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ORIGINAL RESEARCH ARTICLE

Duloxetine Exposure During Pregnancy and the Risk of Offspring Being Born Small for Gestational Age or Prematurely: A Nationwide Danish and Swedish Safety Study

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Abstract

Background Depression or depressive symptoms are common among pregnant women. The use of antidepressants during pregnancy has grown steadily. The risk of offspring being born small for gestational age or prematurely when exposed to duloxetine during pregnancy is not established.

Objective We aimed to investigate the association between duloxetine exposure during pregnancy and offspring being born small for gestational age or prematurely.

Methods We conducted an observational study including live births in Sweden and Denmark (2004–2016). Duloxetine exposure during early (0–140 days) or late (141 to delivery) pregnancy compared with duloxetine-non-exposed, selective serotonin reuptake inhibitor-exposed, venlafaxine-exposed, and duloxetine discontinuers.

Results In total, 2,083,467 pregnancies were identified, where 1589 and 450 were duloxetine exposed in early and late pregnancy, respectively. For small for gestational age, no increased risk was seen for duloxetine across comparators. In the early and late exposure windows, propensity score-matched odds ratios for small for gestational age ranged between 0.64 (95% confidence interval 0.44–0.95) and 1.48 (95% confidence interval 0.85–2.57). For preterm birth, the findings differed across comparators and exposure-time windows, but trended towards an increased risk for duloxetine-exposed when compared with duloxetine-non-exposed, selective serotonin reuptake inhibitor-exposed, and duloxetine discontinuers in both early exposure and late exposure. The odds ratios ranged between 1.17 and 2.04, of which some did not reach statistical significance. No clear association was observed when compared with venlafaxine exposed, 0.91 (95% confidence interval 0.73–1.14) for early exposure and 1.26 (95% confidence interval 0.86–1.86) for late exposure. Most preterm births (79.2%) occurred in weeks 33–36 of gestation.

Conclusions Duloxetine exposure during pregnancy is unlikely to increase the risk of small for gestational age. Although not consequently statistically significant across comparisons, a trend towards an increased risk of preterm birth was observed for duloxetine exposed. Therefore, an increased risk of preterm birth cannot be excluded, especially for women exposed to duloxetine throughout pregnancy.

Key Points

The risk of offspring being born small for gestational age or prematurely after exposure to duloxetine during pregnancy was investigated in a bi-national cohort.

It is unlikely that exposure to duloxetine during pregnancy increases the risk of small for gestational age.

A risk of preterm birth was observed in some analyses and can therefore not be excluded.

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1 Introduction

In Europe and the USA, approximately 10% of all births are preterm births (< 37 weeks of gestation), being the leading cause of perinatal deaths and long-term disabilities [1]. A birth weight below the tenth percentile for the gestational age is considered small for gestational age (SGA). Infants born SGA are at a greater risk of death and are more likely to develop diabetes mellitus, cardiovascular disease, schizophrenia, and other conditions [1, 2].

Depression or depressive symptoms are common among pregnant women [3–6]. Despite a drop in recent years [7], the use of antidepressants during pregnancy has grown steadily [8]. In Denmark, the most commonly used antidepressants include selective serotonin reuptake inhibitors (SSRIs) [8], followed by serotonin and norepinephrine reuptake inhibitors (SNRIs) [7, 8], reflecting that SSRIs are first-line treatment according to national guidelines, with SNRIs being second-line treatment. Maternal use of SSRIs during pregnancy has been associated with preterm birth [9–12], low birth weight [10, 11], and SGA [10, 13], although evidence is conflicting [14]. The significance of time of exposure to antidepressants during pregnancy is also uncertain; SSRI use late in pregnancy has been associated with preterm birth [10, 11, 15], low birth weight [10, 11], and SGA [16], but most studies do not take potential confounding into account. Consequently, the independent effects of medications and depression severity are unclear, and it is uncertain to what extent observed associations are a result of biologic or behavioral factors (e.g., smoking, substance abuse, or a poor diet are common among women with mood disorders) to the medications, or a combination. Possible risks associated with SNRIs have not been fully elucidated. However, as both SSRIs and SNRIs affect serotonin levels, SNRIs can, in theory, be expected to be associated with similar adverse effects as SSRIs. This might be the reason why some studies have reported an increased risk of preterm birth and SGA in patients treated with non-SSRI antidepressants [10, 12].

A recent study based on data from the USA investigated early and late pregnancy exposures to duloxetine and found no increased risk of preterm birth, and a potentially small increased risk of SGA [17]. Because of the limited amount of available data in previous studies, the aim of the present study was to investigate the association between duloxetine exposure during pregnancy and preterm birth and SGA in a population consisting of all pregnancies from Sweden and Denmark over 12 years, with detailed information about potential confounders and various comparators.

2 Methods

This was a nationwide observational cohort study. Based on Danish and Swedish national registers, live births were identified, including information about SGA and preterm birth. Mothers exposure to antidepressants as well as potential confounders were collected.

The cohort consisted of all pregnancies with a registered live birth from 2004 to 2016, identified via the national Danish and Swedish medical birth registers, respectively. Exclusion criteria included mothers emigrating between 365 days prior to the last menstrual period (LMP) until 30 days post-delivery, pregnancies with a missing or implausible gestational age (before week 20 or after week 45), and missing birth weight.

Information about preterm birth and SGA was gathered from the medical birth registers. Preterm birth was defined as a live birth between the 20th and 37th week of gestation. Duration of pregnancy was based on LMP (mothers self-reported date and two subsequent ultrasounds in the first and second trimester), and date of delivery. Small for gestational age was defined as birth weight under the tenth percentiles stratified on pregnancy week and sex, and the cut-offs were calculated using the nationwide, separately for Sweden and Denmark. Analyses of SGA were stratified on diagnosis for congenital malformation (yes/no), information on which was obtained from the national patient registers between birth and 365 days postpartum.

Maternal exposure to medication was defined as at least one redeemed prescription from a community pharmacy. Two exposure-time windows were used: early exposure from LMP to 140 days post-LMP, and late exposure from 141 days post-LMP to date of delivery. Women with duloxetine (ATC: N06AX21) exposure in the early-exposure and late-exposure windows were compared with four prespecified comparison groups: (1) women not exposed to duloxetine (hereafter referred as duloxetine non-exposed); (2) women exposed to SSRIs (hereafter referred as SSRI exposed; ATC: N06AB), to have a comparison group with exposure to antidepressants, but in another drug class than duloxetine; (3) women exposed to venlafaxine (hereafter referred as venlafaxine exposed; ATC: N06AX16), to have a comparison group with exposure to an antidepressant in the same drug class as duloxetine and therefore a comparable indication for the treatment (e.g., depression severity); or (4) duloxetine discontinuers (at least one redeemed prescription of duloxetine between 365 days prior to LMP, but not during the exposure-time window), to have a comparison group of women known to recently have an indication for duloxetine. The comparison groups were not mutually exclusive and were analyzed separately. When comparing duloxetine-exposed women with duloxetine-non-exposed, SSRI-exposed, and

venlafaxine-exposed women, an additional exclusion criterion was applied, where women with duloxetine exposure from 90 days prior to LMP were excluded from the comparison groups. This *washout period* was applied to avoid misclassification of women with duloxetine exposure being grouped in the comparison groups.

Prespecified potential confounders were used based on the literature, clinical knowledge, and the availability of data: data source (Sweden/Denmark), birth year (2004–2008, 2009–2012, 2013–2016), maternal age (18–24, 25–29, 30–34, > 34 years), previous spontaneous abortions (0/1/≥ 2), previous stillbirths (yes/no), smoking during pregnancy (yes/no), psychiatric hospitalizations (1 year prior to LMP: yes/no), psychiatric outpatient visits (1 year prior to LMP: yes/no), household income (year of LMP, quartiles within country), and highest completed education (year of LMP: < 11, 11–15, and > 15 years). Comorbidities 5 years prior to LMP (see Table S1 of the Electronic Supplementary Material [ESM] for International Classification of Diseases, Ninth Revision and ATC codes) included affective disorder, anxiety or phobia, depression, gestational diabetes, diabetes, diabetic peripheral neuropathy, hyperthyroidism and hypothyroidism, hypertension, obesity, renal failure, severe stress reaction, and stress urinary incontinence. Co-medication (at least one redeemed prescription between 90 days prior to LMP to the end of the relevant exposure-time window; see Table S2 of the ESM for ATC codes) included antiepileptic drugs, antihypertensive drugs, antipsychotics, anxiolytics, danazol, estradiol, fluconazole, glucose-lowering medications, non-steroidal anti-inflammatory drugs, opioids, progesterone, steroid hormone, thyroid hormone, and triptans.

In Sweden and Denmark, individuals can be identified across national registers via a personal identification number. This study used data from the Danish and Swedish national patient registers [18, 19] (information about hospital admissions), the medical birth registers [20–22] (prenatal and postnatal information about the mother and offspring), the national prescription registers [23–25] (information about redeemed prescriptions), and national educational, income, and migration registers [26–28]. For Sweden, the National Prescription Register is available from 2005, and therefore the exposure groups were followed from 2005.

2.1 Statistical Analyses

The outcomes of interest, preterm birth, and SGA were defined as an indicator variable (yes/no) and analyzed by logistic regression. The comparison groups were not mutually exclusive, meaning that a SSRI-exposed woman could also be venlafaxine exposed and that an early exposed woman may also be late exposed. Therefore, the analyses were performed with each comparison group individually.

The following analyses were performed: (1) unadjusted logistic regression; (2) adjusted logistic regression; and (3) conditional logistic regression with the matched group ID as a strata variable after propensity score (PS) matching. Each model was fitted individually, and covariates were removed if the model could not be estimated. For the PS, we performed logistic regression and greedy matching using the SAS macro *OneToManyMTCH* [29], with an extension to secure only women with a maximum difference of 0.2 logit of the PS for matching. Ratios of 1:4, 1:2, 1:1, and 1:1 were used to match duloxetine-non-exposed, SSRI-exposed, venlafaxine-exposed, and duloxetine discontinuers, respectively. Individuals with no match were excluded from the PS-matched analyses. Standardized differences were calculated using the SAS macro *stddiff macro* to assess the balance of covariates with PS matching [30, 31]. Selective serotonin reuptake inhibitor and venlafaxine comedication were not part of the PS model. The definition of duloxetine-exposed did not allow SSRI and venlafaxine comedication in the relevant exposure-time window, and, therefore, these covariates 100% predicted the exposure group and cannot be part of the PS model. Consequently, SSRI and venlafaxine comedication will appear unbalanced in the baseline tables.

Missing values for income were imputed 1 year prior to LMP or 1 year after LMP. Education was imputed 1 year after LMP. This resulted in few missing values and the analyses were carried out assuming missing at random; hence, persons with missing values were deleted from the analysis.

Four prespecified sensitivity analyses were conducted. To challenge the exposure definition of a minimum one redeemed prescription, sensitivity analyses were conducted with exposure redefined to a minimum of two redeemed prescriptions and redefined to an overlap between the exposure-time window and days' supply of redeemed prescriptions. Days' supply was based on the number and strength of redeemed pills compared with the World Health Organization's daily defined dose [32]. Sensitivity analyses restricting the cohort to the first pregnancy within the study period were performed. Sensitivity analyses using the body mass index as a covariate were conducted. Information on the maternal body mass index was available from the medical birth registers but was missing for a considerable number of women.

SAS Enterprise Guide 7.15 was used. A significance level of 5% was applied. Validation of the programming was performed; shorter programs (3–20 lines of coding) were reviewed, and longer programs were double coded by an independent statistical programmer.

3 Results

Overall, 2,083,467 pregnancies were included in the study (63.9% from Sweden), of which 1589 and 450 were duloxetine exposed in early and late pregnancies, respectively. Figure 1 shows a flowchart of the cohort.

Tables 1, 2 shows baseline characteristics for the duloxetine-exposed women and the four comparison groups (full cohort and the PS-matched subset). For the full cohort, patient characteristics of duloxetine non-exposed were at least similar to duloxetine exposed, compared to the venlafaxine-exposed and duloxetine discontinuers. Overall, after PS matching, the comparison groups became more similar to duloxetine exposed with most standardized mean differences below 0.1. Table S3 of the ESM shows baseline characteristics for all covariates for all main analyses.

A large overlap was seen among early and late exposure, with 74–99% of late exposed also being early exposed. Among the 450 duloxetine exposed in late pregnancy, 421 (94%) were also duloxetine exposed in early pregnancy.

3.1 Small for Gestational Age

In the early-exposure window, no increased risk of SGA was observed when duloxetine exposed were compared to duloxetine-non-exposed, SSRI-exposed, venlafaxine-exposed, or duloxetine discontinuers (Fig. 2). The PS-matched odds ratios (ORs) were 0.88 (95% confidence interval [CI] 0.73–1.08), 0.84 (95% CI 0.69–1.04), 1.03 (95% CI 0.81–1.30), and 1.05 (95% CI 0.83–1.34), respectively.

For the late-exposure window, no increased risk of SGA was observed for duloxetine exposed when compared with duloxetine-non-exposed, SSRI-exposed, and duloxetine discontinuers. The PS-matched ORs were 0.64 (95% CI 0.44–0.95), 0.85 (95% CI 0.56–1.29), and 0.72 (95% CI 0.45–1.14), respectively. When compared with venlafaxine exposed, the point estimate suggested an increased risk of SGA; however, the observation was statistically non-significant with wide CIs: PS-matched OR was 1.48 (95% CI 0.85–2.57) [Fig. 3].

Similar findings were seen in the analyses stratified on malformation. For the early-exposure and late-exposure windows without malformation, and the early-exposure window with malformation, no increased risk of SGA was observed for duloxetine-exposed across comparators. A few point estimates suggested an increased risk but were statistically non-significant with wide CIs (Figures S1–S3 of the ESM). In the analyses of the late-exposure window and SGA with malformation, all estimates had wide CIs and were statistically non-significant, which was attributable to the relatively small sample size (Fig. S4 of the ESM). Similar results were observed in the sensitivity analyses (results not presented).

3.2 Preterm Birth

For the early-exposure window, an increased risk of preterm birth was observed for duloxetine-exposed when compared

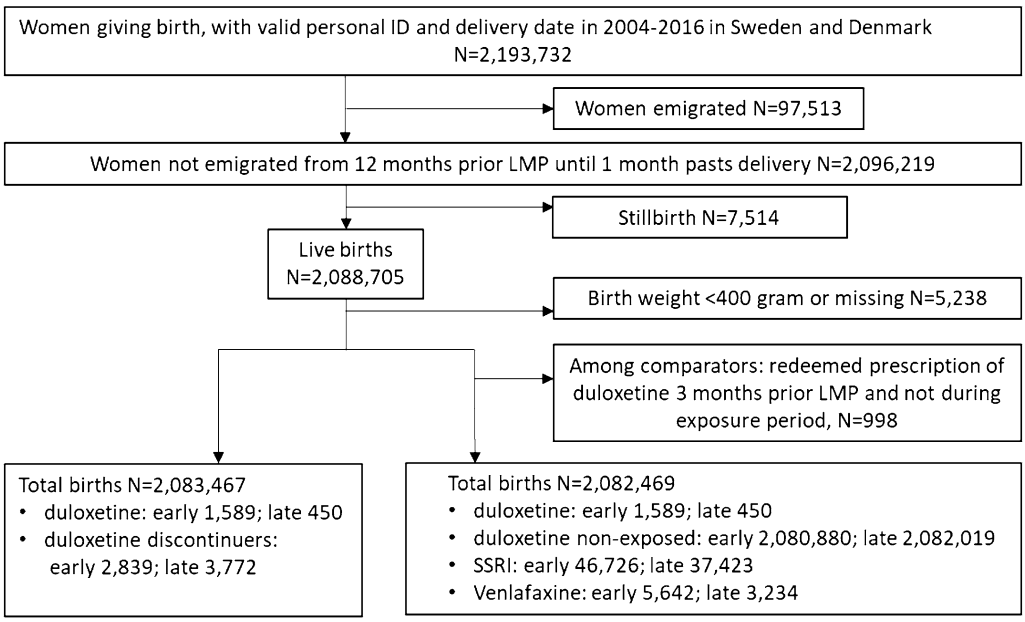

Fig. 1 Flow chart of the population. All registered births in Sweden and Denmark. Exposure-time windows: early: from last menstrual period (LMP) to 140 days post-LMP; late: from 141 days post-LMP to the date of delivery. The same cohort is used for the analyses of small for gestational age and preterm delivery

Table 1 Baseline characteristics for duloxetine exposed, duloxetine non-exposed, and SSRI exposed, early-exposure window

Variable	Value	Duloxetine before matching $n = 1589$	Duloxetine vs duloxetine non-exposed					Duloxetine vs SSRI				
			Before matching		After matching			Before matching		After matching		
			Duloxetine non-exposed $n = 2{,}080{,}880$	SMD	Duloxetine $n = 1442$	Duloxetine non-exposed $n = 5768$	SMD	SSRI $n = 46{,}726$	SMD	Duloxetine $n = 1513$	SSRI $n = 3026$	SMD
Age,years, continuous	Mean	30.9 (27.3; 35.1)	30.2 (26.7; 33.7)	0.17	30.8 (27.3; 35.0)	30.9 (26.7; 35.1)	0.04	30.7 (26.9; 34.4)	0.09	30.8 (27.3; 35.0)	30.5 (26.5; 34.7)	0.08
Age, years, grouped	18–24	232 (14.6%)	324,068 (15.6%)	0.18	223 (14.8%)	977 (16.2%)	0.06	7330 (15.7%)	0.07	223 (14.7%)	483 (16.0%)	0.05
	25–29	468 (29.5%)	685,957 (33.0%)		448 (29.7%)	1707 (28.3%)		13,745 (29.4%)		450 (29.7%)	935 (30.9%)	
	30–34	403 (25.4%)	593,017 (28.5%)		381 (25.2%)	1461 (24.2%)		12,714 (27.2%)		382 (25.2%)	708 (23.4%)	
	35–60	486 (30.6%)	477,838 (23.0%)		458 (30.3%)	1895 (31.4%)		12,937 (27.7%)		458 (30.3%)	900 (29.7%)	
Household income	Quartile1	595 (37.6%)	460,639 (22.3%)	0.41	573 (37.9%)	2315 (38.3%)	0.00	13,978 (30.1%)	0.19	575 (38.0%)	1212 (40.1%)	0.05
	Quartile2	413 (26.1%)	516,135 (25.0%)		389 (25.8%)	1573 (26.0%)		12,056 (26.0%)		389 (25.7%)	774 (25.6%)	
	Quartile3	331 (20.9%)	548,650 (26.5%)		313 (20.7%)	1294 (21.4%)		11,442 (24.7%)		314 (20.8%)	604 (20.0%)	
	Quartile4	245 (15.5%)	542,322 (26.2%)		235 (15.6%)	858 (14.2%)		8906 (19.2%)		235 (15.5%)	436 (14.4%)	
Education, no. of years	<11	357 (22.6%)	252,782 (12.3%)	0.39	343 (22.7%)	1696 (28.1%)	0.12	8515 (18.4%)	0.19	343 (22.7%)	682 (22.5%)	0.05
	11–15	843 (53.4%)	1,002,034 (48.8%)		803 (53.2%)	3060 (50.7%)		22,996 (49.6%)		806 (53.3%)	1657 (54.8%)	
	>16	379 (24.0%)	800,252 (38.9%)		364 (24.1%)	1284 (21.3%)		14,864 (32.1%)		364 (24.1%)	687 (22.7%)	
Depression	Yes	549 (34.6%)	39,329 (1.9%)	0.93	515 (34.1%)	2187 (36.2%)	−0.04	8672 (18.6%)	0.37	518 (34.2%)	1041 (34.4%)	−0.00
Anxiety or phobia	Yes	205 (12.9%)	19,375 (0.9%)	0.49	193 (12.8%)	786 (13.0%)	−0.01	4691 (10.0%)	0.09	194 (12.8%)	389 (12.9%)	−0.00
Severe stress reaction	Yes	186 (11.7%)	21,321 (1.0%)	0.45	165 (10.9%)	714 (11.8%)	−0.03	2375 (5.1%)	0.24	168 (11.1%)	329 (10.9%)	0.01
Stress urinary incontinence	Yes	<5 (0%)	<5 (0%)	0.00	<5 (0%)	<5 (0%)	0.00	<5 (0%)	0.00	<5 (0%)	<5 (0%)	0.00
SSRI comedication	Yes	<5 (0%)	46,726 (2.2%)	−0.21	<5 (0%)	1082 (17.9%)	−0.66	N/A	N/A	N/A	N/A	N/A
Venlafaxine comedication	Yes	<5 (0%)	5,642 (0.3%)	−0.07	<5 (0%)	221 (3.7%)	−0.28	936 (2.0%)	−0.20	<5 (0%)	78 (2.6%)	−0.23

Table 2 Baseline characteristics for duloxetine exposed, venlafaxine exposed, and duloxetine discontinuers, early-exposure window

Variable	Value	Duloxetine before matching $n = 1589$	Duloxetine vs venlafaxine					Duloxetine vs duloxetine discontinuers				
			Before matching		After matching			Before matching		After matching		
			Venlafaxine $n = 5642$	SMD	Duloxetine $n = 1502$	Venlafaxine $n = 1502$	SMD	Duloxetine discontinuers $n = 2839$	SMD	Duloxetine $n = 1504$	Discontinuers $n = 1504$	SMD
Age, years, continuous	Mean	30.9 (27.3; 35.1)	30.5 (26.5; 34.6)	0.10	30.8 (27.3; 35.0)	30.5 (26.8; 34.9)	0.04	30.3 (26.6; 34.3)	0.12	30.8 (27.3; 35.0)	30.7 (27.0; 34.6)	0.06
Age, years, grouped	18–24	232 (14.6%)	990 (17.5%)	0.11	223 (14.8%)	217 (14.4%)	0.05	467 (16.4%)	0.10	222 (14.8%)	222 (14.8%)	0.05
	25–29	468 (29.5%)	1615 (28.6%)		446 (29.7%)	476 (31.7%)		904 (31.8%)		449 (29.9%)	460 (30.6%)	
	30–34	403 (25.4%)	1464 (25.9%)		376 (25.0%)	365 (24.3%)		699 (24.6%)		378 (25.1%)	388 (25.8%)	
	35–60	486 (30.6%)	1573 (27.9%)		457 (30.4%)	444 (29.6%)		769 (27.1%)		454 (30.2%)	435 (28.9%)	
Household income	Quartile1	595 (37.6%)	2036 (36.4%)	0.05	569 (37.9%)	599 (39.9%)	0.04	1038 (36.7%)	0.08	570 (37.9%)	563 (37.4%)	0.03
	Quartile2	413 (26.1%)	1529 (27.3%)		388 (25.8%)	376 (25.0%)		808 (28.6%)		387 (25.7%)	393 (26.1%)	
	Quartile3	331 (20.9%)	1187 (21.2%)		311 (20.7%)	300 (20.0%)		590 (20.9%)		312 (20.8%)	314 (20.9%)	
	Quartile4	245 (15.5%)	849 (15.2%)		234 (15.6%)	227 (15.1%)		389 (13.8%)		234 (15.6%)	235 (15.6%)	
Education, no. of years	<11	357 (22.6%)	1298 (23.3%)	0.05	340 (22.6%)	335 (22.3%)	0.03	707 (25.1%)	0.05	340 (22.6%)	335 (22.3%)	0.03
	11–15	843 (53.4%)	2836 (50.8%)		798 (53.1%)	790 (52.6%)		1439 (51.0%)		799 (53.2%)	807 (53.6%)	
	>16	379 (24.0%)	1448 (25.9%)		364 (24.2%)	377 (25.1%)		675 (23.9%)		364 (24.2%)	363 (24.1%)	
Depression	Yes	549 (34.6%)	1436 (25.5%)	0.20	510 (34.0%)	513 (34.2%)	−0.00	793 (27.9%)	0.14	510 (33.9%)	507 (33.7%)	0.01
Anxiety or phobia	Yes	205 (12.9%)	545 (9.7%)	0.10	191 (12.7%)	210 (14.0%)	−0.04	318 (11.2%)	0.05	190 (12.6%)	189 (12.6%)	0.00
Severe stress reaction	Yes	186 (11.7%)	383 (6.8%)	0.17	161 (10.7%)	155 (10.3%)	0.01	269 (9.5%)	0.07	165 (11.0%)	147 (9.8%)	0.04
Stress urinary incontinence	Yes	<5 (0%)	<5 (0%)	0.00	<5 (0%)	<5 (0%)	0.00	<5 (0%)	0.00	<5 (0%)	<5 (0%)	0.00
SSRI comedication	Yes	<5 (0%)	936 (16.6%)	−0.63	<5 (0%)	230 (15.3%)	−0.60	679 (23.9%)	−0.79	<5 (0%)	391 (26.0%)	−0.84
Venlafaxine comedication	Yes	<5 (0%)	N/A	N/A	N/A	N/A	N/A	93 (3.3%)	−0.26	<5 (0%)	49 (3.3%)	−0.26

LMP last menstrual period, *N/A* , *SMD* standardized mean difference, *SSRI* selective serotonin reuptake inhibitor

Use for analyses of small for gestational age without stratification of malformation and preterm birth. Early-exposure window: from last menstrual period to 140 days post- LMP. Comorbidity was defined as diagnoses 5 years prior to LMP. SSRI and venlafaxine were defined as redeemed prescriptions between 90 days prior to LMP to 140 days post-LMP or end of pregnancy, whichever came first. SSRI and venlafaxine comedication were not included in the propensity score model

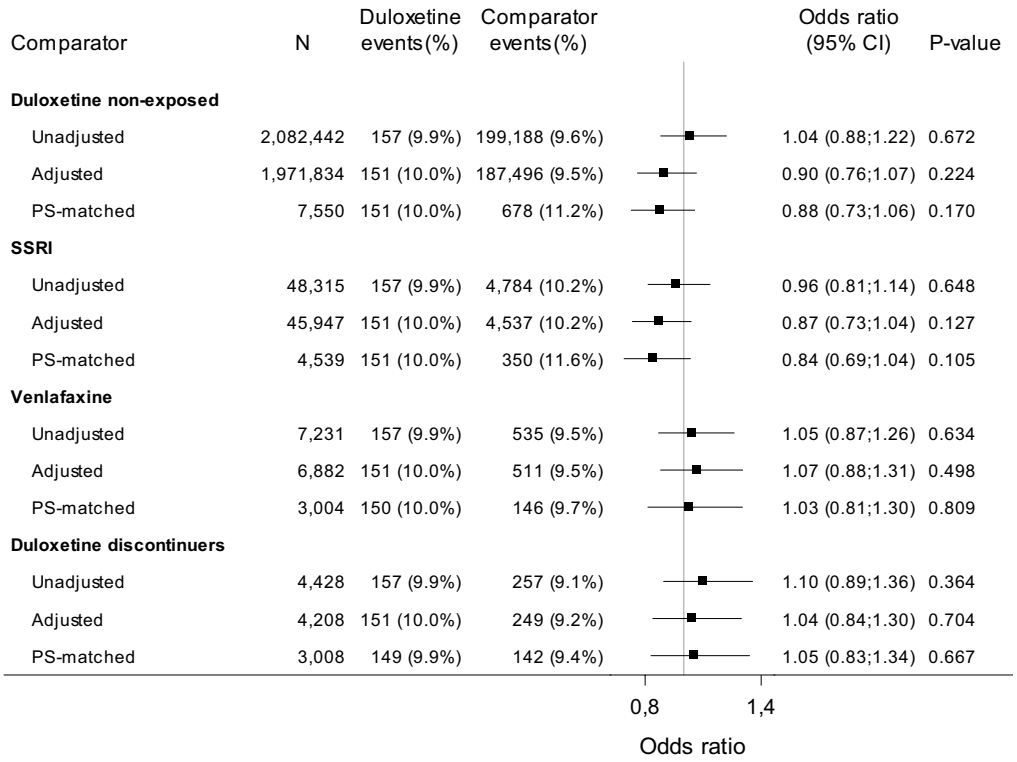

Fig. 2 Small for gestational age (SGA), early-exposure window: duloxetine versus four comparators. Exposure definition: one or more redeemed prescription. Early-exposure window: from last menstrual period to 140 days post-last menstrual period. Adjusted and propensity score (PS)-matched analyses based on conditional logistic regression models were based on covariates covering comorbidity, comedication, hospital contacts, education, and income. For the complete list of the individual analyses, see Table S4 of the ESM. *N* number of observations in analyses, *CI* Wald 95% confidence intervals, *SSRI* selective serotonin reuptake inhibitor

with duloxetine non-exposed: PS-matched OR was 1.33 (95% CI 1.10–1.60). The estimates suggested an increased but not statistically significant risk for duloxetine exposed when compared to SSRI-exposed and duloxetine discontinuers: PS-matched ORs were 1.21 (95% CI 0.99–1.47) and 1.17 (95% CI 0.93–1.49), respectively. When compared to venlafaxine exposed, no increased risk was seen for duloxetine: PS-matched OR was 0.91 (95% CI 0.73–1.14) [Fig. 4].

For the late-exposure window, an increased risk for preterm birth was seen for duloxetine when compared with duloxetine-non-exposed, SSRI-exposed, and duloxetine discontinuers: PS-matched ORs were 1.76 (95% CI 1.28–2.42), 1.79 (95% CI 1.25–2.56), and 2.04 (95% CI 1.29–3.23), respectively. When compared with venlafaxine exposed, the point estimate also suggested an increased risk for duloxetine, but was statistically insignificant: PS-matched OR was 1.26 (95% CI 0.86–1.86) [Fig. 5]. Similar patterns were observed in the sensitivity analyses (results not presented).

Table 3 shows the duration of the preterm pregnancies and indicates that the pregnancies ending in preterm births have a similar gestational duration across comparison groups. The median durations differed with 2 days, with a range from 247 to 249 days, with most preterm births (79.2%) occurring between weeks 33 and 36 across comparison groups, early and late exposure, for the full cohorts and the PS-matched cohort.

4 Discussion

Results from this observational register study, based on all live births in Sweden and Denmark between 2004 and 2016, showed no increased risk of SGA with duloxetine exposure across comparison groups, in early-exposure and late-exposure windows, and with and without stratification on congenital malformation. These findings are supported by a recent Swedish study [33] investigating women exposed to any antidepressant (not SNRIs specifically) and a US study [17] investigating duloxetine; both showed no increased risk of SGA.

For preterm birth, an increased risk with early duloxetine exposure was observed when compared with duloxetine-non-exposed women. However, when compared to SSRI-exposed, venlafaxine-exposed, and duloxetine discontinuers,

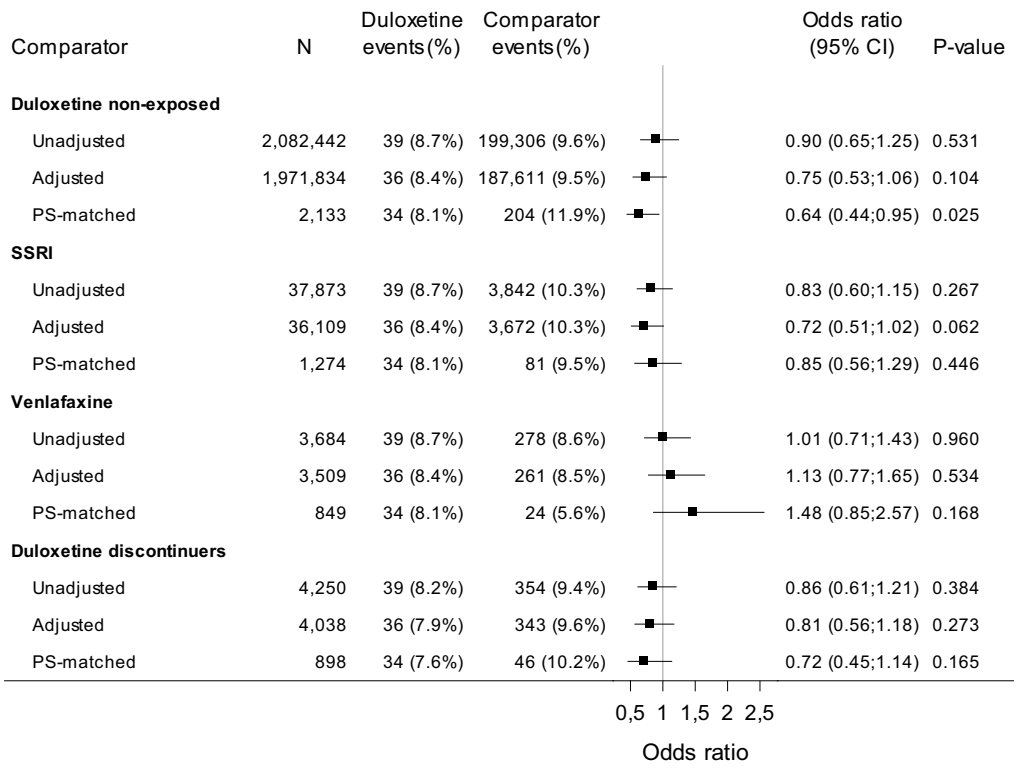

Fig. 3 Small for gestational age (SGA), late-exposure window: duloxetine versus four comparators. Exposure definition: one or more redeemed prescription. Late-exposure window: from 141 days post-last menstrual period to the date of delivery. Adjusted and propensity score (PS)-matched analyses based on conditional logistic regression models were based on covariates covering comorbidity, comedication, hospital contacts, education, and income. For the complete list of the individual analyses, see Table S4 of the ESM. *N* number of observations in analyses, *CI* Wald 95% confidence intervals, *SSRI* selective serotonin reuptake inhibitor

no statistically significant increased risk was seen for duloxetine.

For the late-exposure window, we found an increased risk of preterm birth for duloxetine-exposed women when compared with duloxetine non-exposed and SSRI exposed, and a nearly doubled risk when compared with duloxetine discontinuers, while no difference in risk was seen when compared to venlafaxine exposed. It is known that approximately 50% of women discontinue antidepressants treatment during pregnancy [8]. Most women who were exposed late in pregnancy were also exposed early. The reasons for being exposed throughout pregnancy could be related to the severity of the disease. However, it is very difficult to entangle these associations in the present analysis. Depression may be related to preterm birth independent of antidepressant use; an increased risk of preterm birth has been found in women with depressive disorders during pregnancy who were not exposed to any antidepressant [34]. Thus, the increased risk observed among duloxetine-exposed women could be attributed to residual confounding associated with pregnant women being severely depressed, or an adverse drug effect, or a combination of both. For the late-exposure window, we realize that duloxetine discontinuers were not the ideal comparator to duloxetine late-exposed women, as those patients who stopped medication prior to pregnancy may have better health conditions than women needing duloxetine during late pregnancy. Consequently, it is challenging to compare duloxetine late exposures to any comparator groups except for venlafaxine, where analyses showed no increased risk for the late-exposure window. A literature review found that the majority of studies investigating preterm birth among women exposed to antidepressants showed an increased risk of similar magnitude to the present study [35]. A study based on the Swedish Medical Birth Register analyzed the risk of preterm birth for late venlafaxine exposure and found an increased adjusted OR of 1.98 (95% CI 1.49–2.63) compared with unexposed [36]. A recent study from the UK compared venlafaxine exposed to antidepressant unexposed and found a statistically insignificant increased OR of 1.51 (95% CI 0.98–2.27) for preterm birth [37]. A study based on claims data from the USA investigated duloxetine and found a relative risk of 1.01 (95% CI 0.92–1.10) for early exposure and 1.19 (95% CI 1.04–1.37) for late exposure [17]. These studies suggest that SNRIs could be associated with preterm birth (especially for late

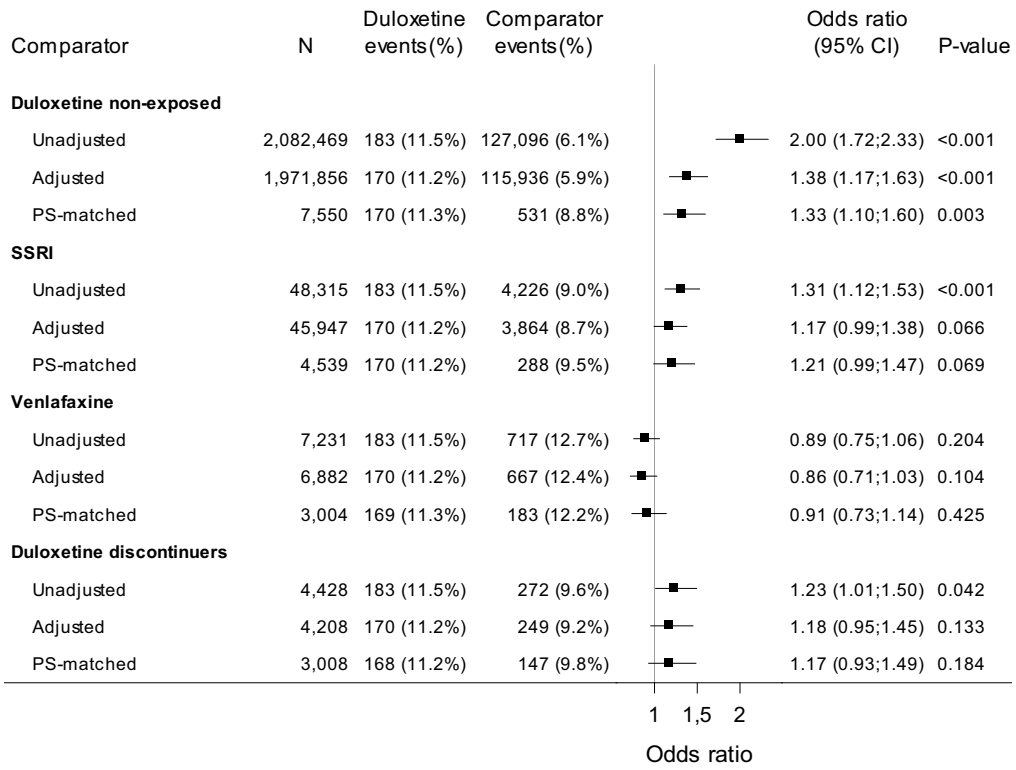

Fig. 4 Preterm birth, early-exposure window: duloxetine versus four comparators. Exposure definition: oen or more redeemed prescription. Early-exposure window: from last menstrual period to 140 days post-last menstrual period. Adjusted and propensity score (PS)-matched analyses based on conditional logistic regression models were based on covariates covering comorbidity, comedication, hospital contacts, education, and income. For the complete list of the individual analyses, see Table S4 of the ESM. *N* number of observations in analyses, *CI* Wald 95% confidence intervals, *SSRI* selective serotonin reuptake inhibitor

exposure) but it is unclear whether this might be a class effect or related to a specific SNRI.

The interpretation of the observed increased risk of preterm birth should take the duration of the pregnancies into account. In the present study, the differences in pregnancy duration among preterm births were limited across comparison groups, early and late exposure, the full cohorts, and the PS-matched cohort. Infants born prematurely have a worse prognosis than infants born at term [38], but the prognosis is better close to term [39]. Still, preterm birth should be avoided if possible, and a risk for preterm birth cannot be excluded, especially for women exposed to duloxetine throughout pregnancy.

A similar design as in the present study has previously been used to investigate the risk of malformation, stillbirth, and abortion [40, 41]. No associations with exposure to duloxetine during pregnancy were found.

4.1 Strengths and Limitations

The present study was based on nationwide Swedish and Danish registers with high validity and completeness. Information on birth weight, delivery date, and LMP was gathered from the medical birth registers covering 99% of all live births. Last menstrual period was based on the mother's self-report and two subsequent ultrasounds in the first and second trimesters and therefore is deemed highly accurate. Drug exposure was based on redeemed prescriptions from community pharmacies. There is a risk that the patient did not ingest the drug. The sensitivity analyses of more than one redeemed prescription used a stricter definition under the assumption that this would increase the likelihood that the medication was ingested. These analyses showed similar findings. Information on antidepressants administered during hospitalization was not available and could have led to misclassification. However, there were few hospitalizations, and we do not believe they have any significant impact on the results. Only 1.6% of the total duloxetine use in the time period was administrated in hospitals in Denmark [42]. The present study includes several statistical tests. Multiple testing was not accounted for, to ensure that a possible true association was not overseen by lowering the threshold for statistical significance.

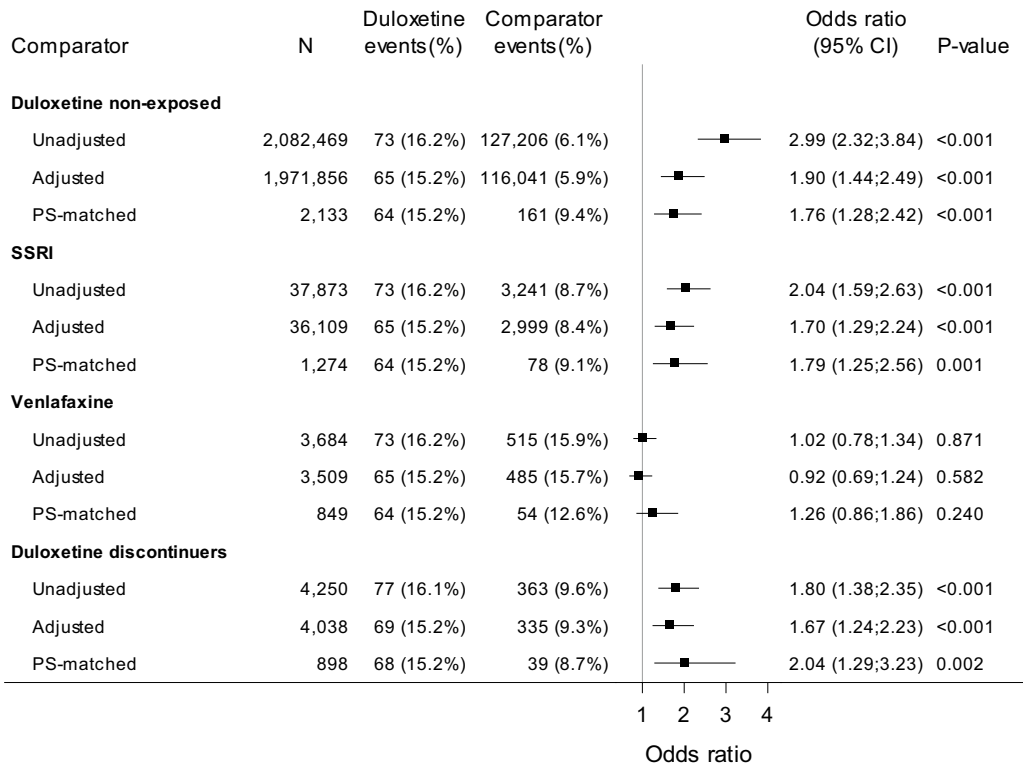

Fig. 5 Preterm birth, late-exposure window. Duloxetine versus four comparators. Exposure definition: one or more redeemed prescription. Late-exposure window: from 141 days post-last menstrual period to the date of delivery. Adjusted and propensity score (PS)-matched analyses based on conditional logistic regression models were based on covariates covering comorbidity, comedication, hospital contacts, education, and income. For the complete list of the individual analyses, see Table S4 of the ESM. *N* number of observations in analyses, *CI* Wald 95% confidence intervals, *SSRI* selective serotonin reuptake inhibitor

Table 3 Duration of pregnancy (days) for preterm deliveries stratified for exposure windows and exposure groups

Exposure window	Median (5th, 25th, 75th, 95th percentiles)				
	Duloxetine	Duloxetine non-exposed	SSRI exposed	Venlafaxine exposed	Duloxetine discontinuers
Early	247 (202, 238, 254, 258)	248 (195, 234, 254, 258)	248 (198, 235, 254, 258)	247 (202, 238, 254, 258)	249 (191, 237, 254, 258)
Late	249 (219, 241, 255, 258)	248 (195, 234, 254, 258)	249 (211, 239, 255, 258)	248 (212, 240, 254, 258)	248 (191, 237, 254, 258)

SSRI selective serotonin reuptake inhibitor

A long list of potential confounders was included in the present study, but information on alcohol, illicit drug use, use of folic acid supplementation during pregnancy, and diagnoses outside of hospitals was not available. Women with a depressive disorder are more likely to have health behavior not recommended during pregnancy [43] compared with women without a depressive disorder. Information about socioeconomic status (education and income) and smoking were covariates and may cover some imbalance of health behavior. Furthermore, SSRI-exposed and venlafaxine-exposed women and duloxetine discontinuers were used as comparison groups because of the concern of unmeasured confounding and confounding by indication, as they are expected to have a similar health behavior as duloxetine-exposed women. We assumed that women exposed to duloxetine were treated because of depression disorder, but indication information was not available. In addition to depression, duloxetine is indicated for diabetic peripheral neuropathy, anxiety, severe stress reaction, and stress urinary incontinence. However, among pregnant women, the prevalence of these disorders is generally low. Hospital diagnoses of neuropathy, anxiety, severe stress reaction, and stress urinary incontinence were covariates to address this possible bias. An important potential confounder is depression severity. A direct measure was not available. Instead, potential confounding by depression severity was addressed

by including hospital depression diagnosis, psychiatric hospitalization, and psychiatric outpatient visits as covariates. As depression is often treated outside of hospitals, we believe that these covariates describe the women with the most severe depression but diagnoses outside of hospitals were not included in this analysis. The comparison group of duloxetine non-exposed was predefined in the protocol and consists primarily of SSRI/SNRI non-exposed, but a small proportion have a history of SSRI or venlafaxine use (2.5%, Tables 1, 2).

5 Conclusions

We conclude that duloxetine exposure during pregnancy is unlikely to increase the risk of SGA. Although not consequently statistically significant across comparisons, a trend towards an increased risk of preterm birth was observed for duloxetine exposed. Therefore, an increased risk of preterm birth cannot be excluded, especially for women exposed throughout pregnancy.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40801-022-00334-2.

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Declarations

Authors' Contributions All authors have participated sufficiently in the work to take public responsibility for the whole content. MZA, JP, JTA, MFSF, HL, TF, and EJS contributed with the concept and design of the study. MZA, JP, JTA, MFSF, HL, SPM, TF, and EJS contributed with the acquisition, analysis and/or interpretation of data. MZA drafted the manuscript. JP, JTA, MFSF, HL, SPM, TF, and EJS revised the manuscript. MZA, and JP performed the statistical analysis. MFSF, HL, and SPM obtained funding. All authors read and approved the final version.

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Availability of Data and Material The researchers do not store any data and cannot hand over data. Data are available by applying to the relevant authorities in Sweden and Denmark.

Code Availability Not applicable.

Conflicts of Interest The study was performed by the Copenhagen Phase IV Unit (Phase4CPH) at the Department of Clinical Pharmacology and the Institute of Applied Economics and Health Research Aps (ApHER), and financed by Eli Lilly, the manufacturer of duloxetine. MZA, JP, and EJS have conducted other studies regarding antidepressants, involving funding from Janssen Pharmaceutical via Phase4CPH. JTA and TF have no relevant financial activities outside the submitted work. TF is a former employee of ApHER and is currently employed by Quantify Research. MFSF is a current employee of Eli Lilly and Company. HL and SPM are former employees of Eli Lilly and Company. HL is currently employed by Gilead Science Inc. and SPM is currently employed by Amgen Inc.

Prior Postings and Presentations The present study is based on a safety study regarding duloxetine and pregnancy outcomes, with the protocol and the full study report available via the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP, EUPAS20253).

Ethics Approval The study was approved in Sweden by the Swedish Regional Ethics Review Board in Gothenburg (ref: 1040-17 and T782-18) and the Swedish National Board of Health and Welfare (ref: 30714/2017), and in Denmark by the Data Protection Agency (j.nr. VD-2018-371, I-Suite nr. 6621). No approval from the Danish Research Ethics Committees for the Capital Region was needed as only national registers were used. Data were gathered and analyzed at Statistics Denmark. The article does not contain clinical studies or patient data.

Consent to Participate Not applicable.

Consent for Publication Not applicable.

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