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ORIGINAL ARTICLE

Incidence and trend of cardiac events among children and young adults exposed to psychopharmacological treatment (2006–2018): A nationwide register-based study

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Aims: The aim of this study was to assess cardiac event incidence and trends by sex and age in young patients on psychopharmacological treatment in Sweden.

Methods: This nationwide incidence study encompassed data from Swedish registers (2006–2018). Patients aged 5–30 years were exposed to one or more psychotropic medications (attention deficit hyperactivity disorder medications, antihistamines, selective serotonin reuptake inhibitors, other antidepressants, anxiolytics, antipsychotics, hypnotics/sedatives). Annual incidences, trends and mean incidences of cardiac events (cardiac arrest, arrhythmias, fainting/collapse, sudden death) and recurrent events were calculated.

Results: Among those exposed ($n = 875\,430$, 2 647 957 patient-years, 55% female), 26 750 cardiac events were identified. The mean annual incidence of cardiac events and first-ever events were 0.99% and 0.80%, respectively, showing significant upward annual trends of 4.26% and 2.48%, respectively ($P < .001$). The highest incidences were among females aged 15–19 years (1.50%) and those exposed to polypharmacy (1.63%), anxiolytics (1.53%) or antihistamines (1.27%). The mean annual incidences of cardiac arrest and arrythmias, for both sexes, were 0.01% and 0.51%, respectively. Fainting/collapse accounted for about half of all events, occurring more often in females. The pattern of rising annual incidence remained after excluding fainting/collapse. In all, 21.1% of events were recurrent. Death, including sudden death, occurred in 13 patients.

Conclusions: The mean annual incidence of cardiac events among young patients receiving psychopharmacological treatment was low, 0.99%, with an upward trend of 4.26% annually. Incidence was highest in adolescent females and patients exposed to polypharmacy. Our study highlights the need for more knowledge regarding the possible association between exposure to psychopharmacological treatment and cardiac events.

KEYWORDS
cardiac arrest, death, paediatric arrhythmias, psychotropic medications

1 | INTRODUCTION

Psychopharmacological treatments, including attention deficit hyperactivity disorder (ADHD) medications, selective serotonin reuptake inhibitors (SSRIs), anxiolytics, antipsychotics and hypnotics, exhibit inconsistent findings regarding cardiac safety in young people.[1–14] Sweden, like many other countries, has had rising prescription rates of these medications, and a shift to newer medications and polypharmacy in children, adolescents and young adults in recent decades.[15–19] Concurrently, there has been a growing trend of young patients admitted to hospitals with cardiac symptoms.[20] This could indicate a knowledge gap regarding drug safety for young people exposed to modern psychopharmacological therapy.

Unlike in the adult population, arrhythmias and cardiac arrests are rare in young people, in the range 1–13 per 100000. Some psychotropic medications may contribute to torsade de pointes, which can lead to lethal arrythmia.[21–26] Syncope, which occurs more often in females than in males, may be caused by a physiological reaction or a serious cardiac event.[21–23,27–29] The trend in arrhythmia incidence shows a clear rise in both sexes in recent years, with males demonstrating higher rates.[30] Females face a higher risk of drug-induced adverse events, particularly with concurrent use of multiple psychotropic medications.[31–34] Age-related pharmacokinetic and pharmacodynamic changes have been described but have not been found to raise cardiac risks related to psychopharmacological treatments.[2,32,35]

Despite the abundance of research on psychopharmacological treatments in the young,[36] it remains unclear if and to what extent this exposed population has experienced an upward trend in cardiac events. In addition, there is insufficient evidence on differences by sex, age, medication and type of cardiac events.[2,37] To address these knowledge gaps and provide valuable insights for clinical and public health disciplines, we conducted a register-based study in Sweden from 2006 to 2018. The study aimed to investigate the incidence of cardiac events by sex, age, medication type, medication number and event type, as well as trends in cardiac events by sex among 5–30-year-olds exposed to psychopharmacological treatment.

What is already known about this subject

- Findings regarding cardiac safety of psychopharmacological treatment are inconsistent in young people.
- Recently, both psychopharmacological treatment and cardiac event admissions have increased among the young population.

What this study adds

- The mean annual incidence of cardiac events in young patients exposed to psychopharmacological treatment in Sweden was 0.99% in 2006–2018.
- Female teenagers and patients with polypharmacy had the highest incidence of cardiac events.
- The incidence of cardiac events increased significantly over time.

2 | METHODS

2.1 | Data source

This nationwide register-based study retrieved data from Swedish national registers. Information on the exposure (psychotropic medications) was retrieved from the Swedish Prescribed Drug Register (SPDR), which includes information on type of prescribed drug based on the Anatomical Therapeutic Chemical classification, as well as age, sex and number of prescriptions for each patient.[38] Information on cardiac events was retrieved from the National Patient Register (NPR)—Inpatient and hospital-based outpatient care. Both the SPDR and the NPR have good national coverage, and a validation of the inpatient register revealed that 85–95% of all diagnoses within this register are valid.[38–40] Information on deaths was retrieved from the Swedish Cause of Death Register (CDR).[41]

The National Board of Health and Welfare linked the SPDR, NPR and CDR using the unique 12-digit personal identity number assigned to each Swedish inhabitant.[39,41] Registrations of health care admittances, diseases, prescriptions and death are supported in law (1988: 543). This study was approved by The Swedish Ethical Review the Swedish Ethical Review Board (D nr 2019–04467 and D nr 2020–05889).[42]

2.2 | Study design

This incidence study included all individuals aged 5–30 years who were prescribed and dispensed a psychotropic medication in Sweden in 2006–2018. Each exposed patient was included in the study from the first day of the prescribed drug dispensation each year.

2.3 | Exposure

Sex, age, type of psychotropic medication and number of medications were recorded for each exposed patient each calendar year. Age at inclusion was calculated by subtracting the birth year of the participant from the year of the drug exposure for each calendar year studied and was stratified into five age groups: 5–9, 10–14, 15–19, 20–24 and 25–30 years. Psychotropic medications were stratified into seven groups based on the following Anatomical Therapeutic Chemical codes, 2022: ADHD drugs (N06BA and C02AC02), antihistamines (R06A) for systemic use, SSRIs (N06AB), other types of antidepressants (N06AA and others, see Table S1), anxiolytics/benzodiazepines

(N05BA), antipsychotics (N05A) and hypnotics and/or sedatives (N05BB, N05BE and N05C). Exposure to three or more medications during the same calendar year was defined as polypharmacy. Further information is presented in the supporting information (Table S1).

2.4 | Outcomes

Information on cardiac events was captured in the NPR based on the International Statistical Classification of Diseases and Related Health Problems, 10th version (ICD-10)-Swedish edition (ICD-10-SE). Only cardiac events that occurred after the exposure and within the same calendar year were included. On an annual basis, each cardiac event, except sudden death, was treated as a new event. Each patient's earliest event in the study was considered a first-ever cardiac event, whereas recurrent events refer to instances where a patient experienced more than one event during the study period. Information on death was separately retrieved from the CDR. Cardiac events were stratified into seven categories based on ICD-10 codes: sudden death (sudden unexpected death, R96.0 and sudden cardiac death, I46.1), cardiac arrest (unspecified with successful resuscitation, I46.9), atrial arrhythmia (I49.5, I49.5A, I49.5C), supraventricular tachycardia (I47.1), ventricular tachycardia (I47.0, I47.2, I47.2C, I47.2, I49.0, I49.1, I49.3), other rare and undefined arrythmias (I49.8, I49.8C, I49.9, R00) and fainting and/or collapse (R55.9). Further information on ICD codes is described in the supporting information (Table S1).

2.5 | Statistical analysis

Each patient was included at most once per calendar year. Stratifications were made by sex, age group and type of medication. Number of cardiac events, except for sudden death, was assessed among those exposed and stratified by type of event, sex and age group. The overall annual incidence of cardiac events was calculated. The numerator represents the number of new events in the calendar year, while the denominator represents the number of exposed patients in the same year in respective sex and age groups. The mean annual incidence was assessed and stratified by sex and age group. The mean incidence for each type of cardiac event was assessed by sex, age group and type of medication. A second analysis, as a measure of sensitivity, was performed by excluding fainting and/or collapse (R55.9). The annual and mean incidence of first-ever cardiac event, as a second sensitivity analysis, were estimated, as well as the number of recurrent events (subsequent events). A third sensitivity, subgroup, analysis was conducted by excluding patients with a single medication delivery. Sudden death was stratified by type and number of medications, sex and age group. Linear regression was used to assess the significance of possible changes in linear secular trends (ln [incidence] ~ year) and adjusted for sex and age. The analysis was performed using the analytical software Stata version 18 (Stata Press, College Station, TX).

2.6 | Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, and are permanently archived in the Concise Guide to PHARMACOLOGY 2023/24.[43]

3 | RESULTS

During the study period, 2006–2018, a total of 875 430 unique individuals (2 647 957 patient-years, 45% male, 55% female) received psychopharmacological treatment, of whom 66% were aged 20 years or older. An upward annual trend of 9.8% in absolute numbers ($P < .05$; Figure 1) could be seen. Males were more often exposed to ADHD medications, whereas females were more often exposed to antidepressants and polypharmacy (Table 1).

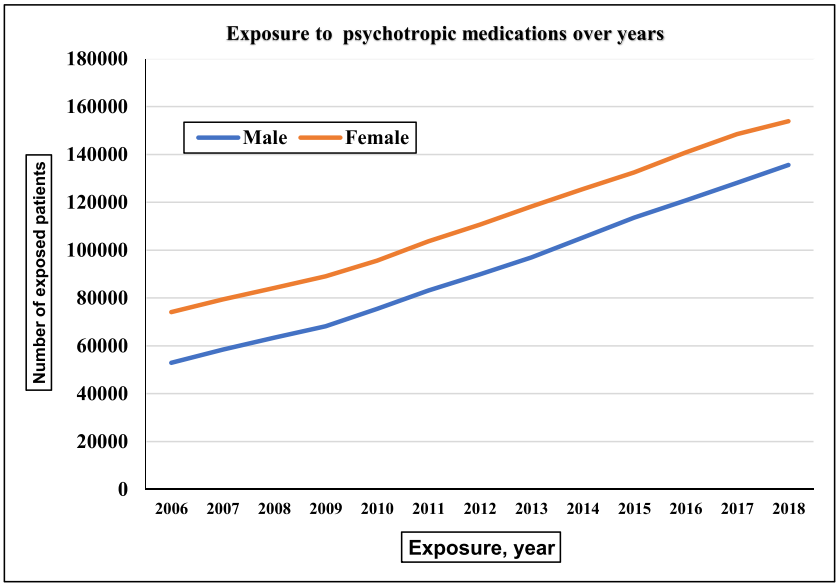


FIGURE 1 Number of children, adolescents and young adults aged 5–30 years on psychopharmacological treatment.

In total, 26 750 cardiac events (excluding sudden death) were identified in those exposed. Most events occurred in females (64%) in the age group 15–30 years. The most common events were fainting and/or collapse (50% of all events) and undefined arrhythmias (42% of all events). The number of unique patients experiencing recurrent events was 2409 (0.28% of the exposed), representing 5655 events (21.1% of all events) (Figures S1 and S2).

3.1 | Incidence and trends of cardiac events (all, first-ever, excluding fainting and/or collapse)

The total mean annual incidence for cardiac events was 0.99% and that for first-ever events was 0.80%, with significant upward annual trends of 4.26% and 2.48%, respectively ($P < .001$; Figure 2A). The cardiac event incidence was highest in females (1.17%), particularly those aged 15–19 years (1.50%) (Table 2, Figure 2B and C). The incidence of recurrent events was 0.21%.

The mean incidence of cardiac events, excluding fainting and/or collapse, was 0.51%, rising with an annual percentage change of 4.52% ($P < .001$). The mean incidence was 0.53% for females and 0.49% for males (Figure 3A, Table S2). Peaks were seen at age 20–24 years for both sexes, and males showed a slightly higher incidence than females in this age group (Figure 3B). The incidence of fainting and/or collapse had an annual percentage increase of 3.89% ($P < .001$) (Figure 3C). The occurrence among females (0.64%) was double that among males (0.32%) (Table 2).

3.2 | Incidence by type of psychopharmacological treatment

The incidence of cardiac events was higher among those exposed to anxiolytics (1.53%), antihistamines (1.27%) or hypnotics and/or sedatives (1.17%) (Table 2). Patients exposed to polypharmacy had a higher mean annual incidence (1.63%) than those not exposed to polypharmacy (0.90%) ($P < .05$; Figure 2D). The incidence of cardiac events was higher in females aged 15 years and older than in males or other age groups. Arrhythmias were more prevalent with polypharmacy than with other cardiac events, in both sexes, particularly in individuals aged 15 years or older (Table S3).

3.3 | Incidence by type of cardiac event

3.3.1 | Cardiac arrest

The mean annual incidence of cardiac arrest was 0.01% (Table 2), and higher in males exposed to anxiolytics (0.1%) or antipsychotics (0.04%) compared with other types of medications, or with females (Table S3).

TABLE 1 Characteristics of patients aged 5–30 years exposed to psychopharmacological treatment during 2006–2018, in patient-years.

2006–2018	Male $n = 1\,191\,717$ *n* (%)	Female $n = 1\,456\,240$ *n* (%)	Total $N = 2\,647\,957$ *n*	Patient-years contributed by each age and medication category, %
Age groups				
5–9 years	71 143 (67.25)	346,48 (32.75)	105 791	4.00%
10–14 years	180, 851(67.86)	85 649 (32.14)	266 500	10.06%
15–19 years	240, 999 (46.70)	275, 040 (53.30)	516, 039	19.49%
20–24 years	277, 627 (40.17)	413, 578 (59.83)	691, 205	26.10%
25–30 years	421, 097 (39.41)	647, 325 (60.59)	1, 068, 422	40.35%
Type of psychotropic medication				
ADHD medications	323, 729 (69.26)	143, 665 (30.74)	467, 394	17.65%
Antihistamines	54, 845 (26.68)	150, 718 (73.32)	205, 563	7.76%
SSRIs	251, 794 (34.54)	477, 101 (65.46)	728, 895	27.53%
Other anti-depressants	102, 069 (42.57)	137, 721(57.43)	239, 790	9.06%
Anxiolytics	63, 254, (44.79)	77 975 (55.21)	141, 229	5.33%
Antipsychotics	66, 478 (58.71)	46 761 (41.29)	113, 239	4.28%
Hypnotics and/or sedatives	329, 548 (43.83)	422 299 (56.17)	751, 847	28.39%
Polypharmacy				
No (<three medications)	1, 019, 419 (85.54)	1, 212, 916 (83.29)	2, 232 335	84.30%
Yes (three or more medications)	172, 298 (14.46)	243, 324 (16.71)	415, 622	15.70%

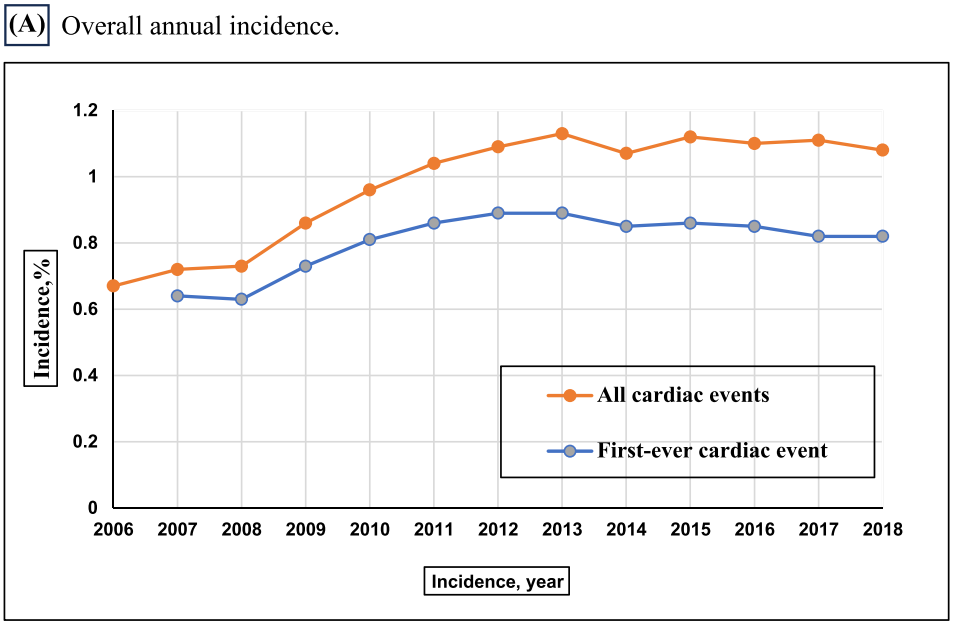
Abbreviations: ADHD: attention deficit hyperactivity disorder; SSRIs: selective serotonin reuptake inhibitors.
Note: Number of unique individuals = 875 430 during the study period 2006–2018, totalling 2 647 957 patient-years.
Further information on coding presented in Table S1.

3.3.2 | Atrial arrhythmias

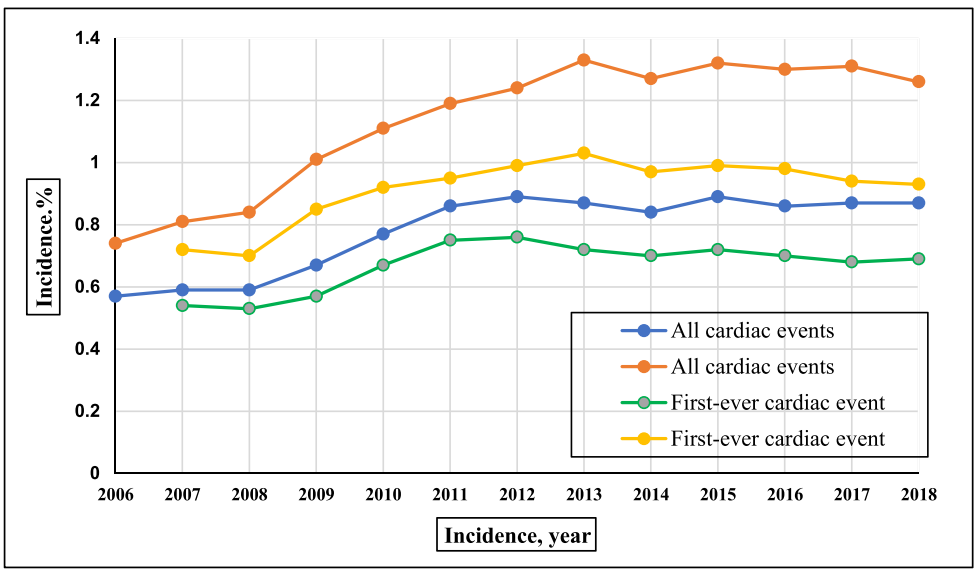
The mean annual incidence of atrial arrhythmias was 0.001%, and higher in males aged 15 years or older exposed to anxiolytics (0.02%).

3.3.3 | Supraventrcular tachycardia (SVT)

The mean annual SVT incidence was 0.04%, higher in males aged 5–9 years using SSRIs (0.12%), aged 15–19 years using antihistamines (0.08%), or aged over 19 years using anxiolytics (0.07%).



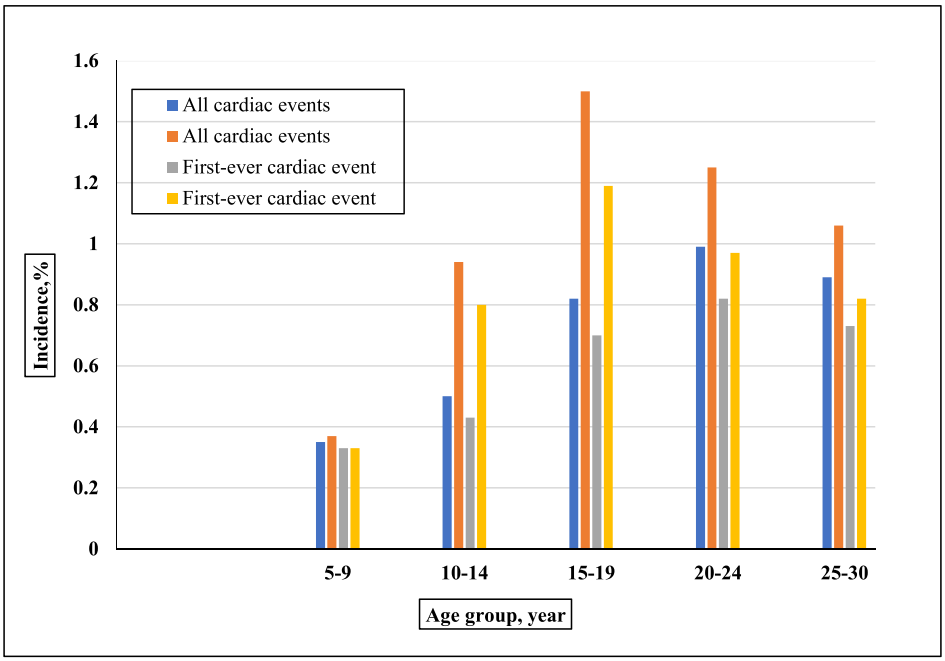
Cardiac events included cardiac arrest, atrial arrhythmias, supraventricular tachycardia, ventricular tachycardia, other rare or undefined arrythmias, and fainting and/or collapse. The overall mean incidence for all events was 0.98% and the overall mean incidence for first-ever events was 0.80%.



The mean annual incidence rate of all cardiac events was 0.8% for males and 1.13% for females.
The mean annual incidence rate of first-ever cardiac events was 0.67% for males and 0.9% for females.

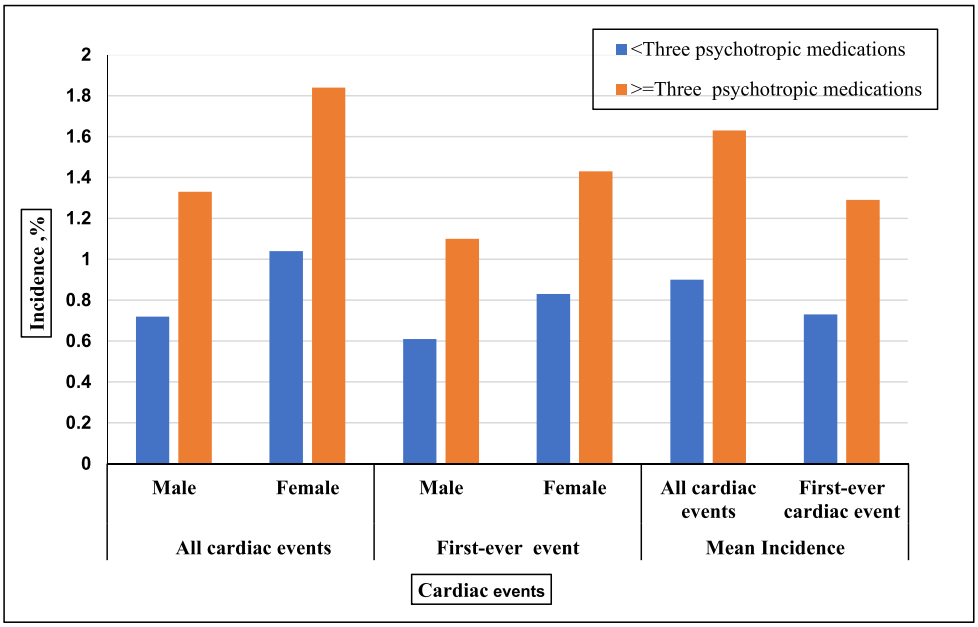
FIGURE 2 Incidence of cardiac events among those aged 5–30 years exposed to psychopharmacological treatment (2006–2018).A Overall annual incidence.B Annual incidence by sex.C Mean overall incidence by sex and age.D Mean overall incidence by polypharmacy and sex.

(C) Mean overall incidence by sex and age.



The mean overall incidence rates of cardiac events, by age group, were: 5–9 y = 0.36%, 10–14 y = 0.64%, 15–19 y = 1.18%, 20–24 y = 1.15%, 25–30 y = 1.00%.The mean overall incidence rates of first-ever events, by age group, were, 5–9 y = 0.33%, 10–14 y = 0.55%, 15–19 y = 0.96%, 20–24 y = 0.91%, 25–30 y = 0.78%.

(D) Mean overall incidence by polypharmacy and sex.



Polypharmacy means receiving three or more psychotropic medications during the calendar year. Mean incidence of polypharmacy was calculated as the average of all annual incidence rates of polypharmacy for each sex. Females had the highest mean incidence when exposed to polypharmacy.

FIGURE 2 (Continued)

TABLE 2 Incidence of cardiac events among those exposed[a] by cardiac event and medication type.

2006–2018	Male Cardiac events $n = 9641$ n (%)	Female Cardiac events $n = 17\,109$ n (%)	Total Cardiac events $n = 26\,750$ n (%)
Type of psychotropic medication			
ADHD medications	1789 (0.55)	1612 (1.12)	3401 (0.73)
Antihistamines	633(1.15)	1977 (1.31)	2610 (1.27)
SSRIs	1762 (0.70)	4373 (0.92)	6135 (0.84)
Other anti-depressant	875 (0.86)	1588 (1.15)	2463 (1.03)
Anxiolytics	833 (1.32)	1321 (1.69)	2154 (1.53)
Antipsychotics	501 (0.75)	669 (1.43)	1170 (1.03)
Hypnotics and/or sedatives	3248 (0.99)	5569 (1.32)	8817 (1.17)
Type of cardiac event			
Cardiac arrest	197 (0.02)	102 (0.01)	299 (0.01)
Atrial arrhythmia	37(0.002)	35 (0.001)	72 (0.001)
SVT	391 (0.03)	679 (0.05)	1070 (0.04)
VT	295 (0.02)	433 (0.03)	728 (0.03)
Undefined arrhythmia	4871 (0.41)	6479 (0.44)	11 350 (0.43)
Fainting and/or collapse	3850 (0.32)	9381 (0.64)	13 231 (0.48)
Mean overall incidence	0.81%	1.17%	0.99%

[a]Exposed are patients aged 5–30 years who received psychopharmacological treatment between 2006 and 2018 based on data in Swedish prescribed drug registers.
Abbreviations: Cardiac arrest: successfully resuscitated cardiac arrest; SVT: supraventricular tachycardia; VT: ventricular tachycardia; ADHD: attention deficit and hyperactivity disorder; SSRIs: selective serotonin reuptake inhibitors.
For detailed information on ICD codes and types of medication, see Table S1.

Females aged 20–24 years using anxiolytics or ADHD medications had higher incidence than was seen for other medications or age groups.

3.3.4 | Ventricular tachycardia (VT)

The overall mean annual incidence was 0.03%. This incidence was higher in males aged 10–14 years exposed to other antidepressants (0.13%), and in females exposed to anxiolytics or antihistamines in the oldest age groups, at 0.08% and 0.05%, respectively.

3.3.5 | Rare and undefined arrhythmias

The mean annual incidence was 0.43%. Females on ADHD medications displayed an average incidence of 0.50%.

3.3.6 | Fainting and/or collapse

The mean annual incidence was 0.48%, and highest in females aged 15–19 years on anxiolytics (1.72%).

3.3.7 | Death

Thirteen cases of death, including sudden death, occurred during the study period, mainly in males aged over 19 years and exposed to hypnotics and/or sedatives, anxiolytics, SSRIs or antipsychotics, corresponding to an incidence of 0.0005%.

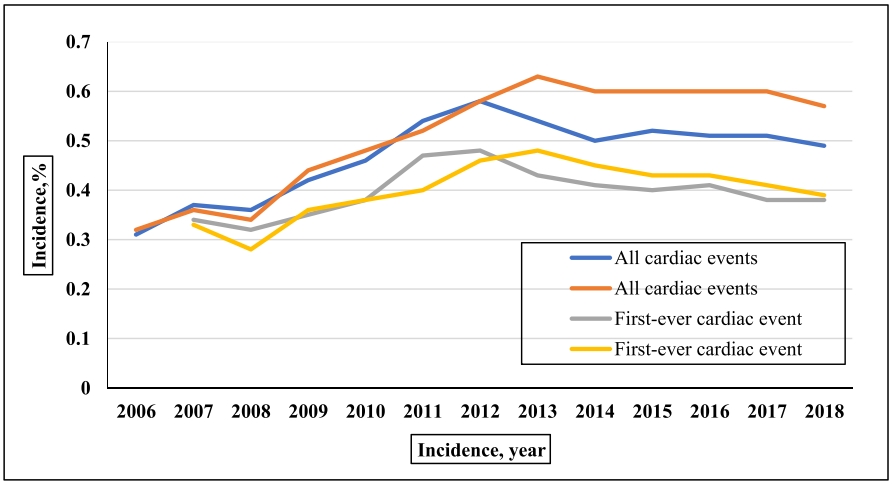
3.3.8 | Subgroup analysis

In the subgroup analysis, after excluding patients with single delivery, the mean annual incidence decreased to 0.97%, though it still followed the upward trend observed in the primary analysis over the study period. The highest incidence was seen in females (1.15%) compared to males (0.76%), and among individuals aged 15–19 years, specifically in females (1.52%) (Figure S3A, B).

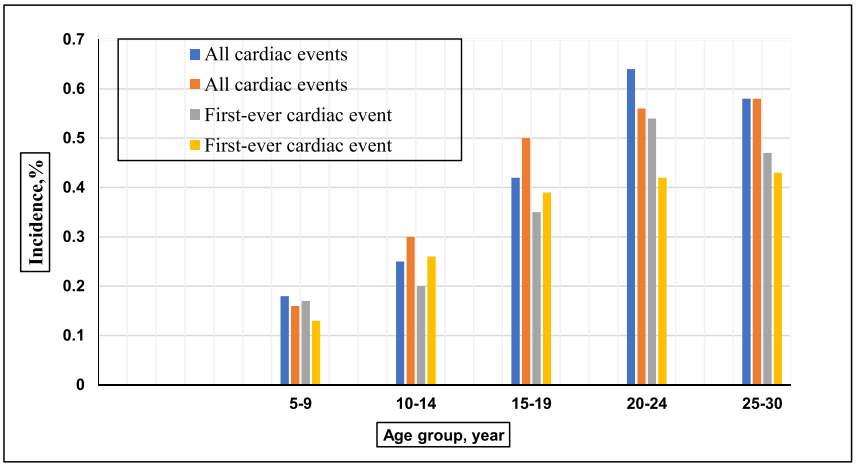
4 | DISCUSSION

In this nationwide register-based incidence study, we found that mean annual incidence of all cardiac events was 0.99% during the study period, with a rising trend. A fifth of cardiac events were recurrent and occurred in a small subset of exposed patients.

(A) Annual incidence by sex.



(B) Mean overall incidence by sex and age.



Mean overall incidence, 0.51%; mean overall incidence in males, 0.49%, in females, 0.53%.

(C) Annual incidence versus incidence of fainting and/or collapse.

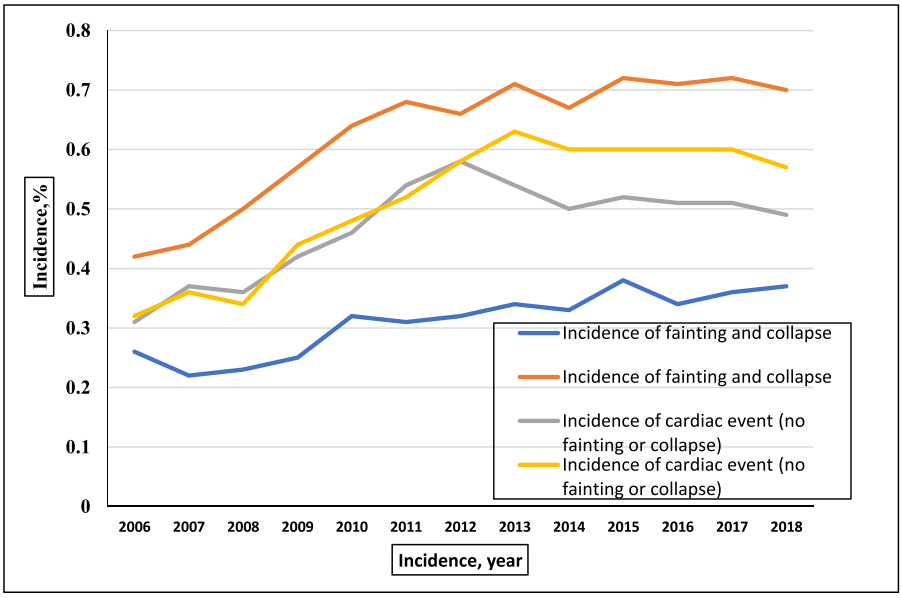


FIGURE 3 Incidence of cardiac events, excluding fainting and/or collapse among those exposed to psychopharmacological treatment (2006–2018).A Annual incidence by sex.B Mean overall incidence by sex and age.C Annual incidence *vs.* incidence of fainting and/or collapse.

4.1 | Sex and age

Like other researchers,[44] we found that females had a higher mean incidence of cardiac events than males, also after exclusion of fainting and/or collapse (Table 2, Table S2). Sex may have an impact on pharmacokinetics and pharmacodynamics, which may, in turn, have an impact on adverse outcomes.[45] Further, fainting and/or collapse occurred twice as often in females (0.64%) as in males (0.32%) (Table 2), a finding that aligns with those of another study.[28] The highest incidence of cardiac events was found in female teenagers (1.50%) (Figure 2C). This could be explained by higher help-seeking behaviour among young females compared with young males or by the sex-based difference in pharmacokinetics, parasympathetic activity and hormonal changes during puberty.[46–48] Upon exclusion of fainting and/or collapse, the peak of incidence shifted from age 15–19 years to age 20–24 years for both sexes, with males showing slightly higher proportions than females in the latter age group (Figure 3B). This underscores the importance of carefully assessing fainting and/or collapse in patients on psychopharmacological treatment.

4.2 | Type of psychopharmacological treatment

4.2.1 | Psychopharmacological monotherapy

In our study, individuals exposed to anxiolytics had a higher mean incidence of cardiac events (1.53%) compared with individuals on hypnotics and/or sedatives (1.17%) or other psychotropic medications (Table 2). This is consistent with other findings, where anxiolytics showed a higher risk of cardiac events than hypnotics.[4] Patients on ADHD medications had the lowest incidence of cardiac events (0.73%) (Table 2), even lower than other in studies.[49,50] This might be related to growing awareness of the cardiac risks with ADHD medications, and good compliance with guidelines on assessing and monitoring cardiac risks in the context of these medications. Despite methodological differences to other pharmacovigilance studies, along with inclusion of a younger age groups in other studies, our findings suggest a varying level of risk among different medications and underscore the need for further research with control groups.

4.2.2 | Psychopharmacological polypharmacy

Patients exposed to polypharmacy had a higher mean incidence, at 1.63%, compared with patients on fewer medications (0.90%), a result which aligns with other findings.[34] However, other findings included a narrow group of patients with concomitant use of only two psychotropic medications. Polypharmacy may induce pharmacodynamic and/or pharmacokinetic interactions and can extend half-life, which may further increase cardiac risks.[31,34,51–53] We found that incidence was higher in females aged 15 years or older with polypharmacy (Figure 2D, Table S3). Female sex and polypharmacy may increase the risk of drug-induced adverse events, possibly due to immunological, hormonal or dosage factors.[32,45]

4.3 | Types of cardiac event

4.3.1 | Cardiac arrest

The incidence of cardiac arrest is low in paediatric patients,[26] which was also seen in our study of young patients exposed to psychotropic medications. Males had a higher incidence of cardiac arrest than females, especially if exposed to antipsychotics or anxiolytics (Table S3). This is in line with other studies reporting that ventricular arrhythmias are linked to antipsychotic medications,[13] and that anxiolytics (diazepam) can cause cardiovascular collapse.[54] Thus, we recommend careful individual risk evaluation of young male patients before exposure to psychotropic medications.

4.3.2 | Arrhythmias

In our study, the incidence of arrhythmias was higher than the overall reported incidence of childhood arrhythmias,[21–23] but was nearly the same in both sexes (Table 2, Table S3). This is not in line with other authors' findings of drug-induced life-threatening arrhythmias suggesting higher incidences among females.[45] This discrepancy may be due to the register-based method used in our study which includes various types of arrhythmias, while other studies have used ECG-verified arrythmias, most often life-threatening, such as long QT syndrome. However, the incidence proportions of SVT and VT at ages 15 years and older in both sexes, as well as in male patients exposed to SSRIs and other antidepressants, align with the findings of others.[11,12,14,55] This may relate to drug-induced inhibition of Na^+, Ca^{2+}, K^+ channels,[56] which may affect pathways in the cardiac conduction system. Further, our study found a notable incidence of arrhythmias in individuals exposed to antihistamines, which are pharmacologically similar to tricyclic antidepressants and are known to cause arrhythmias in children.[57,58] Females exposed to ADHD medications showed a higher incidence of rare and undefined arrhythmias than males, in line with findings of other studies.[33] All these findings suggest that age and sex are important factors to considered when assessing the cardiac safety of psychopharmacological treatments.

4.3.3 | Fainting and/or collapse

The incidence of fainting and/or collapse was 0.48% in our study (Table 2), with the highest incidence in females on anxiolytics (1.72%) (Table S3). This was higher than the reported incidence of syncope in young people.[27] Syncope is common in this age group and can be a natural physiological response.[29] However, fainting can also be a sign of a medically induced cardiac event.[54,59] Harmful fainting must be

distinguished from benign events in all patients, especially those on psychopharmacological treatment. We argue for careful assessment and awareness of the potential for pharmacologically induced fainting.

4.3.4 | Death

The incidence of death, including sudden death, was low (5/1000000)—lower than the reported incidence of death or sudden death in the general population in the same age groups.[24,25] Some psychotropic medications, such as hypnotics,[3,4] antipsychotics and SSRIs,[5,6] have been considered to protect against death in young adults, as well as against suicide at all ages. However, these medications, as well as anxiolytics, have been reported to increase the risk of sudden death in children, adolescents and young adults.[10–14] Patients who died in our study were exposed to hypnotics and/or sedatives, anxiolytics, antipsychotics and/or SSRIs. The well-known risk of death and sudden death linked to any underlying psychiatric disease must sometimes carry more weight in the decision-making process concerning treatment risks.

4.4 | Strengths and limitations

This incidence study examines cardiac events among young people exposed to psychotropic medication on a national level, using prospectively collected data from well-validated national registers. This approach strengthens the study. As a preliminary investigation into cardiac events in this patient group, our results suggest the need for further risk assessment studies and comparisons with unexposed controls. This study includes patients up to 30 years old, exceeding the World Health Organization's (WHO) definition of 'young people' as those up to 24 years old. By covering a longer age range and including a broader patient group, the study aims to capture any long-term effects, while still focusing on relatively young individuals, most of whom are less likely to be affected by other somatic diseases. Additionally, the study seeks to track prescription rates and trends into adulthood, potentially enhancing its overall strength.

The analysis method, which considered exposure and events within the same calendar year, may have resulted in missed events and underestimated incidence. For instance, a patient prescribed medication late in one year could have an event the following year, which would not be captured by this approach. To check this risk of underestimation, we calculated the number of events the year following the late exposure. We found only 243 events occurring following the year of exposure, including the whole study period, and we believe the risk of underestimation due to the method used is limited. Patient adherence to the prescribed medications was unknown, as this is not recorded in the registers and to overcome that, a sensitivity analysis was performed excluding patients with single delivery. The study did not cover all psychotropic or non-psychotropic medications, such as non-legal substances. Nor did it cover non-cardiac adverse events, or other medications and diseases. Further, the NPR does not contain diagnoses from non-specialized outpatient care, and thus there is a risk of underestimating the incidence of cardiac events.

The current study did not include medications such as anticonvulsants or antiepileptics, as these medications are primarily used for neurological diseases such as seizure disorders. This incidence study lacks a control group with no possibility to adjust for confounding factors and other diseases such as seizures. Future studies should include all medications used for psychiatric diseases. Moreover, lithium is included as it is primarily used for treatment of bipolar and manic disorders, and to our knowledge has no non-psychiatric indications. Lithium prescription rates have also continued to rise among young individuals in Sweden the last decades. Studies in real-world settings assessing the association between psychotropic medications and cardiac events are needed to identify confounding factors.

5 | CONCLUSIONS

This nationwide register-based study found that young patients on psychopharmacological treatment had a 0.99% mean annual incidence of cardiac events, which increased over the period 2006–2018. Exclusion of fainting and collapse events did not alter the rising trend. Incidence was highest among those aged 15–19 years, those exposed to anxiolytics, antihistamines or polypharmacy. A small group of patients contributed a fifth of all cardiac events. Our findings suggest the need for more studies to assess the possible association between exposure to psychotropic medications and cardiac events.

AUTHOR CONTRIBUTIONS

Howaida Elmowafi: Study design, statistical analysis, data interpretation, and drafting of the manuscript. **Estelle Naumburg:** Protocol development and analytical framework, study design, and in-depth reviewing of the manuscript. **Linda Halldner, David Gyllenberg and Jenny M. Kindblom:** Critical reviewing of the study design and the manuscript.

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CONFLICT OF INTEREST STATEMENT

There are no conflicts of interest to declare. The funders have had no input regarding framing of the study, design, interpretation of data, reviewing or submission for publication.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from Socialstyrelsen (the Swedish National Board of Health and Welfare; https://bestalladata.socialstyrelsen.se/ [Swedish]), but restrictions apply to their availability. The data were used under licence for the current study and are not publicly available.

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REFERENCES

1. Cooper WO, Habel LA, Sox CM, et al. ADHD drugs and serious cardiovascular events in children and young adults. *N Engl J Med*. 2011;365(20):1896-1904. doi:10.1056/NEJMoa1110212
2. Zhang L, Yao H, Li L, et al. Risk of cardiovascular diseases associated with medications used in attention-deficit/hyperactivity disorder: a systematic review and meta-analysis. *JAMA Netw Open*. 2022;5(11):e2243597. doi:10.1001/jamanetworkopen.2022.43597
3. Lan TY, Zeng YF, Tang GJ, et al. The use of hypnotics and mortality—a population-based retrospective cohort study. *PLoS ONE*. 2015;10(12):e0145271. doi:10.1371/journal.pone.0145271
4. Kim YH, Kim HB, Kim DH, Kim JY, Shin HY. Use of hypnotics and the risk of or mortality from heart disease: a meta-analysis of observational studies. *Korean J Intern Med*. 2018;33(4):727-736. doi:10.3904/kjim.2016.282
5. Lagerberg T, Fazel S, Sjolander A, Hellner C, Lichtenstein P, Chang Z. Selective serotonin reuptake inhibitors and suicidal behaviour: a population-based cohort study. *Neuropsychopharmacology*. 2022;47(4):817-823. doi:10.1038/s41386-021-01179-z
6. Hassan A, De Luca V, Dai N, et al. Effectiveness of antipsychotics in reducing suicidal ideation: possible physiologic mechanisms. *Healthcare (Basel)*. 2021;9(4):389. doi:10.3390/healthcare9040389
7. Samuels JA, Franco K, Wan F, Sorof JM. Effect of stimulants on 24-h ambulatory blood pressure in children with ADHD: a double-blind, randomized, cross-over trial. *Pediatr Nephrol*. 2006;21(1):92-95. doi:10.1007/s00467-005-2051-1
8. Dalsgaard S, Kvist AP, Leckman JF, Nielsen HS, Simonsen M. Cardiovascular safety of stimulants in children with attention-deficit/hyperactivity disorder: a nationwide prospective cohort study. *J Child Adolesc Psychopharmacol*. 2014;24(6):302-310. doi:10.1089/cap.2014.0020
9. Arcieri R, Germinario EA, Bonati M, et al. Cardiovascular measures in children and adolescents with attention-deficit/hyperactivity disorder who are new users of methylphenidate and atomoxetine. *J Child Adolesc Psychopharmacol*. 2012;22(6):423-431. doi:10.1089/cap.2012.0014
10. Weich S, Pearce HL, Croft P, et al. Effect of anxiolytic and hypnotic drug prescriptions on mortality hazards: retrospective cohort study. *BMJ*. 2014;348:g1996. doi:10.1136/bmj.g1996
11. Jerrell JM, McIntyre RS. Cardiovascular and neurological adverse events associated with antidepressant treatment in children and adolescents. *J Child Neurol*. 2009;24(3):297-304. doi:10.1177/0883073808323523
12. Funk KA, Bostwick JR. A comparison of the risk of QT prolongation among SSRIs. *Ann Pharmacother*. 2013;47(10):1330-1341. doi:10.1177/1060028013501994
13. Wu CS, Tsai YT, Tsai HJ. Antipsychotic drugs and the risk of ventricular arrhythmia and/or sudden cardiac death: a nation-wide case-crossover study. *J Am Heart Assoc*. 2015;4(2):e001568. doi:10.1161/jaha.114.001568
14. Chu A, Wadhwa R. Selective serotonin reuptake inhibitors. In: *StatPearls [Internet]*. : StatPearls Publishing; 2023. https://www.ncbi.nlm.nih.gov/books/NBK554406/.
15. Chang Z, Ghirardi L, Quinn PD, Asherson P, D'Onofrio BM, Larsson H. Risks and benefits of attention-deficit/hyperactivity disorder medication on behavioral and neuropsychiatric outcomes: a qualitative review of pharmacoepidemiology studies using linked prescription databases. *Biol Psychiatry*. 2019;86(5):335-343. doi:10.1016/j.biopsych.2019.04.009
16. Gomez-Lumbreras A, Garcia Sangenis A, Prat Vallverdu O, et al. Psychotropic use in children and adolescents in Scandinavia and Catalonia: a 10-year population-based study. *Psychopharmacology (Berl)*. 2021;238(7):1805-1815. doi:10.1007/s00213-021-05809-8
17. Mancini J, Thirion X, Masut A, et al. Anxiolytics, hypnotics, and antidepressants dispensed to adolescents in a French region in 2002. *Pharmacoepidemiol Drug Saf*. 2006;15(7):494-503. doi:10.1002/pds.1258
18. Kalverdijk LJ, Bachmann CJ, Aagaard L, et al. A multi-national comparison of antipsychotic drug use in children and adolescents, 2005-2012. *Child Adolesc Psychiatry Ment Health*. 2017;11(1):55. doi:10.1186/s13034-017-0192-1
19. Raman SR, Man KKC, Bahmanyar S, et al. Trends in attention-deficit hyperactivity disorder medication use: a retrospective observational study using population-based databases. *Lancet Psychiatry*. 2018;5(10):824-835. doi:10.1016/s2215-0366(18)30293-1
20. Socialstyrelsen Statistical Database. In-patient Care Diagnoses. https://sdb.socialstyrelsen.se/if_par/resultat.aspx. Accessed October 11, 2024.
21. Kafali HC, Ergul Y. Common supraventricular and ventricular arrhythmias in children. *Turk Arch Pediatr*. 2022;57(5):476-488. doi:10.5152/TurkArchPediatr.2022.22099
22. Priori SG, Wilde AA, Horie M, et al. HRS/EHRA/APHRS expert consensus statement on the diagnosis and management of patients with inherited primary arrhythmia syndromes: document endorsed by HRS, EHRA, and APHRS in May 2013 and by ACCF, AHA, PACES, and AEPC in June 2013. *Heart Rhythm*. 2013;10(12):1932-1963. doi:10.1016/j.hrthm.2013.05.014
23. Schwartz PJ, Ackerman MJ, Antzelevitch C, et al. Inherited cardiac arrhythmias. *Nat Rev Dis Primers*. 2020;6(1):58. doi:10.1038/s41572-020-0188-7
24. Stiles MK, Wilde AAM, Abrams DJ, et al. 2020 APHRS/HRS expert consensus statement on the investigation of decedents with sudden unexplained death and patients with sudden cardiac arrest, and of their families. *Heart Rhythm*. 2021;18(1):e1-e50. doi:10.1016/j.hrthm.2020.10.010
25. UNICEF. Child and youth mortality ages 5-24. 2023. https://data.unicef.org/topic/child-survival/child-and-youth-mortality-age-5-24/. Accessed October 11, 2024.
26. Franciosi S, Abrams DJ, Ingles J, Sanatani S. Sudden cardiac arrest in the paediatric population. *CJC Pediatr Congenital Heart Dis*. 2022;1(2):45-59. doi:10.1016/j.cjcpc.2022.02.001
27. Wieling W, Ganzeboom KS, Saul JP. Reflex syncope in children and adolescents. *Heart*. 2004;90(9):1094-1100. doi:10.1136/hrt.2003.022996
28. van Dijk N, Wieling W. Fainting, emancipation and the 'weak and sensitive' sex. *J Physiol*. 2009;587(Pt 13):3063-3064. doi:10.1113/jphysiol.2009.174672
29. Hu E, Liu X, Chen Q, Wang C. Investigation on the incidence of syncope in children and adolescents aged 2-18 years in Changsha. *Front Pediatr*. 2021;9:638394. doi:10.3389/fped.2021.638394
30. Ehdaie A, Cingolani E, Shehata M, Wang X, Curtis AB, Chugh SS. Sex differences in cardiac arrhythmias: clinical and research implications. *Circ Arrhythm Electrophysiol*. 2018;11(3):e005680. doi:10.1161/CIRCEP.117.005680
31. Jerrell JM, McIntyre RS. Adverse events in children and adolescents treated with antipsychotic medications. *Hum Psychopharmacol*. 2008;23(4):283-290. doi:10.1002/hup.932
32. Rademaker M. Do women have more adverse drug reactions? *Am J Clin Dermatol*. 2001;2(6):349-351. doi:10.2165/00128071-200102060-00001
33. Kok FM, Groen Y, Fuermaier ABM, Tucha O. The female side of pharmacotherapy for ADHD-A systematic literature review. *PLoS ONE*. 2020;15(9):e0239257. doi:10.1371/journal.pone.0239257
34. Zhang C, Spence OM, Reeves G, DosReis S. Cardiovascular risk of concomitant use of atypical antipsychotics and stimulants among commercially insured youth in the United States. *Front Psych*. 2021;12:640244. doi:10.3389/fpsyt.2021.640244

35. Mangoni AA, Jackson SH. Age-related changes in pharmacokinetics and pharmacodynamics: basic principles and practical applications. *Br J Clin Pharmacol*. 2004;57(1):6-14. doi:10.1046/j.1365-2125.2003.02007.x
36. Hartz I, Skurtveit S, Steffenak AK, Karlstad O, Handal M. Psychotropic drug use among 0-17 year olds during 2004-2014: a nationwide prescription database study. *BMC Psychiatry*. 2016;16(1):12. doi:10.1186/s12888-016-0716-x
37. Zhang L, Li L, Andell P, et al. Attention-deficit/hyperactivity disorder medications and long-term risk of cardiovascular diseases. *JAMA Psychiatry*. 2024;81(2):178-187. doi:10.1001/jamapsychiatry.2023.4294
38. Wettermark B, Hammar N, Fored CM, et al. The new Swedish prescribed drug register—opportunities for pharmacoepidemiological research and experience from the first six months. *Pharmacoepidemiol Drug Saf*. 2007;16(7):726-735. doi:10.1002/pds.1294
39. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekbom A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. *Eur J Epidemiol*. 2009;24(11):659-667. doi:10.1007/s10654-009-9350-y
40. Ludvigsson JF, Andersson E, Ekbom A, et al. External review and validation of the Swedish national inpatient register. *BMC Public Health*. 2011;11:450. doi:10.1186/1471-2458-11-450
41. Brooke HL, Talbäck M, Hörnblad J, et al. The Swedish cause of death register. *Eur J Epidemiol*. 2017;32(9):765-773. doi:10.1007/s10654-017-0316-1
42. Swedish Ethical Review Authority (Etikprövnings myndigheten). https://etikprovningsmyndigheten.se/en/. Accessed October 11, 2024.
43. Alexander SPH, Mathie A, Peters JA, et al. The concise guide to PHARMACOLOGY 2023/24: ion channels. *Br J Pharmacol*. 2023;180(S2):S145-S222. doi:10.1111/bph.16178
44. Yokohara S, Hashiguchi M, Shiga T. Psychotherapeutic drug-induced life-threatening arrhythmias: a retrospective analysis using the Japanese adverse drug event report database. *J Arrhythm*. 2023;39(6):928-936. doi:10.1002/joa3.12936
45. Anderson GD. Gender differences in pharmacological response. *Int Rev Neurobiol*. 2008;83:1-10. doi:10.1016/s0074-7742(08)00001-9
46. Moyer AM, Matey ET, Miller VM. Individualized medicine: sex, hormones, genetics, and adverse drug reactions. *Pharmacol Res Perspect*. 2019;7(6):e00541. doi:10.1002/prp2.541
47. Sato N, Miyake S. Cardiovascular reactivity to mental stress: relationship with menstrual cycle and gender. *J Physiol Anthropol Appl Human Sci*. 2004;23(6):215-223. doi:10.2114/jpa.23.215
48. Olde Nordkamp LR, van Dijk N, Ganzeboom KS, et al. Syncope prevalence in the ED compared to general practice and population: a strong selection process. *Am J Emerg Med*. 2009;27(3):271-279. doi:10.1016/j.ajem.2008.02.022
49. Shin JY, Roughead EE, Park BJ, Pratt NL. Cardiovascular safety of methylphenidate among children and young people with attention-deficit/hyperactivity disorder (ADHD): nationwide self controlled case series study. *BMJ*. 2016;353:i2550. doi:10.1136/bmj.i2550
50. Jackson JW. The cardiovascular safety of methylphenidate. *BMJ*. 2016;353:i2874. doi:10.1136/bmj.i2874
51. Man KKC, Shao SC, Chang YC, et al. Cardiovascular and metabolic risk of antipsychotics in children and young adults: a multinational self-controlled case series study. *Epidemiol Psychiatr Sci*. 2021;30:e65. doi:10.1017/s2045796021000494
52. Bellis JR, Kirkham JJ, Thiesen S, et al. Adverse drug reactions and off-label and unlicensed medicines in children: a nested case-control study of inpatients in a pediatric hospital. *BMC Med*. 2013;11(1):238. doi:10.1186/1741-7015-11-238
53. English BA, Dortch M, Ereshefsky L, Jhee S. Clinically significant psychotropic drug-drug interactions in the primary care setting. *Curr Psychiatry Rep*. 2012;14(4):376-390. doi:10.1007/s11920-012-0284-9
54. Dhaliwal JS, Rosani A, Saadabadi A. Diazepam. In: *StatPearls [Internet]*. : StatPearls Publishing; 2023. https://www.ncbi.nlm.nih.gov/books/NBK537022/.
55. Tisdale JE, Chung MK, Campbell KB, et al. Drug-induced arrhythmias: a scientific statement from the American Heart Association. *Circulation*. 2020;142(15):e214-e233. doi:10.1161/CIR.0000000000000905
56. Pacher P, Kecskemeti V. Cardiovascular side effects of new antidepressants and antipsychotics: new drugs, old concerns? *Curr Pharm Des*. 2004;10(20):2463-2475. doi:10.2174/1381612043383872
57. Richelson E. Tricyclic antidepressants block histamine H1 receptors of mouse neuroblastoma cells. *Nature*. 1978;274(5667):176-177. doi:10.1038/274176a0
58. Dwyer JB, Bloch MH. Antidepressants for pediatric patients. *Curr Psychiatr*. 2019;18(9):26-42f.
59. Reynisson B, Tanghöj G, Naumburg E. QTc interval-dependent body posture in pediatrics. *BMC Pediatr*. 2020;20(1):107. doi:10.1186/s12887-020-1959-8

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