



Specific SSRIs and birth defects: bayesian analysis to interpret new data in the context of previous reports

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ABSTRACT

OBJECTIVE

To follow up on previously reported associations between periconceptional use of selective serotonin reuptake inhibitors (SSRIs) and specific birth defects using an expanded dataset from the National Birth Defects Prevention Study.

DESIGN

Bayesian analysis combining results from independent published analyses with data from a multicenter population based case-control study of birth defects.

SETTING

10 centers in the United States.

PARTICIPANTS

17 952 mothers of infants with birth defects and 9857 mothers of infants without birth defects, identified through birth certificates or birth hospitals, with estimated dates of delivery between 1997 and 2009.

EXPOSURES

Citalopram, escitalopram, fluoxetine, paroxetine, or sertraline use in the month before through the third month of pregnancy. Posterior odds ratio estimates were adjusted to account for maternal race/ethnicity, education, smoking, and prepregnancy obesity.

MAIN OUTCOME MEASURE

14 birth defects categories that had associations with SSRIs reported in the literature.

RESULTS

Sertraline was the most commonly reported SSRI, but none of the five previously reported birth defects associations with sertraline was confirmed. For nine previously reported associations between maternal SSRI use and birth defect in infants, findings were consistent with no association. High posterior odds ratios excluding the null value were observed for five birth defects with paroxetine (anencephaly 3.2, 95% credible interval 1.6 to 6.2; atrial septal defects 1.8, 1.1 to 3.0; right ventricular outflow tract obstruction defects 2.4, 1.4 to 3.9; gastroschisis 2.5, 1.2 to 4.8;

and omphalocele 3.5, 1.3 to 8.0) and for two defects with fluoxetine (right ventricular outflow tract obstruction defects 2.0, 1.4 to 3.1 and craniosynostosis 1.9, 1.1 to 3.0).

CONCLUSIONS

These data provide reassuring evidence for some SSRIs but suggest that some birth defects occur 2-3.5 times more frequently among the infants of women treated with paroxetine or fluoxetine early in pregnancy.

Introduction

The association between maternal use of antidepressants, especially selective serotonin reuptake inhibitors (SSRIs), during pregnancy and birth defects in the infants has been the topic of much discussion in recent years. After initial reports of an association between paroxetine and heart defects, the US Food and Drug Administration published an advisory warning of this potential association in December 2005.¹ Recent meta-analyses and systematic reviews combining data from more than 20 epidemiological studies have reached conflicting conclusions and this uncertainty influences perceptions of the safety of antidepressant use in pregnancy.^{2,3} In a recent study, 69% of women thought that it was definitely or probably acceptable to take such drugs when not pregnant or breast feeding, but only 33% of women thought that it was definitely or probably acceptable to do so when pregnant.⁴ SSRIs are increasingly used by women of reproductive age and during pregnancy, but the inconsistent reports have limited opportunities for clinicians to carefully evaluate the risk compared with benefit of specific SSRIs for a given patient during pregnancy.⁵⁻⁷

We reviewed the literature for any reports that assessed the relation between specific SSRIs and one or more of the specific birth defects that are also included in the US National Birth Defects Prevention Study (NBDPS).^{2,8-13} To provide a more robust estimate of the association between individual SSRIs and birth defects, information that is necessary for decision making by patients who are being treated with these drugs and their physicians, we used bayesian methods both to summarize independent findings identified in the literature and to update those findings using the entire set of data from the NBDPS.¹⁴

Methods

Study population

For this analysis we used data from the NBDPS, a population based case-control study of birth defects. The study's methods have been described previously.¹⁵⁻¹⁷ Briefly, cases of birth defects were identified through birth defects surveillance systems in the US states of Arkansas, California, Georgia, Iowa, Massachusetts,

WHAT IS ALREADY KNOWN ON THIS TOPIC

Selective serotonin reuptake inhibitors (SSRIs) are increasingly used by women of reproductive age and during pregnancy

However, inconsistent reports on the association with birth defects have limited opportunities for clinicians to carefully evaluate the risk compared with benefit of specific SSRIs during pregnancy

WHAT THIS STUDY ADDS

This study combined summarized results from published literature with data from the National Birth Defects Prevention Study using bayesian analysis

It showed consistent results for 7 of 21 evaluated associations between specific SSRIs and birth defects

New Jersey, New York, North Carolina, Texas, and Utah. Cases could be live born, stillborn, or induced abortions with one of over 30 major birth defects. The NBDPS excluded cases with known chromosomal or monogenic disorders. Unmatched liveborn controls from the same geographical region and time period were selected from birth certificates or birth hospital records. More cases than controls were included overall because the study was designed for the assessment of individual defects, where controls, which were the same for all case groups, outnumbered even the largest case group. Mothers were asked to participate in a telephone interview in English or Spanish between six weeks and two years after the estimated date of delivery.

For this analysis we included cases and controls if they were born on or after 1 October 1997 and had an estimated date of delivery on or before 31 December 2009. Overall participation was 67.4% for cases and 64.8% for controls. A previous NBDPS analysis of the association between SSRI use during pregnancy and birth defects, included in table 1 as Alwan and colleagues, included data from 1997 to 2002.⁸ To avoid double counting, these NBDPS data were excluded from the meta-analyses used to calculate prior odds ratios in the current study, but we used significant findings from the previous analysis along with those of the other studies listed in table 1 to determine which birth defect-SSRI combinations to assess. Because of the strong association between diabetes and birth defects, we excluded case and control mothers who reported pregestational diabetes (type 1 or type 2).¹⁸ We also excluded mothers who reported the use of any of the following known teratogenic treatments: misoprostol, methotrexate, mycophenolate mofetil, thalidomide, or isotretinoin.¹⁹

SSRI use

During the interview for the NBDPS, no specific question addressed depression. Mothers were asked if they had any illnesses other than the ones already discussed (for example, hypertension or diabetes) and whether they took any medication for the illness. Women could report depression here, which would then be followed by a question about any medications taken for the illness. There were also specific medication related questions: “between three months before conception and [the baby’s] date of birth, did you take any of the following medications? Prozac? Paxil? Zoloft? Celexa?” There was no specific question for Lexapro. For this analysis, we considered women exposed if they reported taking citalopram (Celexa), escitalopram (Lexapro), fluoxetine (Prozac), paroxetine (Paxil), or sertraline (Zoloft) at least once in the period from one month before conception through the third month of pregnancy. Women who reported taking more than one type of SSRI were only included in the multiple SSRI category. We considered women as unexposed if they did not take any antidepressants in the period from three months before to the end of the pregnancy and did not report any depression, anxiety, bipolar disorder, or obsessive compulsive disorder. Women who did not answer all medication related questions, used SSRIs in a period other than the period of interest, or took antidepressants other than SSRIs (for example, bupropion and venlafaxine) were excluded.

Birth defects

The NBDPS includes over 30 categories of major birth defects. After ascertainment in population based surveillance systems, the diagnostic information was

Table 1 | Previous studies that assessed use of individual selective serotonin reuptake inhibitors (SSRIs) during early pregnancy in mother and individual birth defects in infant

Authors	Study design	Controls/ comparison group	Population	Included birth years	SSRIs	Birth defect categories assessed	Included confounders
Alwan et al 2007 ⁸	Case-control (subset of current study)	Liveborn infants without major defects	10 sites in USA	1997-2002	Fluoxetine, paroxetine, sertraline	All defects, with at least three exposed	Race/ethnicity, obesity, smoking, income
Louik et al 2007 ¹¹	Case-control	Non-malformed infants	Boston, Philadelphia, Toronto, San Diego, New York State	1993-2004	Citalopram, fluoxetine, paroxetine, sertraline	All defects	Maternal age, race/ethnicity, education, year of last menstrual period, study center, smoking, alcohol, family history, body mass index, parity, seizures, diabetes, infertility, hypertension, folic acid use
Bakker et al 2010 ⁹	Case-control	Fetuses and children with chromosomal or single gene disorder	Population based birth defects registry in Northern Netherlands	1997-2006	Paroxetine	Heart defects categories	Year of birth
Kornum et al 2010 ¹⁰	Cohort	Children of women without SSRI prescription	Northern Denmark	1991-2007	Citalopram, escitalopram, fluoxetine, paroxetine, sertraline	Septal heart defects	Smoking, age, birth order, birth year
Reis and Kallen 2010 ¹³	Cohort	Children of women without antidepressant use	Sweden	1995-2007	Citalopram, fluoxetine, paroxetine, sertraline	Hypospadias	Year of birth, age, parity, smoking and body mass index
Malm et al 2011 ¹²	Cohort	Children of women without SSRI prescription reimbursements	Finland	1996-2006	Citalopram, escitalopram, fluoxetine, paroxetine, sertraline	All defects	Age, parity, year of birth, marital status, smoking, other psychiatric medicines, diabetes

reviewed by clinical geneticists at each site to establish eligibility. Designated individual clinical geneticists reviewed all cases with a particular defect to ensure consistency across sites.¹⁶ Because the primary intent of this analysis was to assess previously reported associations with SSRIs and to determine if those associations were supported by NBDPS data, we included only outcomes with at least one previous report in the peer reviewed literature suggesting a possible association with SSRIs: neural tube defects (international classification of diseases, ninth revision (ICD-9): 740-742.0), anencephaly (ICD-9: 740), all septal defects (ICD-9: 745), ventricular septal defects (ICD-9: 745.4), right ventricular outflow tract obstructions (ICD-9: 746.0-746.1), cleft palate (ICD-9: 749.0), cleft lip with or without cleft palate (ICD-9: 749.2-749.4), esophageal atresia (ICD-9: 750.3), anal atresia (ICD-9: 751.23-751.24), hypospadias (ICD-9: 752.6), any limb reduction defect (ICD-9: 755.2), craniosynostosis (ICD-9: 756.0), gastroschisis (ICD-9: 756.71), and omphalocele (ICD-9: 756.70). Some defects reported in other studies (for example, cystic kidney) could not be evaluated in this analysis because they were not included in NBDPS.¹³

Development of priors

A bayesian approach requires specification of prior distributions for each of the variables in the model used to estimate the potential association between risk of birth defect and use of SSRIs. These prior distributions are probabilistic summaries of beliefs about the true values of the unknown variables before assessment of new data. The bayesian approach allowed us to incorporate existing information on the association between each SSRI and the birth defect outcome of interest. Prior distributions were developed based on literature review. A systematic review identified six studies published before 2010 that had available specific information on SSRI-birth defect combinations (table 1).⁸⁻¹³

We created categories of birth defects based on those reports, which corresponded as closely as possible to the NBDPS birth defect categories (table 1).⁸⁻¹³ The approach used to summarize the information presented in these publications for each of the SSRI-birth defect combinations of interest depended on the number of available studies; to avoid duplication of cases in the current analysis, we did not include the results from the earlier NBDPS analysis.⁸ If one published assessment was only available, then the prior distribution for the log of the odds ratio relating the birth defect and use of SSRIs was assumed to be normal, with a mean given by the log odds ratio estimate reported in the study and variance defined using the corresponding reported confidence interval. If two or more studies were identified, we used bayesian meta-analysis methods to summarize the results. The goal of the meta-analysis was to produce an estimate of the log odds ratio relating the specific birth defect and SSRI across studies, taking into account the study specific estimates and their associated sampling errors. The assumed meta-analysis model included a term corresponding to the true underlying log odds ratio relating SSRI use and risk of birth

defects and a collection of random study level effects.²⁰ All available information was included in developing the meta-analysis based prior estimates, including results indicating no association between risk of birth defects and SSRI use from other published studies. If no information other than the previous NBDPS analysis⁸ was identified, then we assumed the log odds ratio relating birth defects and SSRI use to have a non-informative prior distribution, defined using a normal distribution with mean zero and a variance of 1000. Using this non-informative prior places virtually the entire weight in developing the bayesian estimates on the information contained in the full NBDPS data.

An alternative approach to this analysis would be to develop estimates of the association between SSRI consumption and risk of birth defects using frequentist methods only focused on the 1997-2009 NBDPS data. These results could be summarized and then included as an additional point in a larger meta-analysis of available information. We chose the bayesian approach for two primary reasons. Firstly, we viewed the collection of information summarized by the meta-analysis as the state of current knowledge concerning potential association between SSRIs and risk of birth defects and the NBDPS data as new information available to update that knowledge. This view is consistent with the bayesian updating paradigm as applied in this analysis. In addition, we believe that only utilizing summary values (for example, estimated odds ratios and their standard errors) from the NBDPS data would be an unnecessary sacrifice of information as opposed to utilizing the individual level data informed by the meta-analysis priors.

Bayesian analysis

We used a bayesian approach to develop estimates for a logistic regression model relating the log odds of a specific defect and the mother's use of SSRIs (see supplementary appendix 1). In addition to a term reflecting the log odds ratio relating birth defects and use of SSRIs, the model also included confounders selected a priori and obtained through the maternal interview: maternal race/ethnicity (non-Hispanic white versus other), maternal education (0-12 years versus >12 years), obesity (body mass index <30 versus ≥30), and smoking (any smoking versus no smoking from one month before to the end of the first trimester). Although prior probabilities for the variable relating birth defect risk and use of SSRIs were developed, we assumed non-informative priors for the odds ratios associated with maternal race/ethnicity, education, obesity, and smoking in the logistic regression model. Posterior estimates for the model variables were developed using Markov Chain Monte Carlo methods. BUGS was used for the bayesian analyses.²¹

The primary results presented here were derived using an analysis based only on NBDPS participants who reported values for all the variables used in the logistic regression model. We also conducted sensitivity analyses focused on assessing the impact of not including participants with missing information, including consideration of a potential association between being

missing and the unknown outcome. This analysis utilized bayesian imputation for missing data both under an assumption that the missing information was missing at random and under plausible assumptions on mechanisms for informative missingness (see supplementary appendix 1).

Results

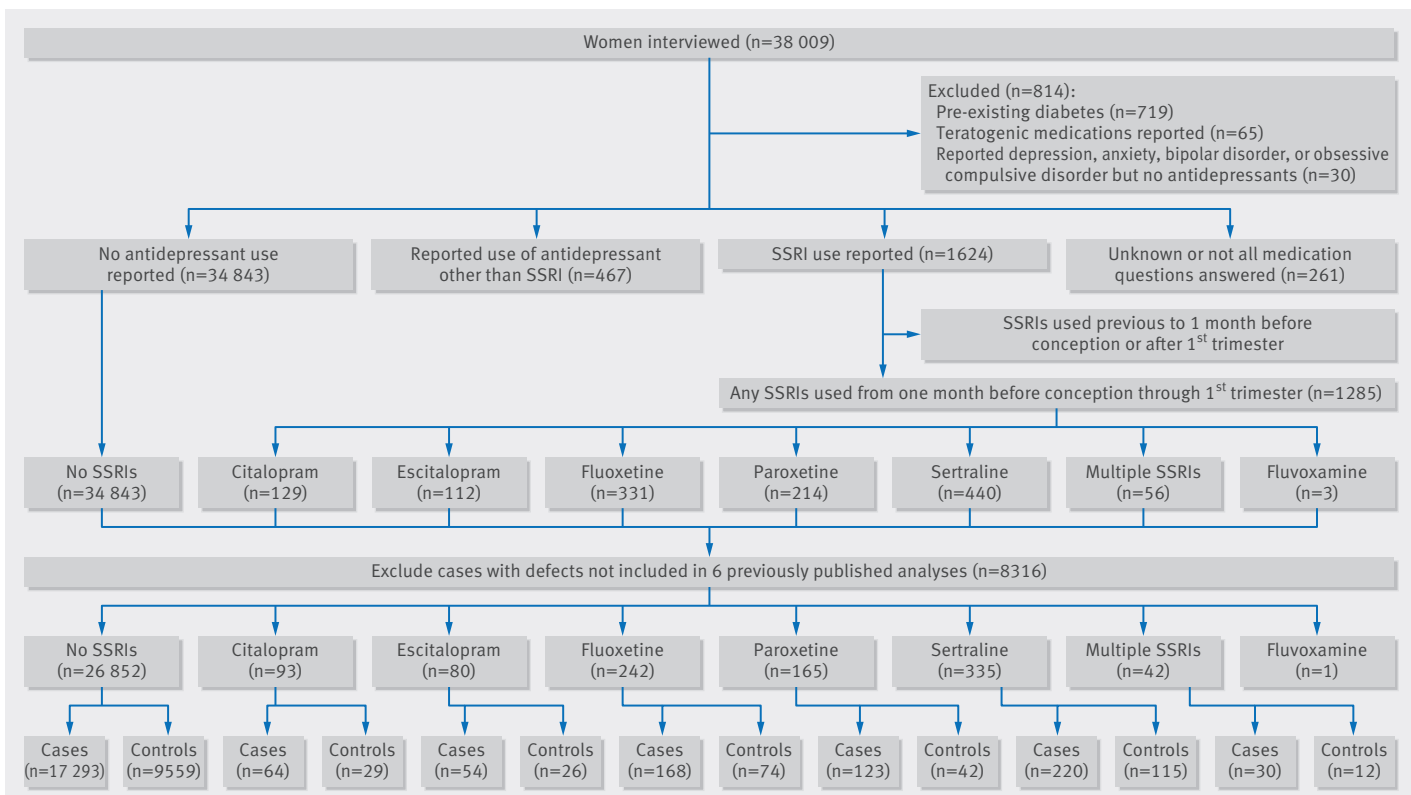
A total of 38 009 women with births between 1997 and 2009 were interviewed for the NBDPS. We excluded women reporting pre-existing diabetes (n=719), known use of teratogenic drugs (n=65), or depression, anxiety, bipolar disorder, or obsessive compulsive disorder but not reporting any antidepressant use (n=30). And, after excluding defects with no previous reported associations with SSRIs, the final analyses included 17 293 unexposed cases, 659 cases exposed to citalopram, escitalopram, fluoxetine, paroxetine or sertraline, 9559 unexposed controls, and 298 controls that were exposed to one of these SSRIs (figure).

Sertraline was the most commonly used SSRI; approximately 40% of control mothers who reported use of an SSRI used sertraline (table 2). Although there was some difference in overall SSRI use by state, the distribution of the specific SSRIs was similar across the study sites. There was no difference in the age distribution among SSRI users except for sertraline, which was more often reported among older mothers. Reported use of citalopram and escitalopram started in 2000 and 2002, respectively, and increased over time. Fluoxetine

reports decreased over time, but not as much as paroxetine use decreased, and sertraline use stayed relatively constant. There was no difference in the use of the specific SSRIs before or after 1 December 2006, the date the American College of Obstetricians and Gynecologists published their committee opinion on SSRI use in pregnancy.^{22 23}

In a bayesian analysis of the current NBDPS data that takes into account non-NBDPS individual drug-specific birth defect associations previously reported in the literature, no association with maternal use of citalopram or escitalopram monotherapy was found, except for a marginal association between citalopram and neural tube defects (table 3). For fluoxetine treatment, associations were seen for ventricular septal defects, right ventricular outflow tract obstruction cardiac defects, and craniosynostosis. Paroxetine had the most previously reported associations, and significant associations were observed for five of the seven defects assessed. Associations between paroxetine and anencephaly, atrial septal defects, and right ventricular outflow tract obstruction cardiac defects found in other studies were confirmed in this independent dataset, and two other associations seen in the previous NBDPS analysis⁸ (gastroschisis and omphalocele) were again seen in this analysis. For sertraline, the most commonly used SSRI in our study, the findings for all five defects assessed were not significant.

A bayesian analysis using a non-informative prior (that is, assuming there were no previously published studies to help develop an informative prior), and



Flow chart of participants through study

Table 2 | Descriptive statistics of control mothers (n=9857) who reported periconceptional use of selective serotonin reuptake inhibitors (SSRIs), National Birth Defects Prevention Study, 1997-2009

Variables	No (%) using SSRIs						
	Any SSRIs	Citalopram	Escitalopram	Fluoxetine	Paroxetine	Sertraline	Multiple SSRIs
Total	298 (3.0)	29 (9.7)	26 (8.7)	74 (24.8)	42 (14.1)	115 (38.6)	12 (4.0)
Study site*:							
New Jersey	7 (1.2)	0	0	1 (14)	3 (43)	3 (43)	0
Texas	17 (1.4)	1 (6)	1 (6)	3 (18)	2 (12)	9 (53)	1 (6)
California	24 (2.1)	1 (4)	2 (8)	8 (33)	2 (8)	8 (33)	3 (13)
Georgia	23 (2.2)	3 (13)	1 (4)	8 (35)	1 (4)	9 (39)	1 (4)
New York	21 (2.5)	2 (10)	1 (5)	4 (19)	5 (24)	8 (38)	1 (5)
Arkansas	43 (3.5)	3 (7)	4 (9)	11 (26)	2 (5)	20 (47)	3 (7)
North Carolina	28 (3.6)	2 (7)	5 (18)	4 (14)	5 (18)	12 (43)	0
Massachusetts	42 (3.6)	5 (12)	2 (5)	12 (29)	7 (17)	16 (38)	0
Iowa	42 (3.9)	3 (7)	5 (12)	9 (21)	10 (24)	13 (31)	2 (5)
Utah	51 (6.1)	9 (18)	5 (10)	14 (27)	5 (10)	17 (33)	1 (2)
Maternal age (years):							
<20	14 (1.4)	2 (14)	0	4 (29)	3 (21)	5 (36)	0
20-24	55 (2.4)	5 (9)	4 (7)	13 (24)	7 (13)	21 (38)	5 (9)
25-29	81 (3.0)	6 (7)	5 (6)	23 (28)	14 (17)	31 (38)	2 (2)
30-34	100 (4.0)	12 (12)	12 (12)	23 (23)	11 (11)	38 (38)	4 (4)
35-39	41 (3.6)	3 (7)	5 (12)	9 (22)	5 (12)	18 (44)	1 (2)
≥40	5 (3.0)	1 (20)	0	2 (40)	2 (40)	0	0
Maternal race/ethnicity†:							
Hispanic	21 (0.9)	0	1 (5)	8 (38)	3 (14)	8 (38)	1 (5)
Non-Hispanic black	13 (1.2)	1 (8)	0	3 (23)	1 (8)	6 (46)	2 (15)
Other	15 (2.1)	3 (20)	1 (7)	3 (20)	2 (13)	6 (40)	0
Non-Hispanic white	249 (4.4)	25 (10)	24 (10)	60 (24)	36 (14)	95 (38)	9 (4)
Maternal education (years)†:							
0-8	4 (0.8)	0	0	1 (25)	1 (25)	2 (50)	0
9-11	27 (2.4)	2 (7)	0	7 (26)	7 (26)	9 (33)	2 (7)
12	66 (2.8)	3 (5)	6 (9)	21 (32)	9 (14)	24 (36)	3 (5)
13-15	98 (3.8)	13 (13)	9 (9)	19 (19)	16 (16)	37 (38)	4 (4)
≥16	102 (3.3)	11 (11)	11 (11)	25 (25)	9 (9)	43 (42)	3 (3)
Pregpregnancy maternal body mass index (kg/m ²)†:							
<18.5	8 (1.6)	1 (13)	0	2 (25)	3 (38)	2 (25)	0
18.5-24.9	162 (3.2)	13 (8)	14 (9)	41 (25)	24 (15)	65 (40)	5 (3)
25-29.9	67 (3.1)	11 (16)	5 (7)	18 (27)	5 (7)	23 (34)	5 (7)
≥30	60 (3.7)	4 (7)	7 (12)	12 (20)	10 (17)	25 (42)	2 (3)
Periconceptional maternal smoking:							
No	215 (2.7)	21 (10)	19 (9)	59 (27)	25 (12)	83 (39)	8 (4)
Yes	82 (4.7)	8 (10)	7 (9)	14 (17)	17 (21)	32 (39)	4 (5)
Periconceptional maternal alcohol use:							
No	147 (2.4)	16 (11)	11 (7)	31 (21)	20 (14)	64 (44)	5 (3)
Yes	149 (4.2)	13 (9)	14 (9)	42 (28)	22 (15)	51 (34)	7 (5)
Year of due date:							
1997-99	34 (2.0)	0	0	11 (32)	9 (26)	14 (41)	0
2000-01	36 (2.2)	4 (11)	0	14 (39)	5 (14)	11 (31)	2 (6)
2002-03	43 (2.8)	7 (16)	1 (2)	9 (21)	6 (14)	17 (40)	3 (7)
2004-05	76 (4.5)	2 (3)	8 (11)	18 (24)	14 (18)	31 (41)	3 (4)
2006-07	52 (3.1)	5 (10)	8 (15)	13 (25)	6 (12)	19 (37)	1 (2)
2008-09	57 (3.6)	11 (19)	9 (16)	9 (16)	2 (4)	23 (40)	3 (5)

*Sites are statewide for Arkansas, Iowa, and Utah. All other sites are selected regions. Years included: Arkansas 1998-2009, California 1997-2009, Georgia 1997-2009, Iowa 1997-2009, Massachusetts 1997-2009, New Jersey 1998-2003, New York 1997-2002 and 2004-09, North Carolina 2003-09, Texas 1997-2009, and Utah 2003-09.

†Variables were recoded to dichotomous categories for adjusted analyses; non-Hispanic white versus other, 0-12 years education versus >12 years, body mass index <30 versus ≥30 kg/m².

sensitivity analyses using bayesian methods in which missing data for confounders were replaced with imputed values showed similar results for most associations except for the association between citalopram and neural tube defects. The prior for that association was based on one cohort study, which found a higher odds ratio, and our logistic regression analysis without

considering this prior study showed no association (see supplementary table).

Discussion

Using data from the US National Birth Defects Prevention Study (NBDPS), we confirmed previously reported associations between right ventricular outflow tract

Table 3 | Odds ratios and 95% confidence interval, resulting prior odds ratio, and Bayesian complete case analysis posterior odds ratio with 95% credible interval, National Birth Defects Prevention Study (NBDPS), 1997-2009

Birth defect by SSRI	Odds ratio (95% CI)				Posterior odds ratio (95% CrI): NBDPS 1997-2009
	Louik et al ¹¹	Bakker et al, ⁹ Kornum et al, ¹⁰ Reis and Kallem ¹³	Malm et al ¹²	Odds ratio (95% CI): Alwan et al ⁸	
Citalopram:					
Neural tube defects	—	—	2.5 (1.2 to 5.1) (n=8)	2.5 (1.2 to 5.1)	1.8 (1.0 to 3.0) (n=5)
Ventricular septal defects	—	—	1.3 (0.9 to 1.8) (n=36)	1.3 (0.9 to 1.8)	1.3 (0.9 to 1.8) (n=6)
Cleft lip with or without cleft palate	3.2 (0.9 to 11.9) (n=4)	—	—	3.2 (0.9 to 11.9)	1.4 (0.7 to 2.7) (n=8)
Hypospadias	1.9 (0.4 to 8.8) (n=4)	1.3 (0.9 to 1.8) ¹³ (n=38)	—	1.3 (0.6 to 2.5)	1.2 (0.7 to 2.0) (n=8)
Escitalopram:					
Septal defects	—	4.2 (1.0 to 17.1) ¹⁰ (n=3)	1.5 (0.7 to 3.0) (n=8) [†]	1.7 (0.7 to 3.7)	1.3 (0.7 to 2.1) (n=11)
Fluoxetine:					
Ventricular septal defects	—	—	1.5 (1.0 to 2.2) (n=26)	1.5 (1.0 to 2.2)	1.4 (1.0 to 1.9) (n=16)
RVOTO	1.0 (0.2 to 3.4) (n=4)	—	2.7 (0.9 to 8.5) (n=3)	1.5 (0.6 to 3.6)	2.0 (1.4 to 3.1) (n=27)
Esophageal atresia	—	—	—	Non-informative prior	1.8 (0.8 to 3.4) (n=10)
Craniosynostosis	—	—	—	Non-informative prior	1.9 (1.1 to 3.0) (n=21)
Paroxetine:					
Anencephaly	—	—	—	3.3 (1.1 to 10.4)	3.2 (1.6 to 6.2) (n=6)
Atrial septal defects	—	5.7 (1.4 to 23.7) ⁹ (n=3)	1.3 (0.4 to 4.0) (n=3)	1.8 (0.7 to 4.5)	1.8 (1.1 to 3.0) (n=15)
RVOTO	3.3 (1.3 to 8.8) (n=6)	—	5.2 (1.6 to 16.3) (n=3)	3.9 (1.4 to 10.4)	2.4 (1.4 to 3.9) (n=16)
Cleft palate	1.5 (0.4 to 5.3) (n=3)	—	2.7 (1.0 to 7.1) (n=4)	1.7 (0.7 to 4.0)	1.3 (0.7 to 2.3) (n=10)
Hypospadias	1.0 (0.3 to 3.3) (n=3)	2.5 (1.1 to 4.6) ¹³ (n=9)	—	1.6 (0.6 to 3.4)	1.1 (0.6 to 1.9) (n=9)
Gastroschisis	—	—	—	Non-informative prior	2.5 (1.2 to 4.8) (n=13)
Omphalocele	—	—	—	Non-informative prior	3.5 (1.3 to 8.0) (n=6)
Sertraline:					
Anencephaly	0.8 (0.1 to 6.3) (n=1)	—	—	0.8 (0.1 to 6.3)	1.2 (0.5 to 2.5) (n=7)
Septal defects	2.0 (1.2 to 4.0) (n=13)	3.3 (1.5 to 7.5) ¹⁰ (n=6)	0.5 (0.2 to 1.3) (n=5) [†]	1.5 (0.6 to 2.9)	1.0 (0.8 to 1.4) (n=47)
Anal atresia	4.4 (1.2 to 16.4) (n=3)	—	—	4.4 (1.2 to 16.4)	1.4 (0.8 to 2.3) (n=11)
Any limb reduction	3.9 (1.1 to 13.5) (n=3)	—	—	3.9 (1.1 to 13.5)	1.2 (0.7 to 2.0) (n=13)
Omphalocele	5.7 (1.6 to 20.7) (n=3)	—	—	5.7 (1.6 to 20.7)	1.4 (0.7 to 2.8) (n=4)

SSRI=selective serotonin reuptake inhibitor; RVOTO=right ventricular outflow tract obstruction cardiac defects.

Adjusted for maternal race/ethnicity, maternal education, obesity, and smoking.

*Priors are only based on studies described in first three columns and exclude Alwan et al.⁸ No informative prior was calculated if the only available data were from Alwan et al, but this association was reported in that earlier analysis using a subset of NBDPS data.

[†]Ventricular septal defect.

obstruction cardiac defects in infants and maternal use of fluoxetine¹² or paroxetine^{8 11 12} early in pregnancy, and between anencephaly^{8 11} or atrial septal defects⁹ in infants and maternal use of paroxetine. This analysis also confirmed associations between gastroschisis or omphalocele and paroxetine and between craniosynostosis and fluoxetine that were reported in the analysis of an earlier subset of NBDPS data;⁸ however, these still require corroboration in an independent data source. It is reassuring that none of the five previously reported associations between sertraline and birth defects^{8 10-12} were confirmed in this analysis, particularly since about 40% of women reporting use of an SSRI in early pregnancy used sertraline. In addition, we did not find support for nine other previously reported associations between maternal SSRI treatment and selected birth defects in the child.

Although our analysis strongly supports the validity of the associations that were observed, the increase in the absolute risks, if the associations are causal, is small. The two strongest posterior odds ratios were seen for maternal paroxetine treatment and anencephaly (3.2) or right ventricular outflow tract obstruction cardiac defects (2.4) in the infant. If these associations are causal, the absolute risks in the children of women who are treated with paroxetine early in pregnancy would increase for anencephaly from 2 per 10 000²⁴ to 7 per 10 000, and for right ventricular outflow tract obstruction cardiac defects from 10 per 10 000²⁵ to 24 per 10 000. The absolute risks for these birth defects are still low.

This analysis confirms the need to assess the association between specific SSRIs and specific birth defects rather than combining an entire drug class or heterogeneous group of birth defects. Although SSRIs are similar pharmacologically, there are chemical differences, and if any of them do have teratogenic activity, it may be completely unrelated to the inhibition of serotonin receptors. SSRIs also differ pharmacokinetically,²⁶ and this could account for differences in teratogenic activity, whether or not the mechanism involved inhibition of serotonin receptors.²⁷

Limitations of this study

This analysis does not address whether the birth defect associations we observed were caused by maternal SSRI treatment, underlying maternal disease, or some other factor. Since there was no specific question on depression and we cannot identify all participants with untreated depression, there is the possibility of confounding by indication.

A recent publication by Furu and colleagues combined data from five Nordic countries.²⁸ Some overlap occurred between the data included in this recent study and the three Nordic studies we included in our meta-analysis, but this study also included data from Norway and Iceland that is not included in our analyses.^{10 12 13} Many of the associations we assessed for septal heart defects and right ventricular outflow tract obstruction cardiac defects showed similar risk estimates in our analysis and the recent study. One clear

different finding is the association reported by Furu and colleagues for anal atresia and sertraline that was also reported by Louik and colleagues but is not evident in the NBDPS data.^{11 28}

Additional limitations of this analysis need to be acknowledged. Periconceptional exposure was based on maternal self report, with interviews conducted six weeks to 24 months after the expected date of delivery. However, Kwon and colleagues reported good concordance between self report of antidepressants and claims data.²⁹

We made 21 comparisons between exposure and outcome using five different models, and it is possible that some statistically significant findings occurred owing to the occurrence of false positive associations expected with multiple comparisons.³⁰ Another limitation is that the small numbers for some of the individual birth defects and some of the specific exposures resulted in unstable estimates. Finally, exposure ascertainment is known to be more complete when women are specifically asked about their use of drugs by name;³¹ the interview did not include a specific question about use of escitalopram.

Strengths of this study

This analysis also has some important strengths. The bayesian analysis enabled consideration of evidence both for and against an association between use of SSRIs and risk of birth defects from previous epidemiological studies in the analyses and used relatively homogenous and discrete classes of birth defects and SSRI monotherapy. As a result, our study provides strong evidence for the reproducibility and validity of the associations that were observed. The sensitivity assessment showed that missing data were unlikely to have affected the results. The association between SSRIs and heart defects is biologically plausible; Sadler²⁷ has suggested that the association may be a result of the key role that the neurotransmitter serotonin (5-hydroxytryptamine) plays in embryonic development of the heart.

A major advantage of this analysis over some previous reports is the ability to assess individual SSRIs and individual birth defects, while accounting for earlier reported associations. Although the data are self reported, they do represent reported use of the medications and not just filling of the prescription. Approximately 30% of mothers stop taking SSRIs during pregnancy,³² and this might not be captured if we relied on prescription information or medical records, since prescriptions might have been filled but not taken after the pregnancy was recognized. We have previously used NBDPS data to show that antidepressant prescription patterns have changed over time,⁵ making it more challenging to study these associations.

Our analyses of a large population based case-control dataset combined with prior odds ratios based on the literature allowed us to show and refine associations between maternal fluoxetine or paroxetine treatment during pregnancy and right ventricular outflow tract obstruction cardiac defects and between maternal use

of paroxetine and anencephaly or atrial septal defects. In contrast, we found no evidence to support 14 other previously reported associations between maternal SSRI use and birth defects. Continued scrutiny of the association between SSRIs and birth defects is warranted, and additional studies of specific SSRI treatments during pregnancy and birth defects are needed to enable women and their healthcare providers to make more informed decisions about treatment. Meanwhile, the current analysis can help guide healthcare providers and women to the safest options for treatment during early pregnancy to minimize the risk of major birth defects, while providing adequate treatment of maternal depression.

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Ethical approval: This study was approved by the institutional review board of the Centers for Disease Control and Prevention and all participating sites.

Data sharing: Previous publications with a subset of this data: Alwan S, Reefhuis J, Rasmussen SA, et al. Use of selective serotonin-reuptake inhibitors in pregnancy and the risk of birth defects. *N Engl J Med* 2007;356:2684-92 and Alwan S, Reefhuis J, Rasmussen SA, et al. Patterns of antidepressant medication use among pregnant women in a United States population. *J Clin Pharmacol* 2011;51:264-70.

Transparency: The leader author (JR) hereby affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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- 1 FDA. FDA advising of risk of birth defects with paxil. 2005. www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2005/ucm108527.htm
- 2 Gentile S. Selective serotonin reuptake inhibitor exposure during early pregnancy and the risk of birth defects. *Acta Psychiatr Scand* 2011;123:266-75.
- 3 Wurst KE, Poole C, Ephross SA, et al. First trimester paroxetine use and the prevalence of congenital, specifically cardiac, defects: a meta-analysis of epidemiological studies. *Birth Defects Res A Clin Mol Teratol* 2010;88:159-70.
- 4 Goodman JH. Women's attitudes, preferences, and perceived barriers to treatment for perinatal depression. *Birth* 2009;36:60-9.
- 5 Alwan S, Reefhuis J, Rasmussen SA, et al. Patterns of antidepressant medication use among pregnant women in a United States population. *J Clin Pharmacol* 2011;51:264-70.

- 6 Huybrechts KF, Palmsten K, Mogun H, et al. National trends in antidepressant medication treatment among publicly insured pregnant women. *Gen Hosp Psychiatry* 2013;35:265-71.
- 7 Tinker SC, Broussard CS, Frey MT, et al. Prevalence of prescription medication use among non-pregnant women of childbearing age and pregnant women in the United States: NHANES, 1999-2006. *Matern Child Health J* 2015;19:1097-106.
- 8 Alwan S, Reefhuis J, Rasmussen SA, et al. Use of selective serotonin-reuptake inhibitors in pregnancy and the risk of birth defects. *N Engl J Med* 2007;356:2684-92.
- 9 Bakker MK, Kerstjens-Frederikse WS, Buys CH, et al. First-trimester use of paroxetine and congenital heart defects: a population-based case-control study. *Birth Defects Res A Clin Mol Teratol* 2010;88:94-100.
- 10 Kornum JB, Nielsen RB, Pedersen L, et al. Use of selective serotonin-reuptake inhibitors during early pregnancy and risk of congenital malformations: updated analysis. *Clin Epidemiol* 2010;2:29-36.
- 11 Louik C, Lin AE, Werler MM, et al. First-trimester use of selective serotonin-reuptake inhibitors and the risk of birth defects. *N Engl J Med* 2007;356:2675-83.
- 12 Malm H, Artama M, Gissler M, et al. Selective serotonin reuptake inhibitors and risk for major congenital anomalies. *Obstet Gynecol* 2011;118:111-20.
- 13 Reis M, Kallen B. Delivery outcome after maternal use of antidepressant drugs in pregnancy: an update using Swedish data. *Psychol Med* 2010;40:1723-33.
- 14 Gelman A, Shalizi CR. Philosophy and the practice of Bayesian statistics. *Br J Math Stat Psychol* 2013;66:8-38.
- 15 Yoon PW, Rasmussen SA, Lynberg MC, et al. The National Birth Defects Prevention Study. *Public Health Rep* 2001;116(Suppl 1):32-40.
- 16 Rasmussen SA, Olney RS, Holmes LB, et al. Guidelines for case classification for the National Birth Defects Prevention Study. *Birth Defect Res A Clin Mol Teratol* 2003;67:193-201.
- 17 Reefhuis J, Gilboa SM, Anderka M, et al. The national birth defects prevention study: a review of the methods. *Birth Defect Res A Clin Mol Teratol* 2015; published online 2 Jun.
- 18 Correa A, Gilboa SM, Besser LM, et al. Diabetes mellitus and birth defects. *Am J Obstet Gynecol* 2008;199:237 e1-9.
- 19 Obican S, Scialli AR. Teratogenic exposures. *Am J Med Genet Part C* 2011;157C:150-69.
- 20 Sutton AJ, Abrams KR. Bayesian methods in meta-analysis and evidence synthesis. *Stat Methods Med Res* 2001;10:277-303.
- 21 Lunn D, Jackson C, Best N, et al. The BUGS book: a practical introduction to Bayesian analysis, CRC Press, 2012.
- 22 Abuhamad AZ. ACOG Practice Bulletin, clinical management guidelines for obstetrician-gynecologists number 98, October 2008 (replaces Practice Bulletin No 58, Dec 2004). Ultrasonography in pregnancy. *Obstet Gynecol* 2008;112:951-61.
- 23 Practice ACoO. ACOG committee opinion No 354: treatment with selective serotonin reuptake inhibitors during pregnancy. *Obstet Gynecol* 2006;108:1601-3.
- 24 Parker SE, Mai CT, Canfield MA, et al. Updated national birth prevalence estimates for selected birth defects in the United States, 2004-2006. *Birth Defects Res A Clin Mol Teratol* 2010;88:1008-16.
- 25 Bedard T, Lowry RB, Sibbald B, et al. Folic acid fortification and the birth prevalence of congenital heart defect cases in Alberta, Canada. *Birth Defects Res A Clin Mol Teratol* 2013;97:564-70.
- 26 Edwards JG, Anderson I. Systematic review and guide to selection of selective serotonin reuptake inhibitors. *Drugs* 1999;57:507-33.
- 27 Sadler TW. Selective serotonin reuptake inhibitors (SSRIs) and heart defects: potential mechanisms for the observed associations. *Reprod Toxicol* 2011;32:484-9.
- 28 Furu K, Kieler H, Haglund B, et al. Selective serotonin reuptake inhibitors and venlafaxine in early pregnancy and risk of birth defects: population based cohort study and sibling design. *BMJ* 2015;350:h1798.
- 29 Kwon A, Bungay KM, Pei Y, et al. Antidepressant use: concordance between self-report and claims records. *Med Care* 2003;41:368-74.
- 30 Rothman KJ. No adjustments are needed for multiple comparisons. *Epidemiology* 1990;1:43-6.
- 31 Mitchell AA, Cottler LB, Shapiro S. Effect of questionnaire design on recall of drug exposure in pregnancy. *Am J Epidemiol* 1986;123:670-6.
- 32 Reefhuis J, Rasmussen SA, Friedman JM. Selective serotonin-reuptake inhibitors and persistent pulmonary hypertension of the newborn. *N Engl J Med* 2006;354:2188-90; author reply 88-90.

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Appendix table: Odds ratios for associations between selected SSRIs and birth defects using different statistical methods

Appendix: statistical methods