40.65 | | not described |
| | | Sinusitis | 10.16 | | not described |
| | | Productive Cough | 20.32 | | not described |
| | | Psoriatic Arthropathy | 54.26 | | not described |
| Watch | | | | | |
| J01DD04 | Ceftriaxone | Dyspnoea | 2.03 | a ≥5 | not described |
| | | Phlebitis | 2.67 | | Literature[a] |
| | | Papule | 3.82 | | not described |
| | | Cough | 2.6 | | not described |
| J01FA09 | Clarithromycin | Phlebitis | 5.98 | a ≥5 | Literature[a] |
| J01DC02 | Cefuroxime | Drug Ineffective | 9.02 | a ≥5 | Literature[b] |
| J01MA02 | Ciprofloxacin | Oedema Peripheral | 3.58 | | not described |
| | | Swelling | 2.26 | a ≥3 a <5 | not described |

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TABLE 1 (*Continued*) Signals not reported on drug labels or post marketing (Brazil, 2022).

| ATC Code | Drug | ADE | ROR | SDR Intensity | Previous description |
|---|---|---|---|---|---|
| | | Vomiting | 2.63 | a ≥5 | Literature[c] |
| J01MA12 | Levofloxacin | Anxiety | 4.87 | | Literature[d] |
| | | Miliaria | 6.19 | | not described |
| | | Loss of Consciousness | 46.4 | a ≥3 a <5 | not described |
| | | Skin Lesion | 8.62 | a ≥5 | Literature[d] |
| J01CR05 | Piperacillin and Tazobactam | Angioedema | 2.5 | | not described |
| | | Decreased Appetite | 5.73 | a ≥5 | not described |
| J01XA02 | Teicoplanin | Skin Lesion | 11.3 | | not described |
| | | Lymphopenia | 226.36 | a ≥3 a <5 | not described |
| J01GB01 | Tobramycin | Eyelid Oedema | 40.65 | a ≥3 a <5 | not described |
| J01MA14 | Moxifloxacin | Petechiae | 10.05 | a ≥3 a <5 | not described |
| Access | | | | | |
| J01GB06 | Amikacin | Colitis | 4.41 | a ≥3 a <5 | not described |
| J01CA04 | Amoxicillin | Influenza | 13.17 | a ≥3 a <5 | not described |
| | | Drug Ineffective | 3.21 | | Literature[e] |
| | | Weight Increased | 19.71 | | not described |
| | | Pneumonia | 6.95 | | not described |
| | | Pyrexia | 2.55 | | Literature[c] |
| | | Suicide Attempt | 49.59 | a ≥5 | not described |
| J01CR02 | Amoxicillin Clavulanic acid | Asthenia | 3.42 | a ≥3 a <5 | not described |
| | | Chest Pain | 5.12 | | not described |
| | | Oedema Peripheral | 5.45 | | not described |
| | | Drug Ineffective | 4.89 | a ≥5 | Literature[a] |
| | | Pneumonia | 11.78 | | not described |
| J01DB04 | Cefazolin | Angioedema | 3.42 | a ≥5 | not described |
| | | Bronchospasm | 5.22 | | not described |
| | | Oedema | 3.42 | | not described |
| | | Eyelid Oedema | 4.29 | | not described |
| | | Lip Swelling | 4.2 | | not described |
| | | Laryngeal Oedema | 4.27 | | not described |
| | | Corneal Oedema | 5.07 | | not described |
| | | Hyperhidrosis | 3.13 | | not described |
| | | Papule | 6.27 | | not described |
| Access | | | | | |
| J01DB04 | Cefazolin | Skin Plaque | 8.69 | a ≥3 a <5 | not described |
| | | Tachycardia | 2.81 | | not described |
| | | Sneezing | 15.04 | | not described |
| | | Ocular Pyperaemia | 4.69 | | not described |
| | | Throat Irritation | 7.51 | | not described |
| J01DB03 | Cefalotin | Paraesthesia | 4.07 | a ≥3 a <5 | not described |
| J01FF01 | Clindamycin | Throat Tightness | 13.18 | a ≥3 a <5 | Literature[d] |
| | | Petechiae | 3.04 | a ≥5 | not described |
| J01GB03 | Gentamicin | Petechiae | 3.74 | a ≥3 a <5 | not described |
| J01CF04 | Oxacillin | Eosinophilia | 3.69 | a ≥5 | not described |
| | | Dermatitis | 1.99 | | not described |
| | | Chemical Phlebitis | 7.1 | | Literature[a] |
| | | Pyrexia | 2.68 | | Literature[b,e] |

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TABLE 1 (*Continued*) Signals not reported on drug labels or post marketing (Brazil, 2022).

| ATC Code | Drug | ADE | ROR | SDR Intensity | Previous description |
|---|---|---|---|---|---|
| | | Pruritus | 1.65 | | Literature[a] |
| | | Hyperthermia | 15.05 | a ≥3 a <5 | Literature[b,e] |
| | | Hypoaesthesia | 11.07 | | not described |
| | | Urticaria Papular | 11.7 | | not described |
| J01EE01 | Sulfamethoxazole Trimethoprim | Urinary Tract Infection | 7.6 | a ≥3 a <5 | not described |

ADE, Adverse drug event; ROR, reporting odd ratio; SDR, signal of disproportionate reporting.
[a]Observational cohort study.
[b]Retrospective countrywide.
[c]Narrative review.
[d]Case report.
[e]Pharmacovigilance study.

biological, psychological, and social factors. Some antibiotics cause suicidal ideation by daedal neuropharmacological interactions involving the GABAergic receptor (Samyde et al., 2016). So, the existence of causal relations cannot be ruled out. In the same way, we did not find reports of the pair chest pain or asthenia with amoxicillin and clavulanate, but for this second ADE, there are 1111 reports of suspicion with this drug in the VigiAccess (World Health Organization, 2022b). Despite being an antimicrobial that has been on the market for a long time and is widely used in outpatient settings, the safety signals should be monitored due to its seriousness and the demographic, genetic, and nutritional patterns in different populations (World Health Organization, 2012).

Fluoroquinolones are antibiotics with numerous adverse effects well established by regulatory agencies (Samyde et al., 2016; Agência Nacional de Vigilância Sanitária, 2019; Food and Drug Administration, 2019). Notwithstanding, some ADE might be underestimated. According to levofloxacin labels, the incidence of anxiety associated with the drug occurs in less than 1%, and there is no report of loss of consciousness as a primary event associated with levofloxacin. However, levofloxacin may trigger important neurologic events (Mazzei et al., 2012; Scavone et al., 2020), resulting in loss of consciousness.

We described several signals without any mention in literature for some antibiotics (ceftaroline fosamil, meropenem, ceftriaxone, piperacillin and tazobactam, teicoplanin, tobramycin, moxifloxacin, and cefazolin) in Table 1. Such signals have less relevance for monitoring given their lower severity and lack of information to strengthen the hypothesis of a causal relationship. Despite everything, knowledge about pharmacovigilance is dynamic, and new data may be added in the future.

ANVISA's Pharmacovigilance Management - Gerência de Farmacovigilância (GFARM)- evaluates notifications received at Vigimed/Vigiflow and forwards them to the WHO Uppsala Center. If the Uppsala Center emits any signal, GFARM initiates an investigation process. If the investigation confirms the causality between the event and drug exposure, GFARM alerts health professionals and drug users and establishes complementary regulatory measures (e.g., drug label change) (Agência Nacional de Vigilância Sanitária, 2022a).

We performed an exploratory analysis of crude data from the Vigimed/Vigiflow database to detect safety signals of antibacterials in a marked strategic period by initial reports in this new Brazilian database and increase of this class of drugs consumption for this population (Sartelli et al., 2020). Disproportionality analysis in pharmacovigilance databases is an effective method for the early detection of these signals, especially for rare ADEs (European Medicines Agency, 2022). Nevertheless, this tool has inherent limitations in data mining studies from spontaneous reporting systems. Some ADE may be underreported, and the absence of a clinical history prevents the analysis of the causality of the reported ADE. We use the Reporting Odds Ratio measure, an example of a frequentist approach for Disproportionality Analysis in pharmacovigilance. It is generally accepted that neither bayesian nor frequentist methods are better than the other (Harpaz et al., 2012; Huang et al., 2014). Frequentist approaches are more computationally efficient than Bayesian measures but may generate more false positives. The Bayesian methods also incorporate information about disproportionality and sample size in a single dimension. Nevertheless, none of the approaches can effectively address reporting biases or confounding in spontaneous reporting systems (Harpaz et al., 2012).

Besides that, every disproportionality measure might require a new reinvestigation of data, including pharmacodynamic analysis of biological plausibility (Montastruc et al., 2011). All in all, signal management consists of several pharmacovigilance processes: 1) signal detection, 2) prioritization, 3) validation, 4) evaluation, and 5) outcome documentation (European Medicine Agency, 2018). Although this analysis may have shown serious undetectable signals in other countries, our findings are limited to Brazil.Boletim de Farmacovigilância No13, 2020.

## Conclusion

Antibiotics were widely used during the COVID-19 pandemic, resulting in a suitable scenario to observe unreported safety signals. Our study detected 95 new safety signals. Three serious signals are associated with ceftazidime/avibactam, a drug recently introduced in the Brazilian market. Suicidal behavior was related to the commonly prescribed antibiotic in community infections, amoxicillin. Gait disturbance, a worrying event, especially in the elderly, was associated with azithromycin. Given the seriousness of these potential signals, we suggested further pharmacoepidemiologic studies for more investigation and monitoring by the regulatory agencies.

## Data availability statement

Publicly available datasets were analyzed in this study. This data can be found here: https://www.gov.br/anvisa/pt-br/acessoainformacao/dadosabertos/informacoes-analiticas/notificacoes-de-farmacovigilancia.

## Author contributions

LB, FS, and EL conceived and presented the idea. LB and AS were responsible for data collection. LB and FS were responsible for the statistical analysis. AS, AC-A, LB, and EL performed data analysis. All authors discussed the results and contributed to the final manuscript.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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# Medically assisted reproduction and the risk of being born small and very small for gestational age: Assessing prematurity status as an effect modifier

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Over the last decade, the use of medically assisted reproduction (MAR) has steadily increased but controversy remains with regards to its risks. We aimed to quantify the risk of being born small for gestational age (SGA) and very SGA (VSGA) associated with MARs overall and by type, namely ovarian stimulators (OS) and assisted reproductive technology (ART). We conducted a cohort study within the Quebec Pregnancy Cohort. Pregnancies coinciding with Quebec's MAR reimbursement PROGRAM period (2010–2014) with a singleton liveborn were considered. MAR was first defined dichotomously, using spontaneous conception as the reference, and categorized into three subgroups: OS alone (categorized as clomiphene and non-clomiphene OS), ART, OS/ART combined. SGA was defined as being born with a birth weight below the 10th percentile based on sex and gestational age (GA), estimated using populational curves in Canada, while VSGA was defined as being born with a birth weight below the 3rd percentile. We then estimated odds ratios (OR) for the association between MAR and SGA as well as VSGA using generalized estimated equation (GEE) models, adjusted for potential confounders (aOR). Two independent models were conducted considering MAR exposure overall, and MAR subgroup categories, using spontaneous conceptions as the reference. The impact of prematurity status (less than 37 weeks gestation) as an effect modifier in these associations was assessed by evaluating them among term and preterm pregnancies separately. A total of 57,631 pregnancies met inclusion criteria and were considered. During the study period, 2,062 women were exposed to MARs: 420 to OS alone, 557 to ART, and 1,085 to OS/ART combined. While no association was observed between MAR and SGA nor VSGA in the study population, MAR was associated with an increased risk for SGA (aOR 1.69, 95% CI 1.08–2.66; 25 exposed cases) among preterm pregnancies; no increased risk of SGA was observed in term pregnancies. MARs are known to increase the risk of preterm birth and our results further confirm that they also increase the risk of SGA among preterm pregnancies.

KEYWORDS

assisted reproduction, perinatal health, perinatal adverse outcomes, obstetrics-high risk, pharmacoepidemiology, effect modifier, epidemiology methods, prematurity

# Introduction

Infertility affects 11.5%–15.7% of women (Bushnik et al., 2012); 8%–20% of couples reported having difficulties conceiving (Hull et al., 1985; Thonneau et al., 1991; Case, 2003; Oakley et al., 2008), and 8%–30% of infertility remain unexplained (European Society for Human Reproduction and Embryology, 1996). Fertility treatments are defined as procedures of medically assisted reproduction (MAR) and include *in vitro* fertilization (IVF), intrauterine insemination (IUI), and ovarian stimulators (OS) (Zegers-Hochschild et al., 2009). We refer to procedures handling oocytes and/or sperm, or embryos to induce a pregnancy as assisted reproductive technology (ART) (Zegers-Hochschild et al., 2009).

In August of 2010, Quebec was the first Canadian province to put in place a universal reimbursement program for MAR. Through the implementation of this program, decision makers aimed to 1) help infertile/subfertile couples procreate, 2) reduce multiplicity with the application of a single embryo transfer policy, and 3) increase Quebec's birth rate (Salois, 2014). The program was halted in October of 2014 following a higher than expected rise in healthcare expenditure. While the program was active in Quebec, no surveillance program was put in place, and as such this made it difficult to establish patterns of MAR use and the impact on these methods on both maternal and perinatal health. Although the Canadian ART Register (CARTR) is in place, it mainly focuses on ART which would exclude OS and IUI, which are both widely used as first line practice to induce pregnancy.

More than eight million children have been conceived specifically through IVF worldwide since the first IVF baby, Louise Brown, was conceived in 1978 (reported in 2019) (Fauser, 2019). A systematic review looking at existing registries reporting ART utilization has described the trends between 2004 and 2013 (Kushnir et al., 2017). During this period, across centers including Australia, the United Kingdom, the United States, Canada, and Japan, over seven million ART cycles resulting in over 1.4 million live-births have been reported (Kushnir et al., 2017). More specifically, CARTR reports demonstrates that ART use has steadily increased, having more than tripled in the last decade (Gunby, 2011), reporting 35,347 cycles in 2019 and 30,764 in 2020 across Canada (CFAS, 2020). ART-conceptions have significantly increased because of the universal reimbursement program; specifically, 2% of all Quebec pregnancies resulted from IVF in 2012-13 versus 1.2% in 2009-10 (Salois, 2014). It was thus foreseeable that all MARs have increased during this time-period in Quebec.

In 2016, 8% of children were born small for their gestational age (SGA) in Canada (Shiraz El Adam et al., 2022). SGA is a composite measure of gestational age and birth weight. A child born SGA ranks among the lowest 10th percentile for their gestational-age specific birth weight according to population-based references (Kramer et al., 2001). Using the same references, a child born VSGA ranks among the lowest 3rd percentile (Kramer et al., 2001). Given that SGA and VSGA are composite measures that account for gestational age at birth, they are known to be a better marker for child development during pregnancy, as opposed to measuring birth weight alone, for example, (Ananth and Platt, 2004).

Our team established that MARs increase the risk of prematurity when compared to spontaneous conception, which is also a known association in the literature (Gorgui and Bérard, 2018; Gorgui et al., 2020). However, the association between MARs and SGA is not well studied and there is limited information on non-IVF MARs such as OS alone and ART methods. For example, when comparing IVF-conceived singletons to those who were spontaneously conceived, studies observed a 1.4-1.6 fold increase in the risk of SGA among IVF singletons (Helmerhorst et al., 2004; Jackson et al., 2004; Katalinic et al., 2004). An additional study published in the United Kingdom found that IVF significantly increased the risk of SGA by two-fold when compared to spontaneous conception (Governent of the United Kingtom, 2010).

MAR conceptions remain on the rise and given the changes in the political landscape in Quebec and the possibility of a new reimbursement program is on the political agenda. Given the significant consequences of SGA and VSGA on children's health and development, our aim was to quantify the association between MARs and SGA primarily as well as VSGA. Additionally, given the known association between prematurity status and MAR (Gorgui et al., 2020), we aimed to assess if prematurity was an effect modifier in these associations. Our hypothesis is that MARs may be associated with an increased risk of SGA and/or VSGA specifically among those born preterm. Lastly, we aimed to quantify this association specifically among women exposed to OS, ART, and OS/ART combined to adjust for confounding by indication, namely infertility/subfertility (Malloy, 2002).

# Materials and methods

## Data source

We conducted a cohort study within the Quebec Pregnancy Cohort (QPC). The QPC is a population-based cohort with prospective data collection which is built through the linkage of three Quebec databases; namely, 1) Régie de l'Assurance Maladie du Québec (RAMQ), which includes medical

services/procedures and pharmaceutical service database (including drug name, start date, dosage, duration, prescribers), 2) MED-ECHO, which includes hospitalization archives data [International Classification of Disease—9th/10th revision (ICD-9 and 10) diagnostic codes, interventions, procedures, and consultations, gestational age], and lastly 3) Institut de la Statistique du Québec (ISQ), which includes sociodemographic data, birth weight, and gestational age. Through a unique patient encrypted identifier, data from each of these databases were linked. All pregnancies of women covered by the Quebec public prescription drug insurance plan that have occurred between 01/1998 and 12/2015 are included in the QPC. Data on mothers and children following the end of pregnancy are also collected, as such, the QPC provides a prospective follow-up from at least 1 year prior to the first day of gestation (1DG), during the entirety of the pregnancy, and until 12/2015. The 1DG is defined as the first day of the last menstrual period. This information is validated against ultrasound measures, which are obtained through patients' charts (Vilain et al., 2008). The QPC and its' data sources are described in further detail in Berard and Sheehy (2014).

## Study population

A pregnancy was eligible if the date of conception occurred between 05/08/2010 and 15/11/2014; was covered by the RAMQ drug plan 1 year before and during pregnancy; and resulted in a singleton liveborn. We specifically chose to study the time-period of 08/2010-11/2014, as the Quebec universal MAR reimbursement program was active at that time. Multiple pregnancies were excluded, because MARs increase the risk of multiplicity and as such could be a potential effect modifier in the association between MAR and SGA, as it is in the causal pathway of the association between MAR and prematurity (Goldenberg et al., 2008). In addition, given that single embryo transfer was enforced during the Quebec MAR reimbursement period, we aimed to study the association between MAR and SGA within a real life experiment. We excluded pregnancies exposed to known fetotoxic medications during pregnancy (Supplementary Table S1) (Koren et al., 1998; Kulaga et al., 2009).

## Study design

A cohort study was performed within eligible pregnancies in the QPC.

## Exposure

MAR was defined as any procedures including egg harvesting, IVF, IUI or at least one prescription filling for OS (clomiphene, estradiol, progesterone, gonadotropins, chorionic gonadotrophin, leuprolide, citorelix, ganirelix, follitropin, choriogonadotropin-α) occurring within 2 months prior to and 1 month after the 1DG (Supplementary Tables S2, S3). We chose to include a 2-month time-window prior to the 1DG to ensure that the studied pregnancy resulted from the identified MAR procedure or OS use. Additionally, we added 1 month following the 1DG to account for late billings by physicians, as the QPC contains data collected mainly for reimbursement purposes (RAMQ for prescription filling and MAR procedures).

We first assessed MAR overall and then categorized MAR in three subgroups as OS alone, ART alone, and OS/ART combined, using pregnancies with spontaneous conception as the reference. Subsequently, we also stratified OS use alone as clomiphene only users and non-users, which is the most commonly prescribed OS in the clinical setting.

## Outcome

SGA is a composite measure of birth weight and gestational age. We identified cases of SGA by using data on gestational age at delivery as well as birth weight and newborn sex. Gestational age and birth weight have been validated against patients' charts (Vilain et al., 2008). SGA was defined as newborns being among the lowest 10th percentile for birth weight according to gestational age and sex using Canadian population-based references (Kramer et al., 2001). Additionally, we looked at very SGA (VSGA) which is defined as newborns being among the lowest 3rd percentile of birth weight according to gestational age and sex using Canadian population-based references (Kramer et al., 2001). Prematurity status was defined using the definition by the World Health Organisation based on gestational age at birth which had to occur before 37 completed weeks of gestation (World Health Organization, 2016). We used the MedEcho database validated against measures in patients charts in addition to the statistics database in order to define SGA (Vilain et al., 2008).

## Covariates

We selected the following potential covariates based on their association with the use of MAR or because they have been reported as risk factors for SGA: 1) Sociodemographic variables on the 1DG including maternal age, receipt of welfare, area of residence (urban vs. rural); 2) Previous pregnancy in the year before the 1DG, ending in delivery, abortion or miscarriage; 3) Maternal history of chronic comorbidities during the year before the 1DG and until the end of the 1st trimester, namely hypertension and diabetes as diagnoses for these conditions are often only obtained at the start of a clinical follow-up

(i.e., during pregnancy follow-up with a general practitioner or obstetrician), 4) Depression/anxiety, asthma, thyroid disorders, epilepsy, coagulopathies, infections and other medication use for conditions other than those described were measured in the year before the 1DG; 5) Obesity and smoking were measured during the year before the 1DG and during pregnancy as these variables are likely reported at prenatal visits. We used a combination of ICD-9 and ICD-10 codes as well as prescription fillings related to the studied health conditions to measure all covariates pertaining to maternal conditions described above in section (4) (Supplementary Table S4).

## Pregnancy complications

Premature birth and therefore SGA/VSGA may also occur due to a number of complications in pregnancy such as premature rupture of membranes, placental dysfunction or preterm labor. MAR-pregnancies are at an increased risk for these complications (Nagata et al., 2019), and as such these variables are in the causal pathway of the studied association. Though we are unable to adjust for them in our multivariate models, we have measured them in compared groups in order to assess if they may be involved in the obtained results.

## Statistical analyses

We performed descriptive statistics to compare MAR conceived and spontaneous conception pregnancies in terms of covariate status. The unit of analysis was a pregnancy. We performed *t*-tests and $X^2$ for continuous and categorical variables, respectively. Pregnancy complications [premature rupture of membranes, placental dysfunction, preterm labor (Supplementary Table S5)] were compared between groups. We estimated crude as well as adjusted odds ratios (ORs and aORs) and 95% confidence intervals (95% CI) to measure the association between MAR and SGA as well as VSGA, with spontaneous conception as reference, using generalized estimated equation (GEE) models. Adjustments were performed to account for potential confounding variables identified above. Using GEE models allows us to account for inter- and intra-pregnancy variability as women could have contributed more than one pregnancy during the study period. Furthermore, in order to assess if prematurity status is an effect modifier in these associations, we performed our main analyses in a cohort comprised of term births and in a cohort comprised of preterm births. By definition, effect modification would occur if the association between MAR and SGA as well as VSGA differs depending on third variable, which in this instance would be prematurity status (Rothman et al., 2008). We hypothesized that babies born preterm would be more at risk of being born SGA and/or VSGA.

In our secondary analysis, we estimated the association between SGA and categories of MAR, namely OS alone (subsequently categorized as clomiphene users vs. non-users), ART alone, ART/OS combined and the risk of SGA. We also estimated the association between subcategories of MAR (OS alone, ART alone, ART/OS combined) and VSGA. For this secondary analysis, we used spontaneous conception as the reference. This sub-categorized analysis was the first method we used to account for the underlying subfertility/infertility, as the severity would differ among exposure categories.

Lastly, we performed sensitivity analyses within a sub-cohort of MAR-exposed women to account for potential confounding by the underlying subfertility/infertility, which would be the main indication for conception through MARs. The restriction to this sub-cohort allows to determine if the association between MAR and SGA is independent of subfertility/infertility. Statistical analyses were performed using SAS (SAS Institute Inc., Version 9.4, Cary, NC).

## Ethics approval

This study was approved by the Quebec Data Access Agency (Commission d'accès à l'information—CAI) and the CHU Sainte-Justine Institutional Review Board. Additionally, the CAI has authorized the linkage between databases composing the QPC.

# Results

Overall, 57,631 singleton pregnancies met inclusion criteria and were considered for analyses; 2,062 (3.6%) were pregnancies conceived through MARs and 55,569 (96.4%) through spontaneous conception (Figure 1). Among all MAR conceptions, 420 (20.4%) women were exposed to OS alone among which 302 women were exposed to clomiphene only, 557 (27.0%) to ART, and 1,085 (52.7%) to OS/ART combined (Figure 2). Among OS alone users, the majority used clomiphene [302 (71.90%)]. Among MAR conceptions, 202 (9.81%) resulted in SGA babies while 5,364 (9.65%) resulted in SGA among those who did not have MAR (Figure 1).

Among MAR conceptions, women were more likely to be older (≥35 years old), welfare recipients, which are known risk factors for prematurity, low birth weight and as such SGA (Table 1) than women with spontaneous conception (SC). MAR conceived babies were born more preterm and with lower birth weights (Table 1). No differences were observed across profiles of maternal comorbidities (e.g., depression, anxiety, epilepsy) which are known risk factors for SGA, except for the history of polycystic ovarian syndrome (Table 1). There were no differences between MAR conceptions and SC women in regard to complications during

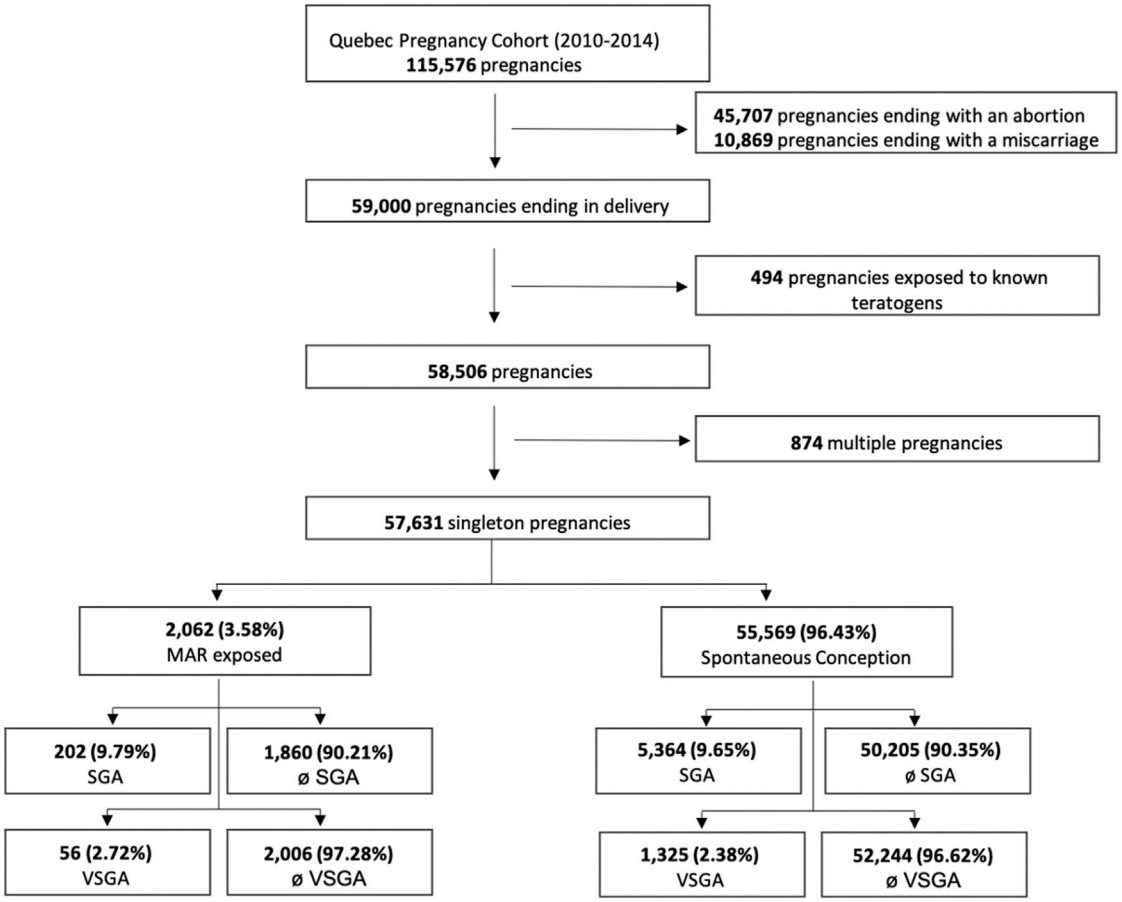


FIGURE 1
Flowchart of the selection process of the study population. MAR, medically assited reproduction; SGA, small for gestational age; VSGAI, very small for gestational age.

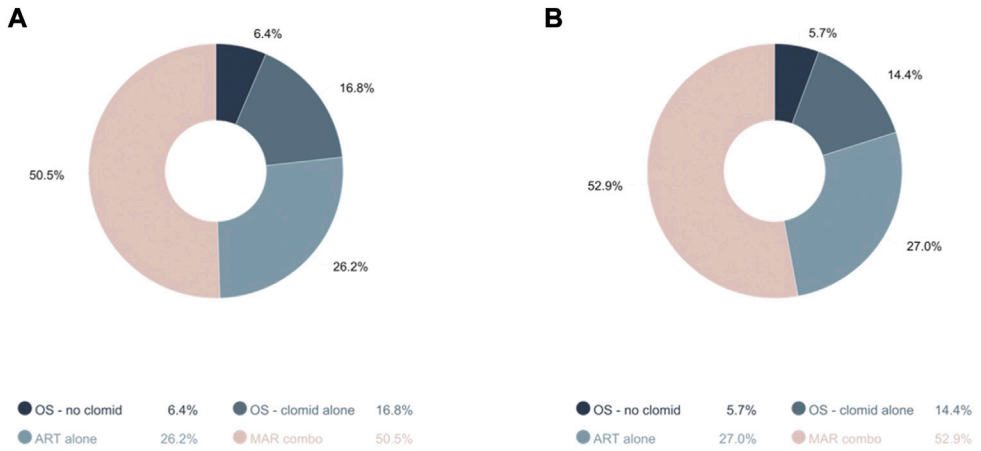


FIGURE 2
Distribution of MAR categories among **(A)** pregnancies resulting in SGA (*n* = 202) and **(B)** non-SGA babies (*n* = 1,860). Legend: ART, assisted reproduction techniques; MAR, medically assisted reproduction; OS, ovarian stimulators; SGA, small for gestational age.

TABLE 1 Characteristics of the study population.

| | MAR conception (n = 2,062) | Spontaneous conception (n = 55,569) | *p*-value[a] |
|---|---|---|---|
| Sociodemographic characteristics | | | |
| Maternal characteristics | | | |
| Maternal age, years—(mean ± SD) | 32.64 ± 5.37 | 29.01 ± 5.60 | **<0.001** |
| Maternal age, years | | | |
| <25 | 4 (0.19) | 441 (0.79) | |
| 25–35 | 147 (7.13) | 12,369 (22.26) | |
| 35–40 | 1,111 (53.87) | 33,015 (59.41) | |
| ≥40 | 800 (38.80) | 9,744 (17.54) | **<0.001** |
| Welfare recipient | 227 (11.01) | 10,621 (19.11) | **<0.001** |
| Urban dweller | 1,775 (86.21) | 45,908 (82.61) | **<0.001** |
| Pregnancy and child characteristics | | | |
| Pregnancy characteristics | | | |
| Preterm delivery (<37 weeks gestation) | 183 (8.87) | 3,496 (6.29) | **<0.001** |
| Low birth weight (<2500 g) | 141 (6.84) | 2,787 (5.02) | **<0.001** |
| Small for gestational age (<10th percentile) | 202 (9.81) | 5,364 (9.65) | 0.81 |
| Very small for gestational age (<3rd percentile) | 56 (4.06) | 1,325 (2.38) | **<0.001** |
| Gestational age at delivery (weeks) | 38.65 ± 2.05 | 38.86 ± 1.73 | **<0.001** |
| Child characteristics | | | |
| Male sex | 1,063 (51.63) | 28,559 (51.39) | 0.83 |
| Birth weight, grams—(mean ± SD) | 3,298.43 ± 583.70 | 3,340.26 ± 526.63 | **<0.001** |
| Maternal comorbidities measured in the 12 months before the 1DG[b] | | | |
| Diabetes | 72 (3.50) | 2,187 (3.94) | 0.31 |
| Hypertension | 25 (1.21) | 681 (1.23) | 0.96 |
| Obesity | 42 (2.04) | 1332 (2.40) | 0.30 |
| Asthma | 164 (7.97) | 4,965 (8.93) | 0.13 |
| Epilepsy | 25 (1.21) | 647 (1.16) | 0.84 |
| Smoking dependence | 38 (1.85) | 1,098 (1.98) | 0.67 |
| Infection | 629 (30.55) | 16,296 (29.32) | 0.23 |
| Polycystic ovarian syndrome | 6 (0.29) | 62 (0.11) | **0.02** |
| Thyroid disease | 77 (3.74) | 2,421 (4.36) | 0.18 |
| Depression/anxiety | 247 (12.00) | 7,180 (12.92) | 0.22 |
| Coagulopathy | 12 (0.58) | 211 (0.38) | 0.25 |
| Previous pregnancy | 227 (11.02) | 6,631 (11.93) | 0.21 |
| Any other medication use[c] | | | |
| None | 1,446 (70.13) | 39,661 (71.37) | |
| 1 | 386 (18.72) | 9,814 (17.66) | |
| 2-3 | 189 (9.17) | 4,934 (8.88) | |
| 4+ | 41 (1.98) | 1,160 (2.09) | 0.48 |
| Pregnancy complications measured in the 12 months before the 1DG | | | |
| Premature rupture of membranes | 103 (5.00) | 3,114 (5.60) | 0.24 |
| Placental dysfunction | 13 (0.63) | 293 (0.53) | 0.52 |
| Preterm Labor | 21 (1.02) | 551 (0.99) | 0.90 |
| Bleeding | 43 (2.09) | 1,353 (2.43) | 0.32 |
| Utilization of healthcare services | | | |
| Follow-up by obstetrician,[d] | 1,210 (58.77) | 31,984 (57.55) | 0.27 |
| Follow-up by general practitioner or specialist[d] | 1,223 (59.40) | 31,925 (57.45) | 0.08 |
| Hospitalization and/or emergency visit[e] | 818 (39.73) | 21,311 (39.73) | 0.21 |

Legend: 1DG, first day of gestation; ART, assisted reproduction techniques; MAR, medically assisted reproduction; OR, odds ratio; OS, ovarian stimulators.
Bold values represent significant, $p < 0.005$.
[a]$p$ value calculated to compared term births to preterm births using Pearson $\chi 2$ test for categorical variable and a $t$ test for continuous variables.
[b]Diagnoses are based on ICD-10 codes and/or a filled prescription in relation to the comorbidity.
[c]Excludes all prescription fillings included in the definitions of all considered comorbidities above.
[d]Defined as five visits or more during the course of the pregnancy.
[e]During the 12 months before the 1DG.

TABLE 2 Use of medically assisted reproduction and the risk of being born small for gestational age overall and by subtype among the main cohort ($n$ = 57,631).

| | SGA ($n$ = 5,565) | No SGA ($n$ = 52,065) | Crude OR (95% CI) | Adjusted OR* (95% CI) | Adjusted OR** (95% CI) |
|---|---|---|---|---|---|
| MAR use overall | | | | | |
| Spontaneous conception | 5,364 (96.39) | 50,205 (96.43) | 1.00 | 1.00 | 1.00 |
| MAR conception | 202 (3.61) | 1,860 (3.57) | 1.01 (0.87–1.17) | 1.08 (0.93–1.25) | 1.09 (0.94–1.27) |
| MAR use by subtype | | | | | |
| Spontaneous conception | 5,364 (96.39) | 50,205 (96.43) | 1.00 | 1.00 | — |
| ART alone | 53 (0.95) | 504 (0.96) | 1.00 (0.76–1.32) | 1.10 (0.83–1.45) | |
| OS alone | 47 (0.84) | 373 (0.72) | 1.20 (0.89–1.62) | 1.23 (0.91–1.66) | |
| OS and ART combined | 102 (1.83) | 983 (1.89) | 0.94 (0.76–1.16) | 1.01 (0.82–1.24) | |

Legend: 1DG, first day of gestation; ART, assisted reproduction techniques; CI, confidence interval; MAR, medically assistedreproduction; OR, odds ratio; OS, ovarian stimulators.
*Adjusted for sociodemographic variables (maternal age, urban dwelling, welfare recipient) as well as maternal comorbidities measured within 12 months prior to the 1DG (hypertension, diabetes, polycystic ovarian syndrome, asthma, epilepsy, depression/anxiety, coagulopathy, infection, and other medication use) and during pregnancy (smoking, obesity). **Adjusted including propensity score prediction using the same variables as those used in the multivariate model.

the current pregnancy (premature rupture of membranes, placental dysfunction, and PT labor—Table 1) nor in their patterns of utilization of healthcare services, which we measured through the use of medication (any medication that was not used to define a comorbidity as above) as well as the follow-up by obstetrician or hospitalization/emergency visit (Table 1). Of note, given that variables measured during pregnancy are more likely to be in the causal pathway between MAR and SGA such as pregnancy complications (e.g., premature rupture of membranes, placental dysfunction, PT labor) (Nagata et al., 2019) we did not adjust for them in all subsequent models.

## Association between medically assisted reproductions and small for gestational age in the main cohort

Adjusting for potential confounders, we found no association between MAR conception and the risk of SGA (aOR 1.08, 95% CI 0.93–1.25, 202 exposed cases) when compared to spontaneous conception (Table 2). We additionally included a propensity score prediction model using the same variables as those used in the multivariate model and found the same result (aOR 1.09, 95% CI 0.94–1.27, 202 exposed cases) (Table 2). Upon categorizing the exposure to MARs, we found that the exposure to OS alone seemed to have a stronger association, although not statistically significant (aOR 1.23, 95% CI 0.91–1.66, 47 exposed cases) (Table 2). Furthermore, when recategorizing OS exposure as clomiphene use or other OS, we can see that the association between clomiphene, the most used OS, and SGA is the strongest when compared to SC, without reaching the desired level of statistical significance (aOR 1.22, 95% CI 0.86–1.73, 34 exposed cases) (Table 3).

## Association between medically assisted reproductions and very small for gestational age in the main cohort

Adjusting for potential confounders, we found no association between MAR conception and the risk of VSGA (aOR 1.20, 95% CI 0.92–1.58, 56 exposed cases) when compared to SC (Table 4). Upon categorizing the exposure to MARs, we found that the exposure to OS alone significantly increased the risk of VSGA (aOR 1.66, 95% CI 1.01–2.72, 16 exposed cases) (Table 5).

## Prematurity status as an effect modifier in the association between medically assisted reproduction and small for gestational age as well as very small for gestational age

To assess if prematurity status is an effect modifier in the studied associations, we performed our analyses stratified on this

TABLE 3 Use of medically assisted reproduction and the risk of being born small for gestational age based on a secondary classification of exposure among the main cohort (*n* = 57,632).

| MAR use by subtype | SGA (*n* = 5,566) | Crude OR (95% CI) | Adjusted OR* (95% CI) |
|---|---|---|---|
| Spontaneous conception | 5,364 (96.37) | 1.00 | 1.00 |
| OS alone (excluding clomid) | 13 (0.23) | 1.17 (0.67–2.06) | 1.16 (0.66–2.05) |
| Clomid alone | 34 (0.61) | 1.21 (0.85–1.72) | 1.22 (0.86–1.73) |
| ART alone | 53 (0.95) | 1.00 (0.76–1.32) | 1.05 (0.79–1.42) |
| OS and ART combined | 102 (1.83) | 0.94 (0.76–1.16) | 0.96 (0.78–1.18) |

Legend: 1DG, first day of gestation; ART, assisted reproduction techniques; CI, confidence interval; MAR, medically assisted reproduction; OR, odds ratio; OS, ovarian stimulators; SGA, small for gestational age. *Adjusted for sociodemographic variables (urban dwelling, welfare recipient) as well as maternal comorbidities measured within 12 months prior to the 1DG (polycystic ovarian syndrome) and during the 1st trimester of pregnancy (hypertension, diabetes).

TABLE 4 Use of medically assisted reproduction and the risk of being born very small for gestational age overall and by subtype among the main cohort (*n* = 57,631).

| MAR use overall | VSGA (*n* = 1,381) | No VSGA (*n* = 56,251) | Crude OR (95% CI) | Adjusted OR* (95% CI) |
|---|---|---|---|---|
| Spontaneous conception | 1,325 (95.94%) | 54,244 (96.43%) | 1.00 | 1.00 |
| MAR conception | 56 (4.06%) | 2,006 (3.57%) | 1.14 (0.87–1.50) | 1.20 (0.92–1.58) |

Legend: 1DG, first day of gestation; ART, assisted reproduction techniques; CI, confidence interval; MAR, medically assistedreproduction; OR, odds ratio; OS, ovarian stimulators. *Adjusted for sociodemographic variables (maternal age, urban dwelling, welfare recipient) as well as maternal comorbidities measured within 12 months prior to the 1DG (hypertension, diabetes, asthma, depression/anxiety, infection, and other medication use) and during pregnancy (obesity).

TABLE 5 Use of medically assisted reproduction and the risk of being born very small for gestational age based on a secondary classification of exposure among the main cohort (*n* = 57,632).

| MAR use by subtype | VSGA (*n* = 1,381) | No VSGA (*n* = 1,381) | Crude OR (95% CI) | Adjusted OR* (95% CI) |
|---|---|---|---|---|
| Spontaneous conception | 1,325 (95.94%) | 52,244 (96.43%) | 1.00 | 1.00 |
| OS | 16 (1.16%) | 407 (0.72%) | 1.62 (0.99–2.66) | 1.66 (1.01–2.72) |
| ART alone | 3 (0.22%) | 147 (0.26%) | 0.85 (0.27–2.64) | 0.92 (0.29–2.87) |
| OS and ART combined | 37 (2.68%) | 1,452 (2.58%) | 1.03 (0.74–1.43) | 1.10 (0.79–1.54) |

Legend: 1DG, first day of gestation; ART, assisted reproduction techniques; CI, confidence interval; MAR, medically assisted reproduction; OR, odds ratio; OS, ovarian stimulators; VSGA, very small for gestational age. *Adjusted for sociodemographic variables (urban dwelling, welfare recipient) as well as maternal comorbidities measured within 12 months prior to the 1DG (asthma, epilepsy, thyroid disease, depression/anxiety, and other medication use) and during the 1st trimester of pregnancy (hypertension, diabetes).

status. No association was identified between MAR and SGA (aOR 1.03, 95% CI 0.88–1.21, 177 exposed cases) (Table 6a) nor between MAR and VSGA (aOR 1.15, 95% CI 0.89–1.62, 48 exposed cases) in the term cohort (Table 7a). However, in the preterm cohort, MAR was associated with a significantly increased risk of SGA (aOR 1.69, 95% CI 1.08–2.66, 25 exposed cases) (Table 6b). Though we did not observe a significant association between MAR and VSGA in the preterm cohort likely due to lack of power, we do observe results in the same range (aOR 1.61, 95% CI 0.76–3.42, eight exposed cases) (Table 7b). These results suggest that prematurity status is indeed an effect modifier in the association between MAR and SGA as well as VSGA given the difference in the point estimates compared to those obtained in the main unstratified cohort (results above).

## Confounding by indication

To address confounding by indication in the main association, we performed two sensitivity analyses in which we performed the same main analyses as shown above in a restricted study cohort of women exposed to MARs overall (*n* = 2,062). Similarly to the results reported above, we found no

TABLE 6 Use of medically assisted reproduction and the risk of being born small for gestational age stratified among term(a) and preterm (b) births ($n$ = 57,631).

| (a) Term cohort ($n$ = 53,952) | SGA ($n$ = 5,200) | No SGA ($n$ = 48,752) | Crude OR (95% CI) | Adjusted OR* (95% CI) |
|---|---|---|---|---|
| MAR use overall | | | | |
| Spontaneous conception | 5,023 (96.6%) | 47,050 (96.5%) | 1.00 | 1.00 |
| MAR conception | 177 (3.4%) | 1,702 (3.5%) | 0.97 (0.83–1.14) | 1.03 (0.88–1.21) |
| **(b) Preterm cohort** ($n$ = 3,679) | **SGA ($n$ = 366)** | **No SGA ($n$ = 3,313)** | **Crude OR (95% CI)** | **Adjusted OR* (95% CI)** |
| MAR use overall | | | | |
| Spontaneous conception | 341 (93.2%) | 3,155 (95.2%) | 1.00 | 1.00 |
| MAR conception | 25 (6.8%) | 158 (4.8%) | 1.46 (0.95–2.58) | 1.69 (1.08–2.66) |

Legend: 1DG, first day of gestation; ART, assisted reproduction techniques; CI, confidence interval; MAR, medically assistedreproduction; OR, odds ratio.*Adjusted for sociodemographic variables (maternal age, urban dwelling, welfare recipient) as well as maternal comorbidities measured within 12 months prior to the 1DG (hypertension, diabetes, asthma, depression/anxiety, infection, and other medication use) and during pregnancy (smoking, obesity).

TABLE 7 Use of medically assisted reproduction and the risk of being born very small for gestational age stratified among term (a) and preterm (b) births ($n$ = 57,631).

| (a) Term cohort ($n$ = 53,952) | VSGA ($n$ = 1,267) | No VSGA (n = 52,685) | Crude OR (95% CI) | Adjusted OR** (95% CI) |
|---|---|---|---|---|
| MAR use overall | | | | |
| Spontaneous conception | 1,219 (96.21%) | 50,845 (96.52%) | 1.00 | 1.00 |
| MAR conception | 48 (3.79%) | 1,831 (3.48%) | 1.09 (0.81–1.45) | 1.15 (0.89–1.62) |
| **(b) Preterm cohort ($n$ = 3,679)** | **VSGA ($n$ = 114)** | **No VSGA (n = 3,565)** | **Crude OR (95% CI)** | **Adjusted OR** (95% CI)** |
| MAR use overall | | | | |
| Spontaneous conception | 106 (92.98%) | 3,390 (95.09%) | 1.00 | 1.00 |
| MAR conception | 8 (7.02%) | 175 (4.91%) | 1.46 (0.70–3.05) | 1.61 (0.76–3.42) |

Legend: 1DG, first day of gestation; CI, confidence interval; MAR, medically assisted reproduction; OR, odds ratio; VSGA, very small for gestational age. **Adjusted for sociodemographic variables (urban dwelling, welfare recipient) and maternal age.

TABLE 8 Use of medically assisted reproduction and the risk of being born small for gestational age by subtype among a cohort of women exposed to medically assisted reproduction ($n$ = 2,062).

| MAR use by subtype | SGA ($n$ = 202) | Crude OR (95% CI) | Adjusted OR* (95% CI) |
|---|---|---|---|
| OS alone | 47 (23.27) | 1.00 | 1.00 |
| ART alone | 53 (26.24) | 0.84 (0.55–1.27) | 0.85 (0.56–1.29) |
| OS and ART combined | 102 (50.50) | 0.83 (0.57–1.19) | 0.83 (0.58–1.20) |

Legend: 1DG, first day of gestation; ART, assisted reproduction techniques; CI, confidence interval; MAR, medically assistedreproduction; OR, odds ratio; OS, ovarian stimulators; SGA, small for gestational age. *Adjusted for sociodemographic variables (urban dwelling, welfare recipient) as well as maternal comorbidities measured within 12 months prior to the 1DG and during the 1st trimester of pregnancy (hypertension and diabetes).

association between exposure to any subcategory of MAR and the risk of SGA (Tables 8, 9).

## Discussion

The prevalence of SGA in our study cohort was (5,566/57,631) 9.66% 9.80% overall, which is higher than the last reported prevalence of 6.10% in Canada. This finding could be attributed to both increased prematurity and MAR conceptions during the study period, specifically in our study population (CARTR Canadian, 2016; Gorgui et al., 2020).

Adjusting for potential confounders, we found no significant association between MAR and SGA as well as VSGA in the main cohort (Tables 2, 4). According to a systematic review and meta-analysis conducted by Jackson *et al.* SGA increased by 1.6-fold

TABLE 9 Use of medically assisted reproduction and the risk of being born small for gestational age based on a secondary classification of exposure among a cohort of women exposed to medically assisted reproduction ($n$ = 2,062).

| MAR use by subtype | SGA ($n$ = 202) | Crude OR (95% CI) | Adjusted OR* (95% CI) |
|---|---|---|---|
| OS alone (excluding clomid) | 13 (6.44) | 1.00 | 1.00 |
| Clomid alone | 34 (16.83) | 1.02 (0.52–2.01) | 1.04 (0.52–2.08) |
| ART alone | 53 (26.24) | 0.85 (0.45–1.62) | 0.88 (0.46–1.68) |
| OS and ART combined | 102 (50.49) | 0.84 (0.46–1.54) | 0.86 (0.47–1.59) |

Legend: 1DG, first day of gestation; ART, assisted reproduction techniques; CI, confidence interval; MAR, medically assisted reproduction; OR, odds ratio; OS, ovarian stimulators; SGA, small for gestational age. *Adjusted for sociodemographic variables (urban dwelling, welfare recipient) as well as maternal comorbidities measured within 12 months prior to the 1DG and during the 1st trimester of pregnancy (hypertension and diabetes).

(OR 1.6, 95% CI 1.3–2.0) with IVF-conceptions compared to SC (Helmerhorst et al., 2004; Jackson et al., 2004). It is important to note however that some individual studies had strong significant associations, while a number of other studies found no association similarly to our current findings (Helmerhorst et al., 2004; Jackson et al., 2004). As such, our findings are in line with the literature and further add to the body of evidence to support an association between MAR and VSGA, which has not yet been studied. We performed sensitivity analyses in order to adjust for potential confounding by the underlying infertility. Results were the same as in our main analyses, suggesting that our findings are robust (Tables 7, 9). Additionally, we performed a *post hoc* sample size calculation and determined that we have more than the needed sample ($n$ = 984) to observe a significant difference of 2% between groups. For reference, the incidence of SGA in IVF (included in our MAR subgroup) pregnancies is estimated around 8%, while it is estimated around 4% in the spontaneously conceived pregnancies (Slavov et al., 2021), hence the conservative choice for a 2% difference in the power calculation above.

When looking at the main cohort, we did not find an association between categories of MARs and SGA, though OS seem to be playing a role in an increased risk of SGA (aOR 1.23, 95% CI 0.91–1.66, 47 exposed cases) (Table 2). Through our analyses, we saw that OS use increases the risk of VSGA (aOR 1.66, 95% CI 1.01–2.72, 16 exposed cases) (Table 5) and may also be playing a role in the association between MARs and SGA (aOR 1.23, 95% CI 0.91–1.66, 47 exposed cases) (Table 2) Exposure to OS has been associated with SGA when compared with SC (RR, 1.71; 95% CI: 1.09–2.69) (Governent of the United Kingtom, 2010), as well as both with (Chung et al., 2006; Mitwally et al., 2006; Imudia et al., 2012) and without IVF (van der Spuy et al., 1988; D'Angelo et al., 2011) yielding similar results. It has been hypothesized in this context that alteration in oocyte quality, decreased receptivity of the endometrium or the production of a poor implantation environment may play a role in this finding. These could be mediated in part through increased estradiol levels, which would impair the implantation process (Kondapalli and Perales-Puchalt, 2013). This hypothesis has been further been confirmed in animal studies (Kondapalli and Perales-Puchalt, 2013).

Basing ourselves on the fact that we had previously identified an association between MAR and prematurity in our data (Gorgui et al., 2020) and knowing that prematurity and SGA/VSGA have the same risk factors, we acknowledge the fact that prematurity may be an effect modifier in the association between MAR and SGA/VSGA. This was imperative to assess as both outcomes increase morbidity and mortality in children. To our knowledge, this study is the first to assess the impact of the prematurity in this association. In fact, our results have demonstrated that the prematurity status is indeed an effect modifier in the association between MAR and SGA as well as VSGA (Tables 6, 7). This is a novel finding in the context of the era of MAR use and suggests that it may be clinically important to make the distinction between MAR babies born term and preterm when assessing their perinatal outcomes, including SGA/VSGA. To further support our conclusion, a study conducted by Clausson et al. (1998) using the Swedish Medical Birth Register first identified the importance to subdivide SGA status based on gestational age as they observed higher mortality rates among preterm-SGA babies.

## Strengths and limitations

Through the QPC, the outcomes and exposures we measure have previously been validated. MARs were defined as a prescription filling or medical procedures. Our research team has previously validated prescription fillings for antidepressants and antibiotics among others against maternal reports in the QPC (positive and negative predictive values > 87%) (Zhao et al., 2017). Though we are aware that prescription fillings do not exactly reflect treatment intake and that we have not specifically validated OS use, we believe that in the context of infertility where the desire to get pregnant is present, we are measuring our exposure to OS appropriately. Furthermore, we used

procedure codes to defined MARs (excluding OS) which are reliable given that they are used for billing purposes by physicians. Additionally, gestational age, which defines our main outcomes in part, has been validated (Vilain et al., 2008). We have also used the most updated population-based reference in Canada for growth curves to measure SGA/VSGA (Kramer et al., 2001) and used the birth weight which is obtained through the ISQ. This data has been compared to medical records and found to be reliable (Vilain et al., 2008; Berard and Sheehy, 2014).

Though we have adjusted for a number of potential confounders, it is important to understand that due to the nature of the analysis, some relevant variables of parameters occurring during pregnancy cannot be taken into account. In the context of the studied association, variables such as infections, premature rupture of membranes, placental issues could be relevant to account for, as they may explain slower development *in utero* and consequently affect birth weight, but are in the causal pathway between MARs and SGA. However, in order to measure the potential impact of these variables, we compared them between our exposure groups and did not find any differences (Table 1). As such, we believe that accounting for these variables is unlikely to modify our estimates.

Our study is limited by the absence of information on the underlying causes of infertility and on the paternal implications in the couple's infertility as this is a mother-child cohort. Additionally, it is difficult to diagnose infertility and for the most part is poorly reported, especially when considering hat 30% of cases remain unexplained (European Society for Human Reproduction and Embryology, 1996). Despite the lack of information on the reasons for infertility due to the nature of the collected data, we aimed to address the potential for indication bias this by performing a number of sensitivity analyses among a sub-cohort of women exposed to MARs, and found similar results to those obtained in the main cohort. This suggests that despite accounting for the underlying infertility through this cohort restriction, no association exists between MARs and SGA prior to stratification on prematurity status.

The universal reimbursement program for MAR allowed an important number of women insured by the public program for their medications (usually of lower socioeconomic status) to resort to MARs. We are aware that the generalizability of our results could be affected as the QPC is not able to capture MAR exposures in the private sector. The private sector grants access to MARs to those with higher family incomes and therefore more likely to have private insurance for their medication. As such, the QPC is unable to capture these women and their exposure. Though this would allow for a higher sample size, we believe that the impact of this on the generalizability of our results would be minimal as our team has demonstrated that women insured by the public and private sectors had similar profiles, through a validation study (Berard and Lacasse, 2009).

## Conclusion

Conception through MAR was not associated with an increased risk of SGA nor VSGA compared to SC in the main cohort. However, prematurity status was revealed to be an effect modifier in this association as MAR increased the risk of SGA among preterm birth. Given the continuous rise in infertility and MAR use as well as the changes in the current political landscape which could lead to increased access to these methods, it is important for physicians and their patients to be aware of the particularity of babies born preterm, which additionally may lead them to have an increased risk of being born SGA.

## Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

## Author contributions

All authors contributed in the study design and in the data interpretation. JG did the analyses under the supervision of OS and AB. JG wrote the first draft of the manuscript which was then revised by all authors.

## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2022.904885/full#supplementary-material

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# The association of gabapentin initiation and neurocognitive changes in older adults with normal cognition

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**Background:** Gabapentin is increasingly prescribed to older adults, which raises concerns about its potential to cause neurocognitive changes. Therefore, we aimed to examine the association of gabapentin use with neurocognitive changes (i.e., cognitive decline, functional status decline, and motor function change) in older adults.

**Methods:** We conducted a retrospective cohort study using the National Alzheimer's Coordinating Center Uniform Data Set (UDS; September 2005-March 2021 data freeze). From the eligible sample (≥age 65 years), we identified cognitively normal new-users of gabapentin and the visit they initiated gabapentin (i.e., index visit). Initiators were matched to randomly selected nonusers on year of UDS enrollment and visit number from enrollment to index. Cognitive decline was defined as any increase in the Clinical Dementia Rating global score (CDRGLOB) and as a 1-point increase in CDR sum of boxes (CDR-SB). Functional status decline was defined as a 3-point increase in the sum of the Functional Activities Questionnaire (FAQ) and as 0.3-point increase in mean FAQ. Decline in motor function was defined as new clinician reports of gait disorder, falls, and slowness. To mitigate confounding and selection bias, we used joint stabilized inverse probability of treatment weights and stabilized inverse probability of censoring weights. All analyses were conducted comparing index to index+1 and index+2 visits.

**Results:** From the eligible UDS participants (N = 23,059), we included 480 initiators (mean age [SD]: 78.7 [6.9]; male 34.4%); 4,320 nonusers (78.3 [7.0]; 34.4%). Gabapentin initiation was significantly associated with cognitive/functional status decline: worsening CDRGLOB at index+1 visit (odds ratio [95% confidence interval]: 1.55 [1.07, 2.25]); CDR-SB at index+1 visit (1.94 [1.22, 3.09]); and mean of FAQ at index+2 visit (1.78 [1.12, 2.83]). After excluding initiators with extant motor dysfunction (n = 21), we identified 459 initiators (78.7 [6.9]; 34.0%) and 4,131 nonusers (78.2 [6.9]; 34.7%); in this sample, gabapentin initiation was associated with increased falls at the index+2 visit (2.51 [1.19, 5.31]).

**Conclusion:** Gabapentin initiation was significantly associated with deleterious neurocognitive changes among older adults with initially normal cognition. Further studies are needed to examine the risk/benefit of prescribing gabapentin in older adults.

KEYWORDS

**gabapentin, older adults, NACC data, cognitive decline, functional status change, motor function change**

# 1 Introduction

Gabapentin was first approved by the United States (US) Food and Drug Administration (FDA) in 1993 to treat partial seizures and additionally approved for postherpetic neuralgia in 2004 (Pfizer, 2017). By 2018, gabapentin was the 6th most prescribed medication in the US market (IQVIA Institute for human data science, 2019). Increasing evidence suggests potential for gabapentin misuse and related adverse events (e.g., respiratory depression, sedation, physical dependence, and depression) (Gomes et al., 2017; Slavova et al., 2018; Tomko et al., 2018; McAnally et al., 2020; Evoy et al., 2021). Therefore, FDA announced a safety concern of severe breathing difficulties when gabapentin is used concurrently with opioids and other CNS depressants (U.S. Food and Drug Administration, 2019). Further, gabapentin was added to the American Geriatrics Society Beers criteria in 2019 as a medication to avoid using with opioids due to higher risks of sedation, respiratory depression, and death (By the 2019 American Geriatrics Society Beers Criteria® Update Expert Panel, 2019).

Older adults have age-related decreases in liver and kidney function (ElDesoky, 2007) and have a high chance of polypharmacy (Charlesworth et al., 2015), thus they could be more vulnerable to adverse effects associated with gabapentin. Using Medical Expenditure Panel Survey data, Johansen et al. reported that gabapentin use increased from 2002 to 2015 in adults age 65 and older (Johansen, 2018). Most gabapentin prescribing is known to be off-label indications, such as neuropathic pain, migraines, substance use disorder, and treatment for psychiatric symptoms (Botts and Raskind, 1999; Frye et al., 2000; Pande et al., 2000; Mathew et al., 2001; Gentry et al., 2002; Moore et al., 2018). Especially in older adults, gabapentin is prescribed to treat behavioral and psychological symptoms of dementia (BPSD) (Kim et al., 2008). Several studies have reported that gabapentin has a deleterious effect on cognition (Leach et al., 1997; Meador et al., 1999; Shem et al., 2018). A prospective observational cohort study has reported that gabapentin initiators with spinal cord injury had a cognitive decrease using neuropsychological tests. However, this study had a small sample size and no control group (Shem et al., 2018). In a randomized crossover study, gabapentin use was associated with worse attention/vigilance, ability to voluntarily maintain wakefulness, and cognitive processing and motor speed in healthy adults (Meador et al., 1999). However, other randomized studies (length of follow-up: 2 weeks (minimum); 26 weeks (maximum)) have reported that gabapentin was not associated with cognitive decline or impairment in patients with partial seizures (Dodrill et al., 1999) nor in healthy adults (Martin et al., 1999; Salinsky et al., 2002).

The association of gabapentin use and neurocognitive change is not well understood, and given how frequently gabapentin is prescribed, it is important to fully examine the benefit and risk of gabapentin use in older adults. The aim of this study was to estimate the association of gabapentin initiation with changes in cognitive status, functional status, and motor changes up to 2 years later, in older adults with initially normal cognition.

# 2 Methods

## 2.1 Data set and participants

The study data was drawn from the National Alzheimer's Coordinating Center's (NACC) Uniform Data Set (UDS) from 2005 to March 2021. NACC was first established in 1999 to aggregate and share data collected at National Institute on Aging-funded Alzheimer's Disease Research Centers (ADRCs) and conduct research related to AD (Morris et al., 2006). Beginning in September 2005, a standard data collection protocol called the Uniform Data Set (UDS) was implemented at all ADRCs. Currently, there are more than 1100 published studies using NACC data which is collected across 26 states (The National Alzheimer's Coordinating Center, 2022). Data submitted to NACC undergo a robust quality control process that assesses conflicting, missing, and impossible values, both within and across study visits, before they are shared with researchers. Approximately annually the participants' information, such as demographics, medical history, cognitive and functional status, and behavioral symptoms, was collected by trained interviewers and clinicians; participants comprise a range of cognitive status, including normal cognition, mild cognitive impairment (MCI), and dementia. For the current study, participants 65 years and older at the time of enrollment in one of the 42 participating ADRCs were included (Figure 1).

## 2.2 Study design

From the eligible cohort, we selected all participants who reported use of gabapentin, and the index visit was defined as the

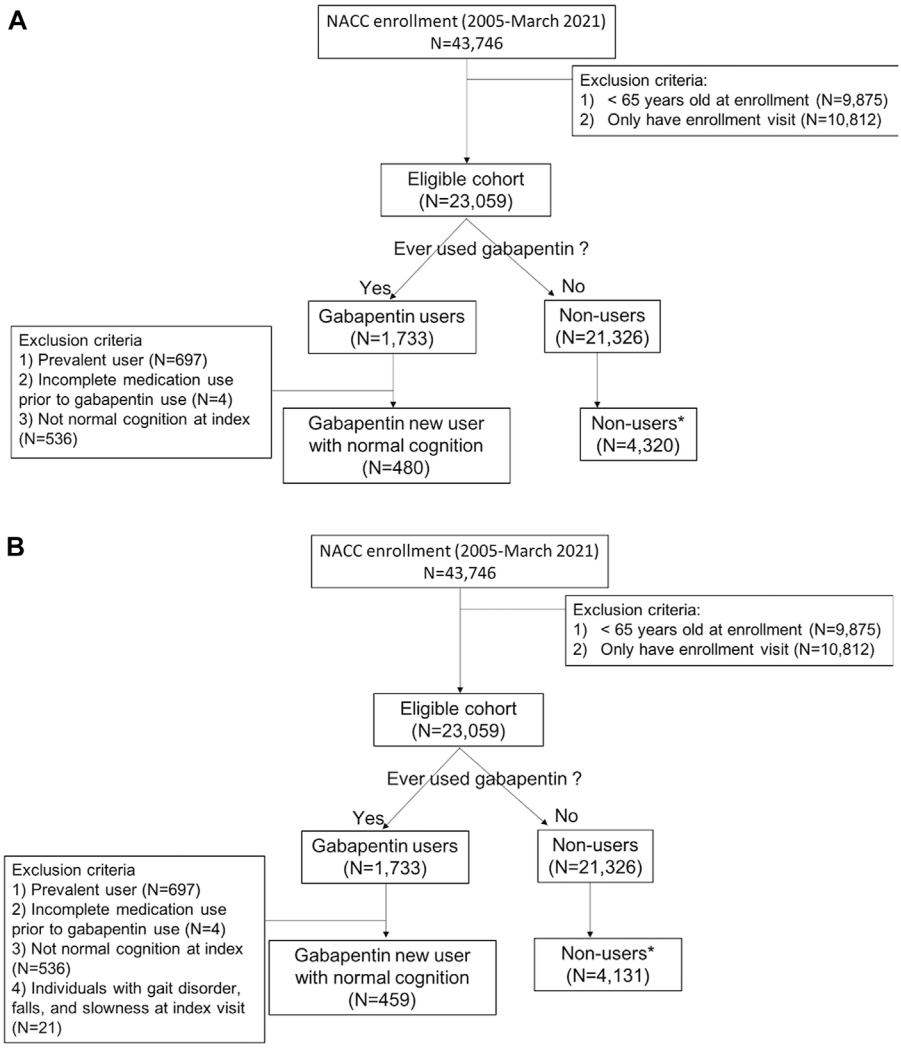


FIGURE 1
Flow diagram of inclusion and exclusion criteria **(A)** for measuring cognitive and functional status decline and **(B)** for measuring motor function change*1 to 9 randomly selected matched by year of first enrollment and visit number to gabapentin initiation from the enrollment.

first reported gabapentin use (Figure 2). We next excluded gabapentin users who: 1) reported gabapentin use at their first UDS visit (prevalent users); 2) had incomplete medication information prior to the index visit; and 3) had any syndromic cognitive diagnosis other than "normal" at the index visit. We excluded the prevalent users to minimize prevalent-user bias, and we implemented a new-user design (Ray, 2003). Once the gabapentin initiators were identified, non-users were randomly selected (1 to 9 ratio) with replacement (i.e., a non-user was allowed to be selected as a comparator multiple times, with each being assigned a different index visit). To minimize bias (e.g., secular trends, survival bias, and attrition bias) due to the long duration of study time (2005–2021), non-users were matched on the year of first enrollment and the number of visits from enrollment to gabapentin initiation to new-users. Non-users were subject to the same exclusion criteria as the gabapentin new-users. For the analyses of motor change, we selected a separate cohort, imposing the additional restriction of no reported motor dysfunction at the index visit [Figure 1, panels A (cognitive and functional outcomes) and B (motor outcomes)].

## 2.3 Gabapentin use determination

Medication use in the UDS is operationalized *via* an interview that asks participants to report all medications, including prescriptions and over-the-counter medications,

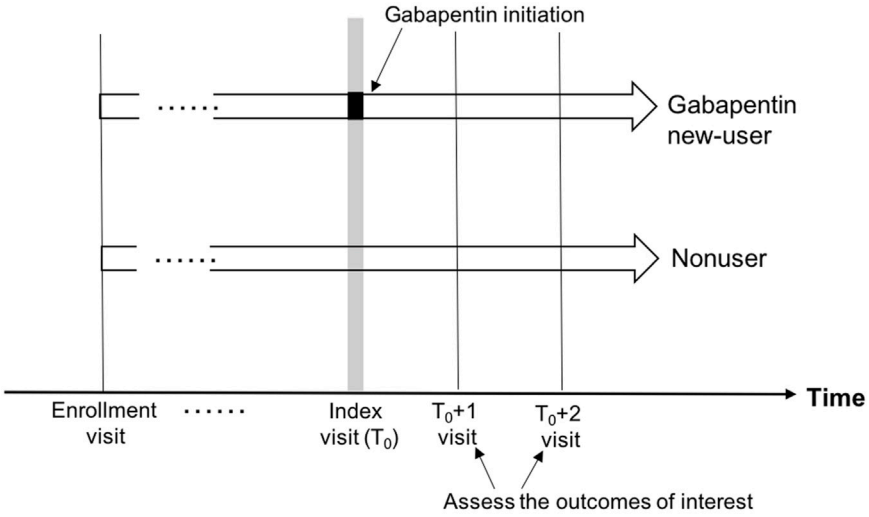


FIGURE 2
Depiction of study design comparing gabapentin initiators and nonusers.

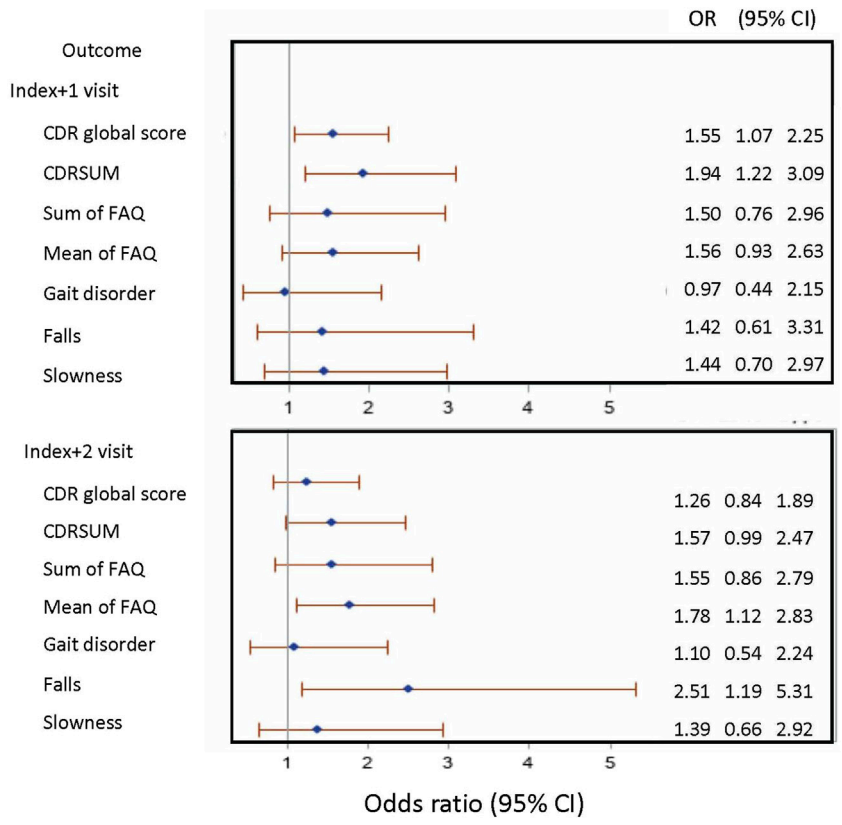


FIGURE 3
Forest plot presenting the odds ratio (95% confidence interval) of outcomes of interest in gabapentin new-users compared to non-users. Note: CDR: Clinical Dementia Rating; CDRSUM: Clinical Dementia Rating sum of boxes; FAQ: Functional Activities Questionnaire; OR: odds ratio; CI: confidence interval.

they have used in the 2 weeks preceding their annual study visit. Gabapentin use was defined as any reported use of gabapentin. Data on indication and dose are not available in the NACC data.

## 2.4 Outcomes description

The outcomes of interest, including cognitive decline, functional status decline, and motor function change, were measured at the first (approximately 1 year later: index+1) and second (approximately 2 years later: index+2) follow-up visits after the index visit (Figure 2).

### 2.4.1 Cognitive decline

Global cognition, measured by the Clinical Dementia Rating global score (CDRGLOB) and sum of boxes (CDR-SB), was assessed at each UDS visit. CDRGLOB is a ordinal rating with five levels (0: no dementia; 0.5: questionable dementia; 1: mild dementia; 2: moderate dementia; and 3: severe dementia) (Morris, 1993). CDR-SB is the sum of the six domain scores (memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care; range from 0 to 18). With the goal of detecting clinically significant decline, we used two definitions to classify participants as showing cognitive decline: compared to the index visit (1) a higher score of CDRGLOB and (2) a 1-point increase of CDR-SB at follow-up. These definitions were based on a previous analysis of the NACC dataset that determined clinically important changes in cognitive status (Andrews et al., 2019).

### 2.4.2 Functional status decline

Functional status was measured with the Functional Activities Questionnaire (FAQ). The participants or co-participants were asked whether the participant had any difficulty or needed help with ten instrumental activities of daily living (e.g., paying bills, assembling tax records, shopping alone for groceries, playing games, turning off the stove, preparing a balanced meal, keeping track of current events, understanding a TV program, remembering appointments, and driving). Each category was scored as 0: normal; 1: has difficulty, but does by self; 2: requires assistance; and 3: dependent. The functional status of each participant in this study was measured through total FAQ score, which includes the participants who did not have missing in any of the ten categories (72% of the total study sample), and the mean of FAQ score, which includes the participants who had a score in any of ten categories (Teng et al., 2010). The participants were categorized as showing functional status decline from the index to the first follow-up or second follow-up after the index visit if they had at least a 3-point increase in their sum of FAQ (Andrews et al., 2019) or 0.3 points increase in their mean of FAQ.

### 2.4.3 Motor function change

Motor change was measured by clinician ratings of gait disorder, falls, and slowness.

## 2.5 Covariates

Confounders included in the propensity score model for inverse probability of treatment weighting were selected using directed acyclic graphs (DAG) (Textor et al., 2011). For measuring cognitive and functional status decline, confounders included demographics (age, sex, education, and race); body mass index (BMI); smoking history; comorbidities (depression, diabetes, and hypertension); medications (opioids, antipsychotics, and benzodiazepines); and *APOE* e4 allele status (Supplementary Figure S1). For measuring motor function change, confounders included demographics (age, sex, education, and race); body mass index; smoking history; comorbidities (depression, diabetes, Parkinson's disease, and anxiety); and medications (opioids, antiseizures, and anxiolytic, sedative, and hypnotics) (Supplementary Figure S2).

The baseline characteristics (except for smoking history [at least 100 cigarettes over lifetime], diabetes, and hypertension) of gabapentin initiators and non-users were measured at the index visit. Some medical history variables (smoking history, diabetes, and hypertension) were only collected at the first UDS visit for each participant. Detailed descriptions for covariates included in this study are in the supplementary (Supplementary Table S1). Briefly, medical history was collected at annual visits *via* a structured interview with a study clinician, querying participants on the presence of diagnosed medical conditions.

## 2.6 Statistical analysis

To mitigate confounding and selection bias, we used joint stabilized inverse probability of treatment weights (SIPTW) and stabilized inverse probability of censoring weights (SIPCW) (Austin and Stuart, 2015). Using SIPTW, we created a balanced distribution of the measured confounders between the initiators and non-users. Since some participants had no follow-up visit after the index (i.e., censored), we generated SIPCW, and the SIPCW were multiplied by SIPTW to obtain joint weights. The weighted population is called the "pseudo-population". In the pseudo-population, the conditional probability of gabapentin initiation is independent of the measured confounders, and the conditional probability of having a follow-up visit is independent of the confounders and gabapentin initiation (Austin and Stuart, 2015). We assessed the success of the weighting procedure by examining the distribution of the weights as well as the standardized mean differences of the measured confounders between initiators and non-users in unweighted and weighted samples (Supplementary

TABLE 1 Baseline characteristics in gabapentin new-users and non-users.

| | Cognitive decline and functional status change analysis | | | Motor function change analysis | | |
|---|---|---|---|---|---|---|
| | New-users (N = 480) | Nonusers (N = 4320) | *p* value | New-users (N = 459) | Nonusers (N = 4131) | *p* value |
| Year of enrollment N (%) | | | | | | |
| 2005 | 28 (5.8) | 252 (5.8) | | 28 (6.1) | 252 (6.1) | |
| 2006 | 125 (26.0) | 1125 (26.0) | | 119 (25.9) | 1071 (25.9) | |
| 2007 | 59 (12.3) | 531 (12.3) | | 56 (12.2) | 504 (12.2) | |
| 2008 | 25 (5.2) | 225 (5.2) | | 25 (5.5) | 225 (5.5) | |
| 2009 | 36 (7.5) | 324 (7.5) | | 36 (7.8) | 324 (7.8) | |
| 2010 | 34 (7.1) | 306 (7.5) | | 31 (6.8) | 279 (6.8) | |
| 2011 | 24 (5.0) | 216 (5.0) | | 23 (5.0) | 207 (5.0) | |
| 2012 | 36 (7.5) | 324 (7.5) | | 36 (7.8) | 324 (7.8) | |
| 2013 | 25 (5.2) | 225 (5.2) | | 24 (5.2) | 216 (5.2) | |
| 2014 | 23 (4.8) | 207 (4.8) | | 22 (4.8) | 198 (4.8) | |
| 2015 | 24 (5.0) | 216 (5.0) | | 23 (5.0) | 207 (5.0) | |
| 2016 | 14 (2.9) | 126 (2.9) | | 10 (2.2) | 90 (2.2) | |
| 2017 | 17 (3.5) | 153 (3.5) | | 16 (3.5) | 144 (3.5) | |
| 2018 | 7 (1.5) | 63 (1.5) | | 7 (1.5) | 63 (1.5) | |
| 2019 | 3 (0.6) | 27 (0.6) | | 3 (0.7) | 27 (0.7) | |
| Age N (%) | | | 0.57 | | | 0.29 |
| 65–74 (years) | 150 (31.3) | 1453 (33.6) | | 141 (30.7) | 1419 (34.4) | |
| 75–84 (years) | 225 (46.9) | 1960 (45.4) | | 216 (47.1) | 1861 (45.1) | |
| 85+ (years) | 105 (21.9) | 907 (21.0) | | 102 (22.2) | 851 (20.6) | |
| Male gender N (%) | 165 (34.4) | 1484 (34.4) | 0.99 | 156 (34.0) | 1434 (34.7) | 0.76 |
| Race N (%) | | | 0.24 | | | 0.18 |
| White | 377 (78.5) | 3518 (81.4) | | 358 (78.0) | 3363 (81.4) | |
| Black | 87 (18.1) | 656 (15.2) | | 86 (18.7) | 638 (15.4) | |
| Other | 16 (3.3) | 146 (3.4) | | 15 (3.3) | 130 (3.2) | |
| Education N (%) | | | <0.0001 | | | <0.0001 |
| High school or less | 115 (24.0) | 645 (14.9) | | 110 (24.0) | 653 (15.8) | |
| College degree | 192 (40.0) | 1847 (42.8) | | 184 (40.1) | 1735 (42.0) | |
| Graduate degree | 173 (36.0) | 1821 (42.2) | | 165 (36.0) | 1734 (42.0) | |
| Unknown | 0 (0) | 7 (0.2) | | 0 (0) | 9 (0.2) | |
| Diabetes N (%) | | | <0.0001 | | | <0.0001 |
| Yes | 106 (22.1) | 512 (11.9) | | 103 (22.4) | 485 (11.7) | |
| Unknown | 165 (34.4) | 1624 (37.6) | | 150 (32.7) | 1500 (36.3) | |
| Hypertension N (%) | | | 0.005 | | | 0.002 |
| Yes | 306 (63.8) | 2441 (56.5) | | 296 (64.5) | 2315 (56.0) | |
| Unknown | 96 (20.0) | 948 (21.9) | | 87 (19.0) | 928 (22.5) | |
| Smoking history N (%) | | | 0.06 | | | 0.024 |
| Yes | 244 (50.8) | 1965 (45.5) | | 234 (51.0) | 1849 (44.8) | |
| Unknown | 2 (0.4) | 37 (0.9) | | 2 (0.4) | 42 (1.0) | |
| Depression N (%) | 62 (12.9) | 339 (7.9) | <0.0001 | 59 (12.9) | 294 (7.1) | <0.0001 |
| Parkinson's disease N (%) | 7 (1.5) | 24 (0.6) | | 2 (0.4) | 23 (0.6) | |
| Anxiety in the last month N (%) | | | 0.02 | | | |
| Yes | 51 (10.6) | 325 (7.5) | | 46 (10.0) | 294 (7.1) | |
| Unknown | 41 (8.5) | 303 (7.0) | | 38 (8.3) | 273 (6.6) | |

(Continued on following page)

TABLE 1 (*Continued*) Baseline characteristics in gabapentin new-users and non-users.

| | Cognitive decline and functional status change analysis | | | Motor function change analysis | | |
|---|---|---|---|---|---|---|
| | New-users (N = 480) | Nonusers (N = 4320) | *p* value | New-users (N = 459) | Nonusers (N = 4131) | *p* value |
| Opioid N (%) | 98 (20.4) | 178 (4.1) | <0.0001 | 93 (20.3) | 169 (4.1) | <0.0001 |
| Antipsychotics N (%) | | | 0.33 | | | 0.36 |
| Yes | 5 (1.0) | 23 (0.5) | | 5 (1.1) | 26 (0.6) | |
| Unknown | 0 (0) | 4 (0.1) | | 0 (0) | 6 (0.2) | |
| Benzodiazepines N (%) | 52 (10.8) | 223 (5.2) | <0.0001 | 50 (10.9) | 228 (5.5) | <0.0001 |
| Anxiolytic, sedative, and hypnotics N (%) | | | <0.0001 | | | <0.0001 |
| Yes | 104 (21.7) | 478 (11.1) | | 101 (22.0) | 468 (11.3) | |
| Unknown | 0 (0) | 4 (0.1) | | 0 (0) | 6 (0.2) | |
| Antiseizures N (%) | 27 (5.6) | 96 (2.2) | <0.0001 | 27 (5.9) | 96 (2.3) | <0.0001 |
| Body Mass Index N (%) | | | <0.0001 | | | 0.0009 |
| Normal | 119 (24.8) | 1467 (34.0) | | 115 (25.1) | 1326 (32.1) | |
| Overweight | 165 (34.4) | 1413 (32.7) | | 160 (34.9) | 1453 (35.2) | |
| Obese | 140 (29.2) | 921 (21.3) | | 132 (28.8) | 881 (21.3) | |
| Underweight | 3 (0.6) | 47 (1.1) | | 3 (0.7) | 58 (1.4) | |
| Unknown | 53 (11.0) | 472 (10.9) | | 49 (10.7) | 413 (10.0) | |
| APOE e4 genotype N (%) | | | 0.44 | | | 0.46 |
| Yes | 113 (23.5) | 1128 (26.1) | | 108 (23.5) | 1048 (25.4) | |
| Unknown | 35 (7.3) | 285 (6.6) | | 34 (7.4) | 256 (6.2) | |

Table S2). To obtain robust standard errors to account for the weighting, as well as to account for within-participant correlation for nonusers matched to more than one initiator, we used generalized estimating equations with an exchangeable working correlation structure to fit logistic regression models to the data.

# 3 Results

## 3.1 Cognitive decline

Among eligible ADRC participants with UDS data (N = 23,059), 480 gabapentin new-users (mean age [SD]: 78.7 [6.9]; male gender = 34.4%) were identified, and 4,320 nonusers (78.3 [7.0]; 34.4%) were randomly selected (Figure 1A). The mean (SD) number of annual visits between the first UDS visit and the index visit was 4.8 (2.8). Gabapentin initiators had less educational attainment (36.0% vs. 42.2% for graduate degree), had more comorbidities (diabetes: 22.1% vs. 11.9%; hypertension: 63.8% vs. 56.5%; depression: 12.9% vs. 7.9%), were taking more medications (opioids: 20.4% vs. 4.1%; benzodiazepines: 10.8% vs. 5.2%), and had higher BMI (≥30: 29.2% vs. 21.3%) compared to nonusers (Table 1). Among nonusers, 79.6% and 62.1% had the first and the second follow-up visit after index, respectively. Among gabapentin new-users who had the first (N [%]: 383 [79.8%]) and second (280 [58.3%]) follow-up visits after index, 58.5% and 50.0% reported gabapentin use at the first and second follow-up visits after index, respectively, After applying the joint weights, the measured confounders were balanced (standardized mean difference <0.1) between the new-users and nonusers (Supplementary Table S2). At the first follow-up visit after index, the association of gabapentin initiation with cognitive decline was statistically significant in CDRGLOB (OR [95% CI]: 1.55 [1.07, 2.25] and in CDR-SB (1.94 [1.22, 3.09]. At the second follow-up visit after index, the ORs were in the same direction but attenuated (CDRGLOB: 1.26 [0.84, 1.89]; CDR-SB: 1.57 [0.99, 2.47]) (Figure 3).

## 3.2 Functional status decline

The same sample was used for assessing functional status change as measuring cognitive decline (Figure 1A). At the first visit after index, the association of gabapentin initiation with functional decline was not significant for either change in FAQ sum (OR [95% CI]: 1.50 [0.76, 2.96]) or FAQ mean (1.56 [0.93, 2.63]). At the second follow-up visit after index, the association of gabapentin initiation and decline in mean FAQ was statistically significant (1.78 [1.12, 2.83]) (Figure 3).

### 3.3 Motor function change

For measuring motor function change, participants who had gait disorders, falls, or slowness at the index visit were excluded from the sample. We identified 459 gabapentin new-users (78.7 [6.9]; 34.0%), and randomly selected 4,131 nonusers (78.2 [6.9]; 34.7%) (Figure 1B). Since only a small number of gabapentin initiators had motor dysfunction at index (n = 21), the mean (SD) number of annual visits between the first UDS visit and the index visit remained 4.8 (2.8). Gabapentin initiators reported more anxiety in the last month (new-users vs. non-user: 10.0% vs. 7.1%) and were more likely to have smoking history (i.e., at least 100 cigarettes) (51.0% vs. 44.8%), and to report using anxiolytic, sedative, and hypnotics (22.0% vs. 11.3%) and antiseizure medications (5.9% vs. 2.3%) than non-users (Table 1).

The association of gabapentin initiation with gait disorder was close to null at both the first (OR [95% CI]: 0.97 [0.44, 2.15]) and the second follow-up visit (1.10 [0.54, 2.24]) after index. For slowness, our results indicated increased odds of slowness in gabapentin initiators at the first (1.44 [0.70, 2.97]) and at the second follow-up visit after index (1.39 [0.66, 2.92]), but the results were not statistically significant. For falls, the association with gabapentin initiation was statistically significant (2.51 [1.19, 5.31]) at the second follow-up visit after index. At the first follow-up visit after index, the association of gabapentin initiation with falls was not statistically significant but was in the same direction (1.42 [0.61, 3.31]) (Figure 3).

## 4 Discussion

Using data from longitudinally followed cognitively normal older adult research volunteers, this study examined the association of gabapentin initiation with neurocognitive outcomes. Our results provide evidence that gabapentin was associated with increased odds of global cognitive decline, functional status decline, and motor function change (e.g., falls and slowness) in the 2 years following gabapentin initiation.

The results from this study are consistent with previous studies that found gabapentin use was associated with deleterious cognitive change. Shem *et al.* conducted a case series including ten patients with spinal cord injury. The results from this study showed that gabapentin therapy was associated with decline in memory, executive function, and attention after 1 week of gabapentin treatment (Shem et al., 2018). In a cross-over randomized controlled study, gabapentin use caused significantly worse attention/vigilance, ability to maintain wakefulness voluntarily, and cognitive processing and motor speed in healthy adults (Meador et al., 1999). A recent retrospective cohort study reported that gabapentin initiation in older adults after surgery was associated with increased risk of delirium and antipsychotic use (Park et al., 2022). However, several previous studies reported that gabapentin is not associated with cognitive functioning in patients with seizures (Leach et al., 1997; Dodrill et al., 1999). Although our study features a large, well-characterized cohort with multiple measures of neurocognitive function, our measure of gabapentin use was limited to self-report at annual visits. Therefore, studies with careful measurement of gabapentin use combined with careful measurements of neurocognitive outcomes are needed. Additionally, given the strong possibility of baseline differences in participants who and do not initiate gabapentin, observational studies must also make every effort to control confounding.

Antiseizure drugs are known to be associated with adverse cognitive effects *via* suppressing neuronal excitability or enhancing inhibitory neurotransmission (Martin et al., 1999; Ortinski and Meador, 2004; Loring et al., 2007; Eddy et al., 2011; Quon et al., 2020). However, gabapentin seems to be different from the traditional antiseizure drugs, and the exact mechanism(s) through which gabapentin exerts both its clinical and potential side effects is still unknown. One hypothesis includes binding to the alpha2-delta subunit of the voltage-dependent calcium channel (Rose and Kam, 2002). Considering that gabapentin may block calcium channels in the brain, it is possible that it would have a neuroprotective effect, but this is controverted by the results of this study. Therefore, further experimental studies are needed to examine the mediators of gabapentin use and neurocognitive changes.

In addition to the neurocognitive outcomes under study, we also found that the gabapentin initiators had higher prevalence of opioid use, as well as antidepressants, antipsychotics, benzodiazepines, and anxiolytics, sedatives, and hypnotics compared to nonusers. This result is consistent to our previous study that examined the concurrent use of gabapentin with CNS-depressant medications (Oh et al., 2022). As the FDA and the Beers 2019 criteria warn about using gabapentin concurrently with some medications due to risk of respiratory depression (U.S. Food and Drug Administration, 2019; By the 2019 American Geriatrics Society Beers Criteria® Update Expert Panel, 2019), further studies are needed to examine the risk of concurrently using gabapentin with other CNS depressants in older adults.

This study has several strengths and limitations. First, the NACC UDS dataset has rich data, including participant medical history and neurocognitive evaluations. Using this resource, we had greater sample size compared to the previous studies and were able to measure the association of gabapentin initiation and neurocognition with various clinically relevant outcomes. To mitigate confounding and selection bias, we employed a new-user design and inverse probability weighting. Also, non-users were randomly selected matching on the year of first enrollment and the number of visits from enrollment to gabapentin initiation to new-users to minimize bias (e.g., secular trends, survival bias, and attrition bias). However, gabapentin initiators were identified by reported medication used within 2 weeks of their UDS visit, so participants could be misclassified as non-users if they used gabapentin only between visits. There is less probability of

misclassifying a non-user as a user in this setting. Although we used causal diagrams to select the set of essential confounders, we note that residual confounding (Suttorp et al., 2015), such as unmeasured (e.g., drug indication), partially measured (e.g., seizure and arthritis), and unknown confounders, remains. In the minimum set of confounders identified by DAG, seizure and arthritis were included for measuring cognitive and functional status decline and for measuring motor function change, respectively. However, seizure and arthritis were only partially measured in our study sample (seizure: 57.8%; arthritis: 40.6%) due to changes in the data collection protocol. Thus, these variables were not included in our model. Additionally, participants in the NACC dataset tend to be highly educated and white race, which limits generalizability.

In conclusion, this study showed that among older adults with normal cognition, initiating gabapentin was significantly associated with clinically meaningful decline in cognitive and functional status and increased falls. Further studies are needed to examine the risk and benefit of prescribing gabapentin in older adults.

## Data availability statement

The datasets presented in this article are not readily available because the data was obtained from the National Alzheimer's Coordinating Center. Requests to access the datasets should be directed to: https://naccdata.org/requesting-data/submit-data-request.

## Ethics statement

The studies involving human participants were reviewed and approved by local Alzheimer's Disease Research Center. The patients/participants provided their written informed consent to participate in this study.

## Author contributions

GO conceptualized and designed the study, conducted the data analysis and the interpretation of the results, and drafted the manuscript. DM, DF, and EA supervised the study design and data analysis, interpreted the data, and reviewed and revised the manuscript.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



## Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2022.910719/full#supplementary-material

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