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Mirtazapine exposure in pregnancy and fetal safety: A nationwide cohort study

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Abstract

Objective: To investigate the association between mirtazapine exposure in pregnancy and risk of specific adverse pregnancy outcomes.

Methods: A register-based nationwide cohort study was conducted including all registered pregnancies in Denmark from 1997 to 2016. Mirtazapine-exposed pregnancies were compared with mirtazapine unexposed pregnancies in a 1:4 ratio matched according to propensity scores. Outcomes were major congenital malformations analyzed using log binomial models, and spontaneous abortion, stillbirth and neonatal death analyzed using Cox proportional hazard regression.

Results: From a source population of 1,650,649 pregnancies, the propensity score-matched cohort included 4475 pregnancies (895 mirtazapine exposed) in the analysis of major congenital malformations. The analyses of spontaneous abortion included 9 500 pregnancies (1900 mirtazapine exposed), and for the analyses of stillbirths and neonatal deaths 9725 (1 945 mirtazapine-exposed) and 4485 pregnancies (897 mirtazapine-exposed) were included, respectively. Thirty-one (3.5%) children were diagnosed with major congenital malformation among the mirtazapine exposed compared with 152 (4.3%) among the unexposed pregnancies (OR=0.81, 95% CI 0.55–1.20). Spontaneous abortion occurred in 237 (12.5%) of the mirtazapine exposed compared with 931 (12.3%) of the unexposed pregnancies (HR = 1.04%, 95% CI 0.91–1.20). The analyses revealed no increased risk of stillbirth (HR = 0.88%, 95% CI 0.34–2.29) or neonatal death (HR = 0.60%, 95% CI 0.18–2.02).

Conclusions: In this nationwide Danish register study, mirtazapine exposure in pregnancy was not associated with major congenital malformations, spontaneous abortion, stillbirth, or neonatal death. Clinicians and patients can be reassured that mirtazapine is safe in pregnancy.

KEYWORDS
congenital abnormality, mirtazapine, perinatal death, pregnancy, spontaneous abortion

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1 | INTRODUCTION

Depression affects approximately 12% of pregnancies and untreated the condition is associated with adverse pregnancy outcomes on both short and long term.[1,2] Thus, pharmacological treatment may be indicated in cases where non-pharmacological treatment is insufficiently effective, and mirtazapine may be prescribed as a second line treatment.[3]

Mirtazapine blocks α_2-adrenergic receptors, serotonine 5-HT_{2A}, 5-HT_{2C} and 5-HT_3 receptors, and histamine H_1-receptors.[4] The use is approved for treatment of major depressive disorder, but might also be effective in anxiety disorders.[4,5] Additionally, mirtazapine has antiemetic effect[6] and might be an effective treatment in hyperemesis gravidarum.[7–9] Thus, knowledge of the safety of mirtazapine use in pregnancy is warranted.

Limited studies on mirtazapine exposure and pregnancy outcome are available. A systematic review from 2016 including 390 exposed neonates found no absolute contraindications for the use of mirtazapine in pregnancy.[10] However, two Scandinavian register-based studies have found an association between mirtazapine exposure in pregnancy and increased risk of spontaneous abortion and elective termination of pregnancy for fetal anomalies, respectively.[11,12]

1.1 | Aims of the study

In this population-based cohort study, we aimed to investigate the association between mirtazapine exposure in pregnancy and specific predefined adverse pregnancy outcomes: major congenital malformations, spontaneous abortion, stillbirth, and neonatal death. To minimize the risk of systematic error including confounding by indication, we compared mirtazapine-exposed pregnancies with propensity score-matched unexposed pregnancies.

Significant outcomes

- In this nationwide propensity score-matched cohort study, mirtazapine exposure in pregnancy was not associated with major congenital malformations, spontaneous abortion, stillbirth, or neonatal death.
- This is the largest available study on mirtazapine and pregnancy outcomes including 1 945 mirtazapine-exposed pregnancies.

Limitations

- Exposure is defined as a filled prescription for mirtazapine which does not necessarily equal intake of mirtazapine. However, compliance too antidepressants is relatively high.
- There might be other relevant adverse outcomes associated with mirtazapine exposure in pregnancy; however, only four pre-planned outcomes were investigated.

2 | MATERIAL AND METHODS

2.1 | Data sources and study cohort

A nationwide cohort study was conducted analyzing prospectively collected data from Danish registers. On December 27, 2019, data were obtained from national registers and linked via the unique personal identification number assigned to all Danish residents.

The source population consisted of all pregnancies in Denmark registered in the Medical Birth Register and/or the National Hospital Register from January 1, 1997, to December 31, 2016.

Data on pregnancies ending in live births and stillbirths were collected from The Medical Birth Register which contains data on maternal and birth-related variables.[13] Data on pregnancies with abortive outcome before 22 weeks of gestation were obtained from The National Hospital Register which contains data on all in- and outpatient contacts including diagnoses according to the International Statistical Classification of Diseases, Tenth Revision (ICD-10).[14] Both registers contain data on gestational age estimated by the crown-rump length measured at the routine first trimester ultrasound scan or, in absence of this, ultrasound scan performed earlier in the first trimester or last menstrual period. We excluded pregnancies with missing and implausible data on gestational age and pregnancies with overlapping dates (Figure 1).

All the remaining pregnancies were included in the analyses of spontaneous abortions and stillbirths, but only live birth pregnancies were included in the analyses of congenital malformations and neonatal deaths.

Data on filled prescriptions including Anatomical Therapeutic Chemical (ATC) code, date, dosage, and package size of filled prescription were collected from the Register of Medicinal Product Statistics,[15] and demographic and socioeconomic data were obtained from

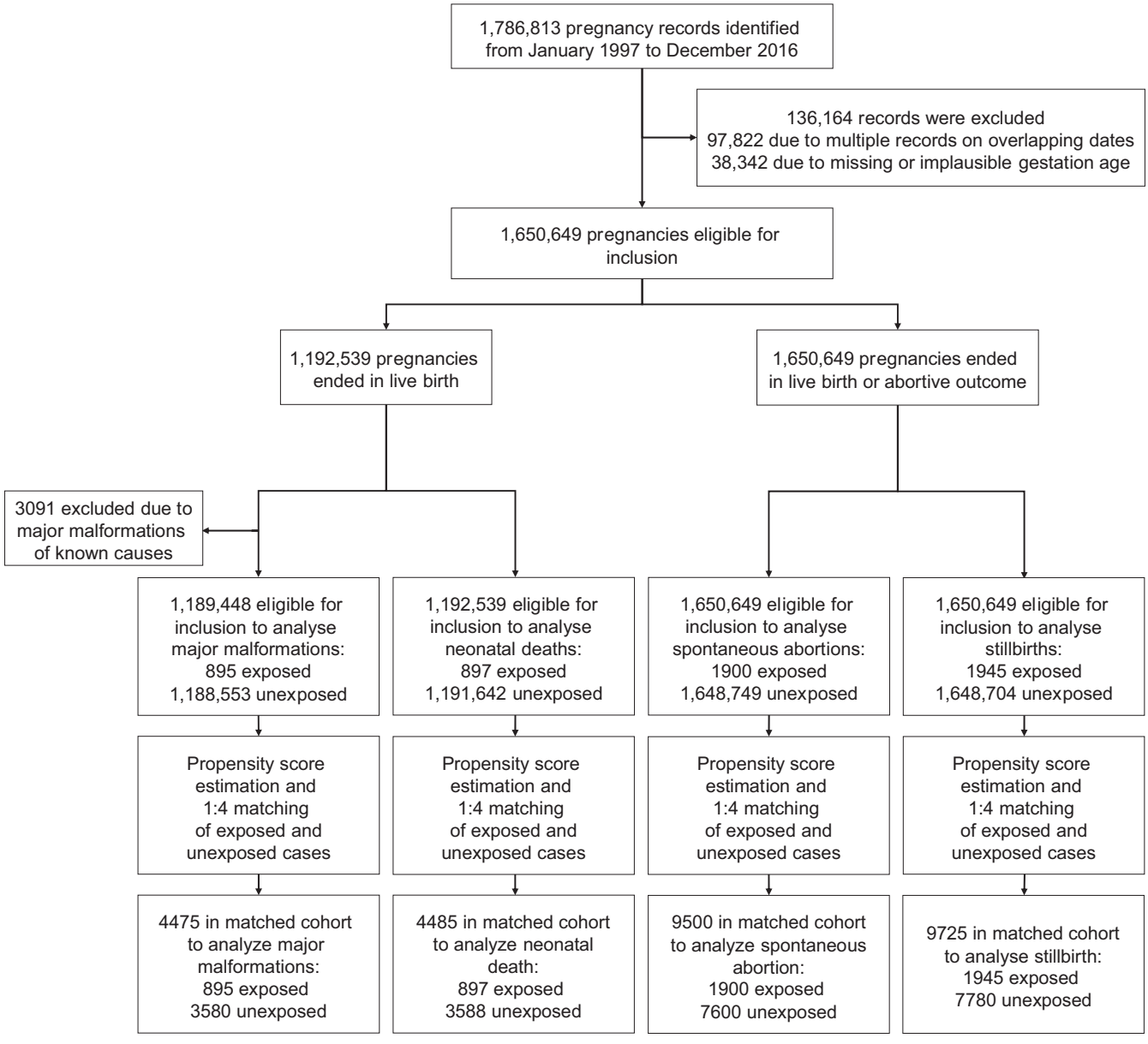

FIGURE 1 Flowchart of study cohorts

the Danish Civil Registration System[16] and Statistics Denmark.

Details on the utilized registers are provided in the Table S1.

2.2 | Exposure

Exposure was defined as at least one filled prescription for mirtazapine (ATC: N06AX11) with the date of filled prescription considered the first day of exposure.

Specific exposure windows were defined for each individual outcome. For congenital malformations, the exposure window was the first trimester. For spontaneous abortions, exposure earlier than 22 completed weeks of gestation were included. For stillbirths and neonatal deaths, we included exposure anytime during pregnancy.

2.3 | Outcomes

Outcomes were major congenital malformations, spontaneous abortions, stillbirths, and neonatal deaths. All outcomes were identified via the National Hospital Register and the Medical Birth Register.

Cases of major congenital malformations were live births where infants were diagnosed with a major congenital malformation according to the European Surveillance of Congenital Anomalies (EUROCAT) classification

system within the first year of life.[17] Subgroups of defects due to chromosomal aberration and syndromes of known causes and minor defects based on the EUROCAT exclusion list were excluded.[18]

Spontaneous abortion was defined as loss of pregnancy between 5 and 22 completed gestational weeks (ICD-10 codes O03 and O021). Spontaneous abortions occurring earlier than week 6 of gestation were excluded due to risk of misclassification, and fetal death later than 22 weeks of gestation was registered as stillbirth. Neonatal death was registered as death of the infant 0–27 days after birth.

2.4 | Covariates

Propensity score matching was performed to control for a wide range of confounding factors.

A logistic regression model assessing numerous baseline variables was used to estimate propensity scores predicting the probability of mirtazapine use during pregnancy. The baseline variables included demographic and socioeconomic characteristics, obstetric history, prescription drug use, and hospital contacts in the last year before pregnancy. All covariates are listed in Table S1.

2.5 | Analyses

For each of the four outcome analyses, the mirtazapine-exposed pregnancies were matched with unexposed pregnancies in a 1:4 ratio based on propensity scores using the greedy nearest neighbor matching algorithm (caliper width 0.02 on the propensity score scale).[19,20] Thus, four separate study cohorts were established, and these were the basis for the outcome analyses.

Missing values (0%–3.9% missing, see Table S2) were imputed using the mode value. The balance between the groups in the separate study cohorts were assessed by standardized differences; an estimate below 10% was considered an indication that the cohort was well balanced.

The analysis of major congenital malformation and subgroupings was performed using log binomial models to estimate relative risk (RR).

The outcomes spontaneous abortions, stillbirths, and neonatal deaths were analyzed using Cox proportional hazard regression to estimate hazard ratios (HRs) with days of gestation as the underlying time scale. Pregnancies were censored in case another event occurred other than the outcome of interest. A Wald test for the interaction between time scale and exposure was used to assess the proportional hazard assumption.

All measures of associations were reported with 95% confidence intervals (95% CI), and tests were two-sided. 95% CIs that did not overlap 1.0 were considered statistically significant.

Pre-planned sensitivity analyses were performed for the outcomes major malformations and spontaneous abortion. These outcomes are commonly assessed in studies on pharmacologic safety in pregnancy, and moreover, these were the outcomes that we found most interesting. The mirtazapine-exposed pregnancies were divided into two subgroups based on accumulated dosage of mirtazapine exposure: a high dosage group with accumulated dosage ≥2000 mg and a low dosage group with accumulated dosage <2000 mg.

For the outcome, major congenital malformations further pre-planned sensitivity analyses included subgroups of malformations as well as an analysis based on exposure narrowed down to gestational weeks 4 through 10, since this is when organogenesis occurs and thus teratogenicity might be detected. Additionally, we analyzed the risk of late elective termination of pregnancy (after week 12) for fetal abnormalities, as to not underestimate the prevalence of malformations by excluding those ending in abortive outcome due to a malformation (ICD-10 code of O053 or O054).

Analyses were performed using SAS software version 9.4 (SAS Institute Inc.).

2.6 | Ethics

Approval of this study was obtained from the Danish Data Protection Authority (P-2021–113). In Denmark, ethical approval and informed consent are not required for register-based studies.

3 | RESULTS

3.1 | Study cohorts

A total of 1,650,649 pregnancies were eligible for inclusion, and of these, 1945 were exposed to mirtazapine. The number of pregnancies ending in live birth was 1,192,539, including 897 pregnancies exposed to mirtazapine (Figure 1).

The cohort included in the analysis of major congenital malformation consisted of 4475 pregnancies (895 mirtazapine-exposed and 3 580 unexposed selected based on propensity scores), and the cohort included in the analysis of spontaneous abortion comprised 9500 pregnancies (1900 mirtazapine-exposed and 7600 propensity score matched unexposed).

For the analyses of stillbirth and neonatal death, the cohorts included 9725 (1 945 mirtazapine-exposed and 7780 unexposed) and 4485 pregnancies (897 mirtazapine-exposed and 3588 unexposed), respectively.

A flowchart of the cohort selection is shown in Figure 1, and the propensity score-matched baseline characteristics are available in Table 1.

Baseline characteristics for the unmatched pregnancies are available in Table S3 and Table S4, and differences for comparison of mirtazapine exposed and unexposed pregnancies before and after matching on propensity scores are available in Table S5.

3.2 | Outcomes

Thirty-one (3.5%) children were diagnosed with a major congenital malformation among the mirtazapine-exposed pregnancies compared with 152 (4.3%) among the unexposed pregnancies (OR = 0.81%, 95% CI 0.55–1.20).

Spontaneous abortion occurred in 237 (12.5%) of the pregnancies exposed to mirtazapine compared with 931 (12.3%) in the unexposed pregnancies (HR = 1.04%, 95% CI 0.91–1.20).

The analyses of stillbirth revealed no increased risk with 5 (0.3%) stillbirths among the exposed and 28 (0.4%) among the unexposed (HR = 0.88, 95% CI 0.34–2.29). Nor did we find an increased risk of neonatal death with 3 cases (0.3%) among the exposed compared with 20 cases (0.6%) among the unexposed (HR = 0.60, 95% CI 0.18–2.02). Numbers are shown in Figure 2.

3.3 | Sensitivity analyses

The sensitivity analyses based on accumulated mirtazapine dosage revealed no increased risk of spontaneous abortion among the pregnancies exposed to high accumulated mirtazapine dosage (n = 53, 10.4%) when compared with neither low accumulated dosage (n = 184, 13.2%) nor with mirtazapine unexposed pregnancies (n = 931, 12.3%).

We saw no increased risk of major congenital malformations in pregnancies exposed to high accumulated mirtazapine dosage (n = 7, 3.1%) when compared with low accumulated dosage (n = 24, 3.6%) and with mirtazapine unexposed pregnancies (n = 152, 4.3%). Additionally, we did not find an increased risk of major congenital malformations when the exposure window was narrowed down to the organogenetic gestational weeks 4 through 10, nor did we find an association between mirtazapine exposure and any subgroup of malformations (Table 2).

Late elective termination of pregnancy for fetal abnormalities occurred in five (0.3%) of the mirtazapine-exposed pregnancies compared with 36 (0.5%) among the unexposed (HR = 0.62%, 95% 0.24–1.58) (Table 2).

4 | DISCUSSION

In this propensity score-matched study based on Danish national register data, we found no association between mirtazapine exposure in pregnancy and increased risk of major congenital malformations, spontaneous abortion, stillbirth, or neonatal death.

The results support the findings of most other studies on the safety of mirtazapine use in pregnancy[10,21]; however, our findings are in contrast with a few studies.

One Danish register-based study partially including the same data as the present study found an association between mirtazapine exposure in pregnancy and spontaneous abortion when compared with unexposed pregnancies diagnosed with depression (unadjusted RR 2.23%, 95% CI 1.34–3.70).[11] However, the authors argue that the finding may reflect depression severity or factors related to the disorder. The propensity score-matched design of the present study reduces the risk of unaccounted confounders in that the unexposed are similar to the exposed on extensive variables, thus indicating that the previously found association may indeed be biased.

Another Scandinavian register-based study used a case-control design to investigate associations between antidepressant use and late termination of pregnancy. Based on data overlapping with the data used in the present study, Kieler et al. found that mirtazapine exposure in pregnancy was associated with increased risk of late termination of pregnancy for fetal anomalies (OR 2.2%, 95% CI 1.1–4.5, 99% CI 0.9–5.7).[12] Our sensitivity analysis on late termination of pregnancy for fetal anomalies did not confirm this association which, albeit based on few cases (N = 5), indicate that the previously found association may be at least partly explained by confounding factors.

Other studies on mirtazapine exposure in pregnancy have investigated other outcomes, and increased risk of poor neonatal adaptation syndrome (PNAS) due to withdrawals after mirtazapine exposure in late pregnancy has been reported.[10,21] PNAS occurs rarely, and this study did not have the strength to investigate this outcome. However, clinicians and pregnant women exposed to mirtazapine in late pregnancy should be aware of this possible association as neonates might need extra surveillance.

4.1 | Strengths and limitations

This study is to our knowledge the largest conducted study on mirtazapine exposure and fetal safety, and the

TABLE 1 Baseline characteristics of propensity score-matched pregnancy cohorts of mirtazapine exposed and unexposed in 1:4 ratio. Values are numbers (percentages)

	Major malformations		Neonatal death		Spontaneous abortion		Stillbirth	
Characteristics	**Mirtazapine ($n = 895$)**	**Unexposed ($n = 3580$)**	**Mirtazapine ($n = 897$)**	**Unexposed ($n = 3588$)**	**Mirtazapine ($n = 1900$)**	**Unexposed ($n = 7600$)**	**Mirtazapine ($n = 1945$)**	**Unexposed ($n = 7780$)**
Age at pregnancy onset								
≤19	19 (2.1)	61 (1.7)	19 (2.1)	74 (2.1)	81 (4.3)	332 (4.4)	82 (4.2)	305 (3.9)
20–24	151 (16.9)	641 (17.9)	151 (16.8)	659 (18.4)	330 (17.4)	1413 (18.6)	334 (17.2)	1479 (19.0)
25–29	225 (25.1)	948 (26.5)	225 (25.1)	925 (25.8)	449 (23.6)	1746 (23.0)	452 (23.2)	1798 (23.1)
30–34	264 (29.5)	1045 (29.2)	265 (29.5)	1048 (29.2)	482 (25.4)	1925 (25.3)	495 (25.5)	2006 (25.8)
≥35	236 (26.4)	885 (24.7)	237 (26.4)	882 (24.6)	558 (29.4)	2184 (28.7)	582 (29.9)	2192 (28.2)
Married or living with partner	605 (67.6)	2425 (67.7)	606 (67.6)	2398 (66.8)	1116 (58.7)	4437 (58.4)	1150 (59.1)	4425 (56.9)
Place of birth								
Denmark	636 (71.1)	2642 (73.8)	637 (71.0)	2643 (73.7)	1374 (72.3)	5740 (75.5)	1405 (72.2)	5858 (75.3)
Europe	56 (6.3)	211 (5.9)	57 (6.4)	232 (6.5)	126 (6.7)	497 (6.5)	129 (6.6)	488 (6.3)
Outside of Europe	203 (22.7)	727 (20.3)	203 (22.6)	713 (19.9	400 (21.1)	1363 (17.9)	411 (21.1)	1434 (18.4)
Region of residence								
Capital	206 (23.0)	812 (22.7)	206 (23.0)	786 (21.9)	1158 (61.0)	4641 (61.1)	1177 (60.5)	4549 (58.5)
Zealand	115 (12.9)	437 (21.2)	115 (12.8)	502 (14.0)	127 (6.7)	513 (6.8)	134 (6.9)	558 (7.2)
Southern Denmark	207 (23.1)	908 (25.4)	207 (23.1)	853 (23.8)	223 (11.7)	956 (12.6)	225 (11.6)	987 (12.7)
Mid Jutland	268 (29.9)	1050 (29.3)	269 (30.0)	1080 (30.1)	283 (14.9)	1085 (14.3)	294 (15.1)	1190 (15.3)
North Jutland	99 (11.1)	373 (10.4)	100 (11.2)	367 (10.2)	109 (5.7)	405 (5.3)	115 (5.9)	496 (6.4)
Gross household income, quartile								
1	483 (54.0)	1955 (54.6)	484 (54.0)	1960 (54.6)	954 (50.2)	3912 (51.5)	966 (49.7)	3933 (50.6)
2	212 (23.7)	890 (24.9)	212 (23.6)	834 (23.2)	535 (28.2)	2092 (27.5)	549 (28.2)	2187 (28.1)
3	124 (13.9)	486 (13.6)	123 (13.7)	496 (13.8)	254 (13.4)	998 (13.1)	265 (13.6)	1092 (14.0)
4	76 (8.5)	249 (7.0)	78 (8.7)	298 (8.3)	157 (8.3)	598 (7.9)	165 (8.5)	568 (7.3)
Education level, years								
<12	463 (51.7)	1857 (51.9)	464 (51.7)	1880 (52.4)	1045 (55.0)	4332 (57.0)	1061 (54.6)	4450 (57.2)
12–13	114 (12.7)	498 (13.9)	114 (12.7)	518 (14.4)	240 (12.6)	873 (11.5)	243 (12.5)	909 (11.7)
14–15	130 (14.5)	491 (13.7)	130 (14.5)	457 (12.7)	265 (14.0)	1073 (14.1)	270 (13.9)	1063 (13.7)
>15	188 (21.0)	734 (20.5)	189 (21.1)	733 (20.4)	350 (18.4)	1322 (17.4)	371 (19.1)	1358 (17.5)

TABLE 1 (Continued)

Characteristics	Major malformations		Neonatal death		Spontaneous abortion		Stillbirth	
	Mirtazapine ($n = 895$)	**Unexposed ($n = 3580$)**	**Mirtazapine ($n = 897$)**	**Unexposed ($n = 3588$)**	**Mirtazapine ($n = 1900$)**	**Unexposed ($n = 7600$)**	**Mirtazapine ($n = 1945$)**	**Unexposed ($n = 7780$)**
Parity								
1	380 (42.5)	1530 (42.7)	381 (42.5)	1630 (45.4)				
2	193 (21.6)	804 (22.5)	193 (21.5)	743 (20.7)				
≥3	322 (36.0)	1246 (34.8)	323 (36.0)	1215 (33.9)				
Multiple birth pregnancy	33 (3.7)	119 (3.3)	34 (3.8)	126 (3.5)				
Smoking during pregnancy	357 (39.9)	1440 (40.2)	357 (39.8)	1444 (40.3)				
Previous pregnancy with the same outcome	31 (3.5)	136 (3.8)	5 (0.6)	26 (0.7)	297 (15.6)	1169 (15.4)	8 (0.4)	24 (0.3)
Prescription drug use in past year								
Antidiabetic drugs	17 (1.9)	70 (2.0)	17 (1.9)	55 (1.5)	29 (1.5)	122 (1.6)	30 (1.5)	99 (1.3)
Antihypertensives	59 (6.6)	177 (4.9)	60 (6.7)	225 (6.3)	140 (7.4)	501 (6.6)	144 (7.4)	510 (6.6)
Thyroid drugs	17 (1.9)	60 (1.7)	17 (1.9)	67 (1.8)	42 (2.2)	163 (2.1)	43 (2.2)	161 (2.1)
NSAIDs	300 (33.5)	1182 (33.0)	300 (33.4)	1159 (32.3)	620 (32.6)	2465 (32.4)	628 (32.3)	2477 (31.84)
Opiates	121 (13.5)	452 (12.6)	121 (13.5)	444 (12.4)	283 (14.9)	1033 (13.6)	290 (14.9)	1111 (14.3)
Antimigraine drugs	62 (6.9)	191 (5.3)	62 (6.9)	227 (6.33)	112 (5.9)	395 (5.2)	118 (6.1)	436 (5.6)
Antidepressants*	538 (60.1)	2259 (63.1)	540 (60.2)	2274 (63.4)	1078 (56.7)	4595 (60.5)	1105 (56.8)	4732 (60.8)
Antacids, H_2-blockers, and PPIs	181 (20.2)	616 (17.2)	181 (20.2)	682 (19.0)	344 (18.1)	1325 (17.4)	351 (18.1)	1370 (17.6)
Oral corticosteroids	29 (3.2)	101 (2.8)	29 (3.2)	117 (3.3)	66 (3.5)	256 (3.4)	66 (3.4)	251 (3.2)
Systemic antivirals used for herpes infections	108 (3.0)	30 (3.4)	30 (3.3)	118 (3.3)	59 (3.1)	237 (3.1)	60 (3.1)	206 (2.7)
Antipsychotics	156 (17.4)	503 (14.1)	156 (17.4)	499 (13.9)	380 (20.0)	1172 (15.4)	384 (19.7)	1167 (15.0)
Antibiotics for systemic use	670 (74.9)	2656 (74.2)	672 (74.9)	2651 (73.9)	1269 (66.8)	5057 (66.5)	1288 (66.2)	5115 (65.8)
Antiemetics and antinauseants	13 (1.5)	58 (1.6)	13 (1.5)	70 (2.0)	25 (1.3)	100 (1.3)	26 (1.3)	102 (1.3)
Anxiolytics	166 (18.6)	589 (16.5)	166 (18.5)	575 (16.0)	394 (21.8)	1416 (18.6)	404 (20.8)	1373 (17.7)
Antiepileptics	76 (8.5)	259 (7.3)	76 (8.5)	239 (6.7)	171 (9.0)	558 (7.3)	179 (9.2)	597 (7.7)
Drugs used for IVF in past 3 months	22 (2.5)	71 (2.0)	22 (2.5)	87 (2.4)	35 (1.8)	138 (1.8)	36 (1.9)	110 (1.4)

(Continues)

TABLE 1 (Continued)

Characteristics	Major malformations		Neonatal death		Spontaneous abortion		Stillbirth	
	Mirtazapine (*n* = 895)	**Unexposed (*n* = 3580)**	**Mirtazapine (*n* = 897)**	**Unexposed (*n* = 3588)**	**Mirtazapine (*n* = 1900)**	**Unexposed (*n* = 7600)**	**Mirtazapine (*n* = 1945)**	**Unexposed (*n* = 7780)**
No. of drugs used								
1–2	410 (45.8)	1752 (48.9)	411 (45.8)	1692 (47.2)	884 (46.5)	3640 (47.9)	909 (46.7)	3799 (48.8)
3–4	318 (35.5)	1262 (35.3)	319 (35.6)	1343 (37.4)	647 (34.1)	2664 (35.1)	657 (33.8)	2630 (33.8)
≥5	125 (14.0)	407 (11.4)	125 (13.9)	385 (10.7)	844 (11.1)	255 (13.4)	261 (13.4)	866 (11.1)
Hospital care utilization in past year								
No. of hospitalization								
1	105 (11.7)	398 (11.1)	105 (11.7)	394 (11.0)	1013 (13.3)	260 (13.7)	266 (13.7)	954 (12.3)
2	23 (2.6)	103 (2.9)	23 (2.6)	78 (2.2)	245 (3.2)	65 (3.4)	65 (3.3)	258 (3.3)
≥3	15 (1.7)	58 (1.6)	15 (1.7)	52 (1.5)	40 (2.1)	147 (1.9)	41 (2.11)	157 (2.0)
No. of outpatient contacts								
1	128 (14.3)	499 (13.9)	128 (14.3)	506 (14.1)	1181 (15.5)	297 (15.6)	301 (15.5)	1154 (14.8)
2	56 (6.3)	239 (6.7)	56 (6.2)	204 (5.7)	523 (6.9)	134 (7.1)	138 (7.1)	524 (6.7)
≥3	27 (3.0)	902.5)	27 (3.0)	113 (3.2)	239 (3.1)	61 (3.2)	62 (3.2)	245 (3.2)

Abbreviations: IVF, in vitro fertilization; NA, not available; NSAID, non-steroid anti-inflammatory drug; PPIs, proton pump inhibitors.

*Antidepressants excluding mirtazapine.

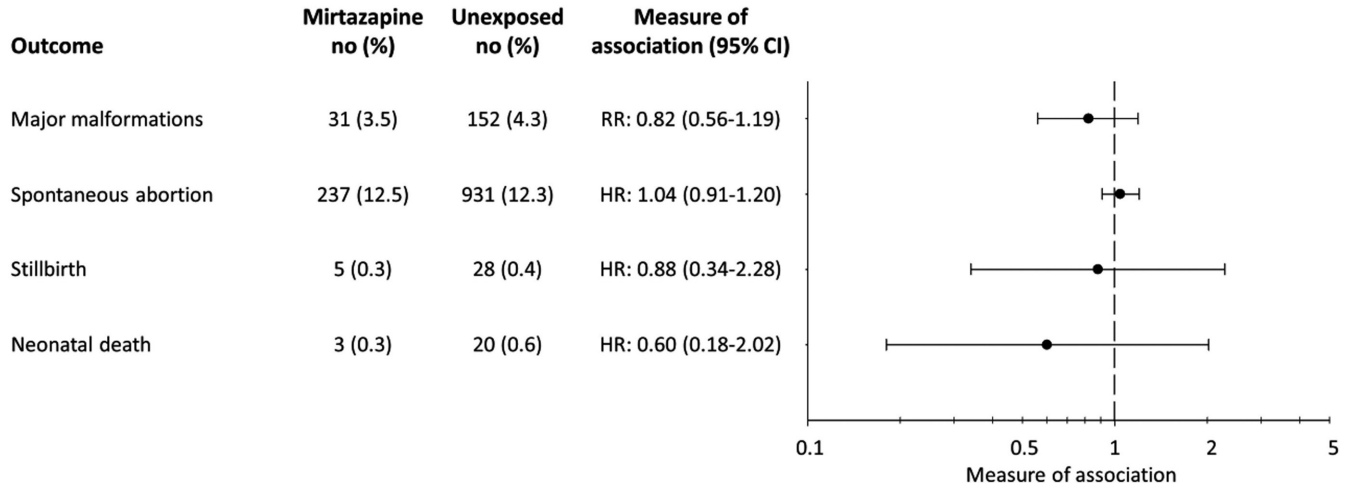

FIGURE 2 Association between mirtazapine exposed compared with unexposed pregnancies and adverse fetal outcomes. HR: hazard ratio. RR: relative risk

TABLE 2 Sensitivity analyses of mirtazapine exposure in pregnancy and adverse fetal outcomes

Sensitivity analyses	Mirtazapine exposed no (%)	Mirtazapine unexposed no (%)	Measure of association (95% CI)
Dose dependency Spontaneous abortion			
Mirtazapine, low accumulated dose <2000 mg	184 (13.2)	931 (12.3)	HR: 1.28 (0.96–1.32)
Mirtazapine, high accumulated dose ≥2000 mg	53 (10.4)	931 (12.3)	HR: 0.83 (0.63–1.09)
Dose dependency Major malformation			
Mirtazapine, low accumulated dose<2000 mg	24 (3.6)	152 (4.3)	RR: 0.84 (0.55–1.28)
Mirtazapine, high accumulated dose ≥2000 mg	7 (3.1)	152 (4.3)	RR: 0.86 (0.59–1.24)
Major malformations, filled prescription only in week 4–10	17 (4.3)	152 (4.3)	RR: 1.00 (0.61–1.63)
Subgroup of major malformations*			
Heart	13 (1.5)	48 (1.3)	RR: 1.08 (0.59–1.99)
Digestive system	3 (0.3)	11 (0.3)	RR: 1.09 (0.31–3.90)
Limb	8 (0.9)	36 (1.0)	RR: 0.89 (0.41–1.91)
Late elective termination of pregnancy for fetal abnormalities	5 (0.3)	36 (0.5)	HR: 0.62 (0.24–1.58)

Abbreviations: HR, hazard ratio; RR, relative risk.

*Only subgroups with outcome ≥3 in the exposure group is included.

analyses include relevant adverse pregnancy outcomes of concern when weighing pros and cons for pharmacological treatment in pregnancy. Previously conducted studies have included smaller patient populations and fewer mirtazapine-exposed pregnancies. Thus, the present study contributes substantially with assertive evidence.

Inclusion of all pregnancies in the Danish registers in the source population minimizes selection bias end thus ensures the external validity of the study. The propensity score-matched design reduces the influence of confounders including confounding by indication. This is specifically relevant to consider when establishing associations between antidepressant use and pregnancy outcome, given that prenatal depression in itself is associated with adverse pregnancy outcomes. In the present study, covariates were well balanced in the propensity score-matched cohorts (Table S5), and even though residual confounding is still possible, propensity score matching is a valuable tool to limit its influence.[22]

A methodological limitation of this study is that exposure is defined as a filled prescription for mirtazapine which does not necessarily equal intake of mirtazapine.

This could bias the results toward the unexposed; however, compliance to dispensed antidepressants is relatively high.[23] Moreover, the sensitivity analysis on accumulated dosage ≥2000 mg which requires more than one filled prescription and thus indicates that the filled prescriptions were indeed administered did not reveal an association with the outcomes. Likewise, the validity of the Danish registers is high and the outcomes congenital malformations and spontaneous abortions have high positive predictive values.[24–26]

To conclude, this nationwide cohort study contributes with substantial evidence that mirtazapine exposure in pregnancy is not associated with increased risk of major congenital malformations, spontaneous abortion, stillbirth, or neonatal death.

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PEER REVIEW

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DATA AVAILABILITY STATEMENT

Sharing of data would need permission of data custodians.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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