Antidepressant use during pregnancy and risk of congenital heart defects: a case-time-control study

Running title: Antidepressant and congenital heart defects

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ABSTRACT

Purpose We estimated the association between maternal antidepressant (AD) use in early pregnancy and risk of congenital heart defects.

Methods We applied a case-time-control design with the aim of controlling for confounding from time-invariant factors and compared the results of the design to results from a cohort design in a population of 792,685 singletons born alive in Denmark during 1995-2008. In the case-time-control design, we identified children diagnosed with a congenital heart defect in the first five years of life (cases) and compared maternal AD use in the risk period (the first three months of pregnancy) and the reference period (gestational months 5-7). A nondiseased control group was included to adjust for time trends of exposure. In the cohort design, we identified children whose mothers redeemed at least one AD prescription in the first three months of pregnancy (the exposed) and two other groups including the unexposed children with maternal AD prescriptions in the 12 months before pregnancy. We applied conditional logistic regression and logistic regression to compute odds ratios (ORs) and 95% confidence intervals (CIs).

Results The case-time-control OR for any congenital heart defect were 1.03 (95% CI: 0.61-1.73), which was similar to the OR (1.09, 95% CI: 0.88-1.35) from the cohort design when we compared the exposed children with the unexposed children with maternal AD use before pregnancy.

Conclusions The case-time-control design provided results similar to the cohort design when the cohort design had a better confounder control strategy. We discussed the strengths and drawbacks of case-time-control design.

Key words: antidepressants; congenital heart defects; pregnancy; case-time-control; cohort design

KEY POINTS

1. Maternal use of antidepressants (ADs) during early pregnancy has been related to risk of congenital heart defects. Recent studies with efforts of controlling maternal characteristics, however, did not support the evidence.
2. The case-time-control study provides an option to adjust for confounding from time-invariant factors by allowing cases to be their own controls and to adjust for time trends of exposure by including a nondiseased control group.
3. The case-time-control design provided results rather similar to the cohort design when the cohort design had a better confounder control strategy, which did not show an increased risk of congenital heart defects among children whose mother redeemed AD prescriptions in early pregnancy.
4. The case-time-control design may be an option in data sets with less detailed information on important confounders.
5. Strength and Limitation of the case-time-control design were discussed.

INTRODUCTION

In the past decade, the safety of maternal use of antidepressants (ADs) during early pregnancy has been questioned, especially the risk related to congenital heart defects in offspring (1, 2). This concern has been strengthened by findings from several studies (3-7). A systematic review showed that maternal AD use in early pregnancy may be associated with an increased risk of congenital heart defects (8) and a recent paper showed that paroxetine use increased the risk of cardiac defects including ventricular/atrial septal defects (9). However, confounding by maternal characteristics, including the depression itself, comorbidities, lifestyle factors, and economic status, may have caused the association. Another study found that associations between AD use during the first trimester and risk of cardiac defects were attenuated after controlling for coexisting maternal conditions (10). Similar results were reported in a recent study that adjusted for several maternal characteristics (11).

The case-only designs, including the case-time-control design, provide a potentially efficient approach for limiting confounding from time-fixed factors such as residence, race, education, socioeconomic status, maternal chronic health conditions, and genetic factors. These designs are based on within-person comparisons using cases as their own controls (12-15). A nondiseased control group in the case-time-control design makes it possible to adjust for time trends of medicine use related to pregnancy.

In this study, we applied the case-time-control design to examine the association between AD use in early pregnancy and risk of congenital heart defects in offspring. We evaluated the design by comparing results with those of a standard cohort design to evaluate proof of concept (16).

METHODS

Study population

We identified 885,278 singletons born alive in Denmark between 1995 and 2008 from the Danish Medical Birth Registry (17). We excluded adopted children (n=4,752), children whose gestational age at birth was less than 20 weeks, greater than 45 weeks, or missing (n=6,109), children with chromosomal defects (n=1,480), and children with no information from the Danish National Prescription Registry on maternal medication use in the six months before and during pregnancy (n=80,252), leaving 792,685 children in the study population. Using the unique personal identification number assigned to all Danish residents at birth or upon immigration, we linked the study population to the Danish National Prescription Registry (18) and the Danish National Patient Registry (19) to get information on maternal AD prescriptions and diagnoses of congenital defects in the offspring. Children with congenital heart defects were identified from birth up to five years of age or until December 31, 2009, whatever came first.

Study design

We used a case-time-control design and a cohort design for comparison. The case-time-control design, like the case-crossover design, uses the study case-base paradigm (20). These designs consist of within-person comparison between different periods of time (21). By using cases as their own controls, time invariant factors including underlying disease severity and genetic

113 factors can be automatically controlled for (12, 13). The case-crossover design can be applied to
114 study acute effects of short transient exposure but it requires no time trend of the exposure (12).
115 The case-time-control design was developed by including a nondiseased control group to adjust
116 for time trend of exposure (13). The function of the nondiseased control group in the case-time-
117 control design is different from the function of the control group in a case-control design, in
118 which the controls help to provide a counterfactual estimate of what would have happened to the
119 exposed had they not been exposed. Controls in the case-time-control design now provide an
120 estimate of exposure variation over time of study. Including such a control group in the case-
121 time-control design extends the case-crossover design for wider applications (13, 22).

122 In the case-time-control design, we defined the risk period as the first three months of pregnancy
123 (gestational months 1-3). A later three-month period (gestational months 5-7) served as the
124 reference period (23). We identified children with a diagnosis of congenital heart defects in the
125 first five years of life (cases) and compared maternal AD use in the risk period and the reference
126 period. We also used an earlier three-month period (4-6 months before pregnancy) as the
127 reference period in a sensitivity analysis. A group of children without a congenital heart defect in
128 the first five years of life (controls) was used to estimate and control for time trend of AD use in
129 the study periods. For both cases and controls, only those whose mothers had discordant
130 information on AD use between the risk period and the reference period (redeemed AD
131 prescriptions only in the risk period or the reference period) were informative and included in the
132 analyses. The case-time-control design for this study is illustrated in Figure 1.

133 In the cohort design, we defined children whose mothers redeemed at least one AD prescription
134 in the first three months of pregnancy as the exposed children, children whose mothers did not
135 redeem AD prescriptions in the first three months of pregnancy but redeemed AD prescriptions

in the 12 months before pregnancy as the unexposed children with maternal AD use before pregnancy, and the rest of the children as the unexposed children with no maternal AD use (neither in the 12 months before pregnancy nor in the first three months of pregnancy).

Information on maternal redemption of antidepressant prescriptions

The Danish National Prescription Registry (18), which provided information on redeemed AD prescriptions, contains close to complete information on all prescription drugs dispensed from Danish community pharmacies to Danish residents since 1995. We had data on redeemed prescriptions and use that information to estimate 'use' of the drugs. In the prescription registry, drugs are coded according to the anatomical therapeutic chemical (ATC) system. The class of ADs was identified by ATC code N06A. We also identified maternal use of selective serotonin reuptake inhibitors (SSRIs) and specific SSRIs (see Table 1 in the Supplementary material for the ATC codes).

Information on congenital heart defects in the offspring

The diagnoses of congenital heart defects were obtained from the Danish National Patient Registry (19), which codes diagnoses according to the International Classification of Diseases, tenth revision (ICD-10). The Danish National Patient Registry contains information on all inpatients and outpatients treated in Danish hospitals and outpatient clinics since 1995. We defined children as having a congenital heart defect if they had a diagnosis coded with Q20-Q26; persistent foramen ovale, patent ductus arteriosus, absence and aplasia of aorta, peripheral pulmonary artery stenosis with a gestational age less than 37 weeks, and persistent left superior vena cava were excluded. Congenital heart defects were further categorized by developmental origin, as suggested by Louik *et al.* (24). These subgroups included looping defects, conotruncal

and major arch defects, atrioventricular canal defects, septal defects, right ventricular outflow tract obstruction, left ventricular outflow tract obstruction, and anomalous pulmonary venous return (see Table 2 in the Supplementary material for the ICD codes). For septal defects, we further categorized them into ventricular and atrial septal defects. If a child was diagnosed with several types of congenital heart defects, he or she was included in the group of a specific type of congenital heart defect in the relevant analyses.

Information on potential confounders

Information on gestational age and birth date was obtained from the Danish Medical Birth Registry (17). In this registry, gestational age has been recorded in days since 1997 and in weeks before 1997. Estimates of gestational age are based on the date of the last menstrual period, often adjusted by ultrasound measures (based on crown rump length). Start of pregnancy was calculated by subtracting gestational age from the date of birth. Information on maternal depression diagnosed before the birth of the child (ICD-8: 296.09, 296.29, 296.99, 298.09, 300.49, 300.19, ICD-10: F32-33) was obtained from the Danish National Patient Registry (19) and the Danish Psychiatric Central Register (25, 26). The Danish Psychiatric Central Register was established in 1938 and computerized in 1969. It contains information on all admissions to psychiatric hospitals and psychiatric wards in general hospitals in Denmark. Information about all psychiatric outpatient contacts has also been included since 1995. However, the data from the Danish Psychiatric Central Register were available from October 1964 to October 2007, while the data from the Danish National Patient Registry were available to this study from 1977 to 2009. Information on maternal education, marital status, family income, and employment status was obtained from the Danish Civil Registration System (27). Family income at the time of birth was based on both parents' income.

Statistical analyses

In the case-time-control design, conditional logistic regression was used to compute odds ratios (ORs) and 95% confidence intervals (CIs). Matched ORs were computed from exposure frequencies in the risk period and in the reference period (28), *i.e.*, the ratio of the number of children whose mothers were prescribed ADs in the risk period only, divided by the number of children whose mothers were prescribed ADs in the relevant reference period only (Figure 1). The OR for cases (OR_{cases}) corresponds to an OR obtained in the case-crossover design. The OR for cases provided a crude estimate of the relative risk of congenital heart defects after maternal AD use in the first three months of pregnancy. The OR for controls ($OR_{controls}$) provided an estimate of the change in exposure prevalence between the risk and reference periods. The case-time-control design is based on two main assumptions: 1) the OR among cases (case-crossover OR) is the product of an OR due to the causal effect of the exposure on the outcome and an OR due to the time trend in exposure prevalence, and 2) the latter is the same among cases and controls (28). Thus, the case-time-control OR ($OR_{case\text{-}time\text{-}control}$) is the OR estimated from the cases divided by the time trend OR estimated from the controls (13, 28).

In the case-time-control design, we made separate analyses for children exposed to one type of AD and for children exposed to more than one type of AD during pregnancy. We presented findings for children exposed to one type of AD although the numbers for some categories of heart defects are small. In the analysis for children exposed to more than one type of AD during pregnancy and the following sub-analyses, we only presented the overall risk for congenital heart defects or the risk for the most common types of congenital heart defects – septal defects – due to limited number of subjects.

It is possible that mothers who redeemed AD prescriptions in the reference period of gestational months 5-7 only still may have taken ADs in the risk period if medication dispensed before pregnancy was available at time of conception. We therefore conducted a sensitivity analysis excluding children whose mothers redeemed AD prescriptions in the three months before pregnancy among both groups of cases and controls whose mothers redeemed AD prescriptions in the reference period of gestational months 5-7 only. To strengthen the validity of the congenital heart defect diagnoses, we restricted the analyses to those with at least two records of diagnoses of congenital heart defects in the register. We also estimated the risk of congenital heart defects diagnosed in the first year of life.

We did a similar analysis for children exposed to any SSRIs in the first three months of pregnancy. We estimated the overall risk of congenital heart defects for children exposed to the mostly commonly used SSRIs: citalopram, fluoxetine, sertraline, and paroxetine.

In the cohort design, we used a logistic regression model to estimate odds ratios (ORs) and 95% confidence intervals (CIs) of congenital heart defects in the first five years for the exposed children compared with both the unexposed children with no maternal AD use and the unexposed children with maternal AD use before pregnancy. We provided both crude and adjusted ORs of congenital heart defects. The adjusted analyses were controlled for maternal age at time of birth (<25, 25-29, 30-34, 35-39, 40+ years), parity (1, 2, 3+), the highest degree of education completed by the mothers (primary, medium, and high), marital status (married, cohabitant, and others, including divorced, single, and separated), employment (no unemployment, unemployment for less than half a year, and unemployment for half a year and more), family income (quantile), maternal antiepileptic medication in the first three months of pregnancy (yes, no), and calendar years of birth (1995-1999, 2000-2004, 2005-2008). We also

restricted the analyses to those who had a diagnosis of depression before or during pregnancy, in which we used different groups of unexposed children as the reference group pursuing to adjust for potential confounding of indication. For example, we categorized the unexposed children with no maternal AD use into two groups according to time of the mother's latest diagnosis of depression, those with a recent diagnosis of depression (within two years before or during pregnancy) and those with a former diagnosis of depression (three years or more before the pregnancy). Since the mothers of unexposed children with no maternal AD use and a recent diagnosis of depression might have been hospitalized and received AD treatment during hospitalization, which would not be included in the prescription registry, we further excluded them from the analysis.

RESULTS

Among 792,685 children, we identified 10,830 (1.4%) whose mothers redeemed at least one AD prescription during pregnancy. In this group, 8,969 (83%) were prescribed only one type of AD and 1,861 (17%) were prescribed more than one type. Among mothers who used one type of AD, the six most frequent medications were citalopram (n=2,564, 28.6%), fluoxetine (n=2,257, 25.2%), sertraline (n=1,521, 17.0%), paroxetine (n=857, 9.6%), venlafaxine (n=419, 4.7%), and escitalopram (n=399, 4.5%).

In the first five years of life, 10,532 (1.3%) children were diagnosed with a congenital heart defect, including 6,934 (60.7%) children diagnosed in the first year of life. There were 4,367 children with a septal defect (2,984 with a ventricular septal defect and 1,656 with an atrial septal defect), 713 children with a conotrunal and major arch defect, 1,149 children with a right ventricular outflow track obstruction, 1,028 children with a left ventricular outflow track obstruction, 273 children with an atrioventricular canal and septal defect, 143 children with

looping defects, and 80 children with anomalous pulmonary venous return. Among the 10,532 children, 2,224 had two or more types of the congenital heart defects defined in this study.

Figure 2 shows the proportion of cases (n=10,532) and controls (n= 782,153) whose mothers used ADs in the six months before and during pregnancy. The mothers of the cases were more likely to use ADs in the six months before and during pregnancy, but the trend of AD use during pregnancy was similar between cases and controls. Both mothers of cases and controls redeemed AD prescriptions more often in the first two months of pregnancy than during the remaining part of the pregnancy.

We identified 169 children diagnosed with a congenital heart defect in the first five years of life whose mothers had redeemed one type of AD during pregnancy. Of these children, 88 had discordant information on maternal use of ADs in the risk period (1-3 months of pregnancy) and the reference period (gestational months 5-7), with 70 children exposed to maternal AD use in the risk period only and 18 children exposed to maternal AD use in the reference period only. We also identified 8,800 children who were not diagnosed with a congenital heart defect in the first five years of life, whose mothers had redeemed one type of AD during pregnancy. Of these children, 5,101 had discordant information on maternal use of ADs in the risk period *vs.* the reference period with 4,035 children exposed to maternal AD use in the risk period only and 1,066 children exposed to maternal AD use in the reference period only.

Figure 3 and 4 presents patterns of maternal AD use in the six months before and during pregnancy among cases and controls whose mothers used one type of AD in pregnancy (n=8,969) when we define the risk period as the first 3 months of pregnancy and the reference period as gestational months 5-7 (Figure 3) or 4-6 months before pregnancy (Figure 4). Table 3

in the Supplementary material presents the characteristics of these cases and controls (n=8,969) according to the exposure pattern in the risk and reference period. Cases and controls with discordant information on maternal AD use in the risk and reference periods showed a similar profile on maternal depression before birth although they might differ on other time-fixed factors like gestational age, maternal age at the birth, and maternal civil status (Table 3 in the Supplementary material).

In the cohort study, we identified 8,805 (1.1%) children whose mothers used ADs in the first three months of pregnancy, 9,138 (1.2%) children whose mothers did not use ADs in the first three months of pregnancy, but used AD in the 12 months before pregnancy, and 774,742 unexposed children with no maternal AD use. The exposed children and the unexposed children with maternal AD use before pregnancy had similar characteristics. They were more likely to be born to mothers of older age, unmarried mothers, and mothers with a low level of education and family income than the unexposed children with no maternal AD use (Table 1).

The case-time-control ORs for any congenital heart defect among children exposed to maternal AD use in the first three months of pregnancy were 1.03 (95% CI: 0.61-1.73) and 1.09 (95% CI: 0.60-1.99) using gestational months 5-7 and 4-6 months before pregnancy as the reference period (Table 2). We observed a large variation in the OR for specific defects. For ventricular septal defects, the case-time-control ORs were 2.51 (95% CI: 0.58-10.79) and 1.77 (95% CI: 0.52-6.04) using gestational months 5-7 and 4-6 months before pregnancy as the reference period. The findings in the sensitivity analyses were similar to the main findings (Table 3). The findings for SSRIs were similar to the findings for any AD (Table 4). We also observed a large variation in the estimates for specific SSRIs associated with large CI due to the small number of events (Table 4).

We identified 47 children diagnosed with a congenital heart defect whose mothers had used more than one type of AD during pregnancy but found no increased risk of congenital heart defects in this group (data not shown in tables).

In the cohort study, the adjusted ORs for congenital heart disease in the exposed children were 1.41 (95% CI: 1.22-1.65) compared with the unexposed group with no maternal AD use and 1.09 (95% CI: 0.88-1.35) compared with the unexposed group with maternal AD use before pregnancy. The adjusted ORs did not differ much from the crude ones (Table 5). When we restricted the analyses to children whose mothers had been diagnosed with depression before or during pregnancy (n=9,315, 1.2%), the adjusted ORs of congenital heart defects among the exposed children varied depending on the characteristics of the reference group, including maternal AD use before pregnancy, time of the latest diagnosis of maternal depression, and whether mothers were hospitalized (Table 5). The ORs were 1.08 (95% CI: 0.72-1.64) compared with the unexposed children whose mother had a recent diagnosis of depression in pregnancy or within two years before pregnancy and 1.37 (95% CI: 0.94-2.01) compared with children whose mother had a former diagnosis of depression three years or more before pregnancy (Table 5).

DISCUSSION

The case-time-control design provided results similar to the cohort design, but only when the cohort design had a better confounder control strategy.

Congenital malformations related to use of ADs during pregnancy have been reported in several papers, but the findings have not been consistent (5, 9-11, 24, 29). A recent paper by Petersen and colleagues indicates that mothers who received ADs six months before or in early pregnancy were more likely obese, had diabetes, had a history of alcohol and illicit drug use, had a history

of smoking before and during pregnancy, and use of other psychotropic medications in pregnancy (11). They did not, however, find that mothers who took ADs in early pregnancy were at greater risk of giving birth to a child with congenital heart malformation after adjustment for these factors (11). Another study from the USA used a propensity score to take into consideration maternal sociodemographic factors (like state of residence, age, race, and parity), maternal chronic illness (like hypertension, diabetes, epilepsy, and renal disease), other psychotropic medications, antidiabetic and antihypertensive medications (10). The most significant findings in the crude analyses disappeared after taking maternal depression and the other covariates listed above into consideration (10). A study on data from five Nordic countries by Furu and colleagues showed that their adjusted findings in a cohort study could not be repeated in a sibling analysis (30). A recently published study demonstrated that associations between exposure to ADs in early pregnancy and several birth and neurological disorders diminished in the adjusted models and in the sibling design analyses, which indicates confounding, especially confounding by indication, or other types of confounding in the study (31). Confounding by indication and confounding by background characteristics have been of concern in observational studies and researchers have been exploring different methods to adjust for those factors (31, 32).

Intake of medication often changes with time, especially during pregnancy. It is known that the case-crossover design does not fit the situation when there is time trend of exposure and the case-only designs have therefore in general been criticized (28, 33). The case-time-control design is, however, expected to perform better (28, 33) in such a situation by adjustment for this trend via a control group. Obtaining data on “controls” for a case-time-control study is not appealing since the process is often time-consuming and subject to selection bias (28, 34, 35). Much of this is

avoided when the study is based on existing registered cohorts of good quality. Prescription registries provide a unique opportunity for conducting post-marketing studies and the case-time-control study may be a good design model even when registries contain limited information on potential confounders(36).

However, the case-time-control design can only make use of information from cases and controls with discordant information on maternal AD prescription in the defined risk and reference periods, which can lead to low statistical power. However, the accumulation of computerized registry datasets would lessen this disadvantage of the design.

Our results on this specific topic should be interpreted with caution. We focused only on congenital heart defects while other studies have reported associations between maternal exposure to ADs and other major or rare birth defects (29). Several studies have reported associations between specific ADs (paroxetine, sertraline, and citalopram) and an increased risk of septal defects (4, 5, 24, 29, 37, 38). The statistical power in this study also limited our capacity to explore the association between the specific ADs and the risk for specific types of congenital heart defects (39). The prescription profile of ADs in our study population may be different from other study populations and the findings may not directly be applied to a population with a different pattern of AD prescriptions during pregnancy (9).

Although time trend of exposure could be adjusted for in the case-time-control design, bias could still occur if the time trend of exposure differs between cases and nondiseased controls (40). The case-time-control design was originally introduced to control for confounding by indication of drugs by assuming that indication for treatment is stable over time but this may be too optimistic (13, 40). Women may discontinue AD use in early pregnancy probably due to their concern of

adverse effects of ADs to fetus, and many pregnant women and new mothers perceive the risks of AD treatment in pregnancy similar to what they perceive for alcohol and smoking (41-43). Women who did not use AD in early pregnancy and started/restarted use of ADs in late pregnancy, however, may have specific characteristics or indication for treatment, for example, poor control of symptoms after stopping use of medication. Our study showed that cases and controls in the analyses of the case-time-control design had a similar profile on maternal depression although they might differ on other time-fixed factors. A previous study indicated that the case-time-control design is quite robust even for autocorrelated exposure within a person(44).

It is important to note that we defined the first three months of pregnancy as the risk period. We used the dates that pregnant women received ADs from a pharmacy as the start of exposure and assumed that they took the medicine soon thereafter, which will not always be the case. This limited our ability to define accurately the periods of exposure and could bias our results(40). A study on the data quality of the prescription register in Denmark indicate that the completeness of psychoanaleptics (N06) is 95.1%.(45) A study has showed that in Denmark about 85% of people who were prescribed ADs took them regularly, which might also apply to AD use before women were aware of their pregnancy.(46) In Denmark medication including antidepressant consumption during pregnancy had been collected in the Danish National Birth Cohort, in which about 100,000 pregnant women were recruited between 1996 and 2002 and self-reported their medication during pregnancy using three telephone interviews with two during pregnancy and one shortly after pregnancy.(47) From the survey data, about 0.5% of children have been exposed to maternal ADs during pregnancy, which was quite consistent with the findings for children born at that period from the register-based study.(48, 49)

The case-time-control study may be more sensitive to misclassification of both exposure and outcome(40). It is suggested to use strict outcome definitions with higher specificity even at the cost of identifying cases with lower sensitivity (50). However, our findings remained in the sensitivity analyses restricted to those children with at least two records of diagnoses of congenital heart defects. As in other observational studies, selection bias can be a problem. In this study, fetuses who did not survive till birth were excluded from the study population. It has been reported that about 11.5% of congenital heart defects lead to fetal death or terminations of pregnancy (51). If ADs increased the risk of severe birth defects, leading to spontaneous and elective abortions, the association between AD use and congenital heart defects among live born children will be underestimated.

Although we should take the limitations of the case-time-control design into consideration when we apply the method in research including pharmacoepidemiologic research, the design could be considered when estimating acute effects of a medicine and if confounding by indication is an outstanding problem.(14) It is encouraged to better use of the self-controlled designs (case-time-control is one of them) in situations in which major validity assumptions are fulfilled.(21) It has been estimated that about 15% of papers using electronic healthcare databases in 2014 could potentially miss opportunity for use of self-controlled designs.(52) The design could be one of better choices especially when a cohort design is not possible to be conducted.

CONCLUSION

404 This study shows that the case-time-control design provides results similar to a better controlled
405 cohort design. The case-time-control design is an option to consider when data sets have less
406 detailed data on important confounders or when a cohort design is not possible to be conducted.

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Compliance with Ethical Standards: The study was approved by the Danish Data Protection Agency (record no. 2013-41-1995).

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Table 1. Characteristics of the study population according to the exposure to maternal antidepressant (AD) use before and during pregnancy

	Exposed children [a]		Unexposed children with maternal AD use before pregnancy [b]		Unexposed children with no maternal AD use [c]	
	No.	%	No.	%	No.	%
Sex of the child						
Boys	4,619	52.5	4,694	51.4	397,444	51.3
Girls	4,186	47.5	4,444	48.6	377,298	48.7
Gestational age (weeks)						
<37	756	8.6	603	6.6	37,621	4.9
37-41	7,657	87.0	8,015	87.7	678,104	87.5
42+	392	4.5	520	5.7	59,017	7.6
Maternal age at the birth (years)						
<25	1,247	14.2	1,443	15.8	106,981	13.8
25-29	2,637	29.9	2,809	30.7	272,187	35.1
30-35	2,961	33.6	3,086	33.8	272,642	35.2
35-39	1,600	18.2	1,505	16.5	106,018	13.7
40+	360	4.10	295	3.2	16,914	2.2

Parity						
1 child	3,873	44.0	3,867	42.3	333,205	43.0
2 children	2,760	31.3	2,998	32.8	291,271	37.6
3+ children	2,172	24.7	2,273	24.9	150,233	19.4
Maternal education at birth						
Primary	2,845	32.3	3,015	33.0	153,536	19.8
Medium	3,522	40.0	3,646	39.9	331,440	42.8
High	2,307	26.2	2,306	25.2	274,516	35.4
Missing	131	1.5	171	1.9	15,250	2.0
Maternal civil status at birth						
Married	4,035	45.8	4,369	47.8	447,168	57.7
Cohabitant	4,097	46.5	4,016	43.9	296,837	38.3
Others	659	7.5	736	8.1	28,589	3.7
Family income (quantiles)						
Low	2,825	32.1	2,936	32.1	192,412	24.8
Low-medium	2,227	25.3	2,366	25.9	193,578	25.0
Medium-high	2,036	23.1	2,084	22.8	194,050	25.0

High	1,717	19.5	1,752	19.2	194,702	25.1
Maternal depression diagnosis before or in pregnancy						
No	6,720	76.3	7,831	85.7	768,819	99.2
Yes	2,085	23.7	1,307	14.3	5,923	0.8
Maternal antiepileptic medication in the first three months of pregnancy						
No	8,581	97.5	9,063	99.2	772,374	99.7
Yes	224	2.5	75	0.8	2,368	0.3
Calendar year						
1995-1999	873	9.9	1,375	15.0	235,850	30.4
2000-2004	3,089	35.1	3,456	37.8	302,243	39.0
2005-2009	4,843	55.0	4,307	47.1	236,649	30.5

[a]: The exposed children refer to those whose mothers redeemed AD prescriptions in the first three months of pregnancy

[b]: The unexposed children with maternal AD use before pregnancy refer to those whose mothers redeemed AD prescriptions in the 12 months before pregnancy but not in the first three months of pregnancy

[c]: The unexposed children with no maternal AD use refer to those whose mothers did not redeem any AD prescription (neither in the first three months of pregnancy nor in the 12 months before pregnancy)

Table 2. The odds ratio (OR) for congenital heart defects diagnosed in the first five years in children whose mothers used antidepressants (AD) [a] in the first three months of pregnancy in a case-time-control study

Types of participants and types of congenital heart defects	Risk period: 1-3 gestational months vs. reference period: gestational months 5-7					Risk period: 1-3 gestational months vs. reference period: 4-6 months before pregnancy				
	Discordant pair [b]	$OR_{among\ controls\ or\ cases}$	$OR_{case\text{-}time\text{-}control}$ [c]	95% CI		Discordant pair [b]	$OR_{among\ controls\ or\ cases}$	$OR_{case\text{-}time\text{-}control}$ [c]	95% CI	
Controls [d]	4,035//1,066	3.79	.	.	.	2,441//761	3.21	.	.	.
Cases										
Any congenital heart defects	70//18	3.89	1.03	0.61	1.73	49//14	3.50	1.09	0.60	1.99
Septal defects	29//10	2.90	0.76	0.37	1.58	24//9	2.67	0.83	0.38	1.8
Ventricular septal defect	19//2	9.50	2.51	0.58	10.79	17//3	5.67	1.77	0.52	6.04
Atrial septal defects	15//8	1.88	0.50	0.21	1.17	10//6	1.67	0.52	0.19	1.43
Right ventricular outflow tract obstruction	7//4	1.75	0.46	0.14	1.58	4//4	1.00	0.31	0.08	1.25
Left ventricular outflow tract obstruction	11//0	.	.	.	.	6//0	.	.	.	.
Conotruncal and major arch defects	5//1	5.00	1.32	0.15	11.32	2//1	2.00	0.62	0.06	6.89
Atrioventricular canal and septal defects	1//2	0.50	0.13	0.01	1.46	1//2	0.5	0.16	0.01	1.72

[a:] The analyses were restricted to children whose mothers used only one type of AD during pregnancy.

[b]: Numbers in the discordant pair refers to the number of children whose mothers redeemed AD prescriptions in the risk period only and the number of children whose mothers redeemed AD prescriptions in the reference period only.

[c]: The OR is adjusted for time trend of AD use between the risk period and the reference period.

[d:] The control group was used to adjust for time trend of AD use between the risk period and the reference period.

Table 3. The odds ratio (OR) for congenital heart defects in children exposed to maternal antidepressant (AD) use [a] in the first three months of pregnancy based on sensitivity analyses in a case-time-control study (Risk period: 1-3 gestational months vs. reference period: gestational months 5-7)

Sensitivity analyses	Discordant pair [b]	$OR_{among\ controls\ or\ cases}$	$OR_{case\text{-}time\text{-}control}$ [c]	95% CI	
Excluding children whose mothers redeemed an AD prescription in the 3 months before pregnancy from children whose mothers redeemed AD prescription only in the reference period [d]					
Controls [e]	4,035//585	6.9	.		
Cases					
Any congenital heart defect	70//11	6.36	0.92	0.49	1.75
Septal defects	29//5	5.8	0.84	0.32	2.18
Ventricular septal defects	19//2	9.5	1.38	0.32	5.93
Atrial septal defects	15//3	5.00	0.72	0.21	2.51
Restricting the analyses to those with at least two records of diagnoses with congenital heart defects in the registry [d]					
Controls [e]	4,064//1,073	3.79			
Cases					
Any congenital heart defect	41//11	3.72	0.98	0.5	1.92
Septal defects	23//6	3.83	1.01	0.41	2.49
Ventricular septal defects	15//0	.	.	.	.
Atrial septal defects	9//6	1.5	0.4	0.14	1.12
ORs of congenital heart defects in the first year of life					
Controls [e]	4,035//1,066	3.79			
Cases					
Any congenital heart defect	51//12	4.25	1.12	0.6	2.11
Septal defects	24//7	3.42	0.91	0.39	2.11
Ventricular septal defects	16//2	8.00	2.11	0.49	9.21
Atrial septal defects	12//5	2.4	0.63	0.22	1.8

[a]: The analyses were restricted to children whose mothers used only one type of AD during pregnancy.

[b]: Numbers in the discordant pair refer to the number of children whose mothers redeemed AD prescriptions in the risk period only and the number of children whose mothers redeemed AD prescriptions in the reference period only

[c]: The OR is adjusted for time trend of AD use between the risk period and the reference period.

[d]: The OR refers to that in the first five years of life.

[e]: The control group was used to adjust for time trend of AD use between the risk period and in the reference period

Table 4. The odds ratio (OR) for congenital heart defects diagnosed in the first five years in children whose mothers redeemed a prescription for selective serotonin reuptake inhibitors (SSRIs) and specific SSRIs [a] in the first three months of pregnancy in a case-time-control study (Risk period: 1-3 gestational months vs. reference period: gestational months 5-7)

SSRIs and specific SSRI	Discordant pair [b]	$OR_{among\ controls\ or\ cases}$	$OR_{case\text{-}time\text{-}control}$ [c]	95% CI	
SSRI					
Controls [d]	3,231//955	3.38	.		
Cases					
Any congenital heart defects	61//17	3.59	1.07	0.62	1.82
Septal defects	27//9	3.00	0.89	0.42	1.89
Ventricular septal defects	18//2	9.00	2.66	0.62	11.49
Atrial septal defects	14//7	0.2	0.59	0.24	1.47
Citalopram					
Controls [d]	1,321//238	5.55			
Cases	26//2	13	2.34	0.55	9.93
Fluoxetine					
Controls [d]	715//399	1.79			
Cases	11//9	1.22	0.68	0.28	1.66
Sertraline					
Controls [d]	558//234	2.38			
Cases	11//4	2.75	1.15	0.36	3.66
Paroxetine					
Controls [d]	370//60	6.17			
Cases	7//2	3.5	0.57	0.12	2.8

[a]: The analyses were restricted to children whose mothers used only one type of AD during pregnancy.

[b]: Numbers in the discordant pair refers to the number of children whose mothers redeemed AD prescriptions in the risk period only and the number of children whose mothers redeemed AD prescriptions in the reference period only

[c]: The OR is adjusted for time trend of AD use between the risk period and the reference period.

[d]: The control group was used to adjust for time trend of AD use between the risk period and in the reference period

Table 5. The odds ratio (OR) of congenital heart defects among children exposed to maternal antidepressants (AD) use in the first three months of pregnancy

Exposure status	Population	Cases, N	Prevalence, %	OR for the exposed children compared with the reference (Ref)				
				Crude OR	Adjusted OR [a]	95% CI		
Ref 1: Unexposed children with no maternal AD use [b]	774,742	10,190	1.32	1.00	1.00			
Ref 2: Unexposed children with maternal AD use before pregnancy [c]	9,138	166	1.82	1.00	1.00			
Exposed children [d]	8,805	176	2.00	1.53	1.41	1.22	1.65	vs. Ref 1
				1.10	1.09	0.88	1.35	vs. Ref 2
Analyses restricted to children whose mothers had a diagnosis of depression before or during pregnancy (n=9,315)								
Ref 1: Unexposed children with no maternal AD use	5,923	113	1.91	1.00	1.00			
Ref 1.1: Unexposed children whose mother had a recent diagnosis of depression [e]	2,009	49	2.44	1.00	1.00			
Ref 1.1.1: Unexposed children whose mother had a recent diagnosis of depression as an outpatient [f]	1,489	30	2.01	1.00	1.00			
Ref 1.2: Unexposed children whose mother had a former diagnosis of depression [g]	3,914	64	1.63	1.00	1.00			
Ref 2: Unexposed children with maternal AD use before pregnancy	1,307	24	1.84	1.00	1.00			

Exposed children	2,085	50	2.40	1.26	1.27	0.90	1.78	vs. Ref 1
				0 .98	1.08	0.72	1.64	vs. Ref 1.1
				1.19	1.24	0.77	1.99	vs. Ref 1.1.1
				1.48	1.37	0.94	2.01	vs. Ref 1.2
				1.31	1.33	0.81	2.18	vs. Ref 2

[a]: Adjusted for maternal age at time of birth (<25, 25-29, 30-34, 35-39, 40+ years), parity (1, 2, 3+), the highest degree of education completed by the mothers (primary, medium, and high), marital status (married, cohabitant, and others like divorced, single, and separated), employment (no unemployment, unemployment for less than half year, unemployment for half year and more), family income (quantile), maternal antiepileptic medication in the first three months of pregnancy (yes, no), and calendar years of birth (1995-1999, 2000-2004, 2005-2008).

[b]: Children whose mothers did not redeem any AD prescription both in the 12 months before pregnancy and the first three months of pregnancy

[c]: Children whose mothers redeemed AD prescriptions in the 12 months before pregnancy but not in the first three months of pregnancy.

[d]: Children whose mothers redeemed AD prescriptions in the first three months of pregnancy.

[e]: Children whose mother had her latest diagnosis of depression in the two years before or during pregnancy

[f]: Children whose mother had her latest diagnosis of depression as an outpatient in the two years before or during pregnancy

[g]: Children whose mother had her latest diagnosis of depression three years or longer before pregnancy

Legends of Figures

Figure 1: Illustration of the case-time-control design used in this study

(Cases are children with a diagnosis of congenital heart defects in the first five years of life; Controls are children without a diagnosis of congenital heart defects in the first five years of life. Cases can be divided into four groups according to maternal use of antidepressant (AD) in the risk period and the reference period - A: the risk period: first 3 months of pregnancy, the reference period: gestational months 5-7; B: the risk period: first 3 months of pregnancy, the reference period: 4-6 months before pregnancy; Only two groups contribute to $OR_{cases,}$ which is the ratio of the number of cases whose mothers used ADs in the risk period only, divided by the number of cases whose mothers used ADs in the reference period only; $OR_{controls,}$ is calculated in the same way, which is used to adjust for time trend of exposure; $OR_{case\text{-}time\text{-}control}$ is the ratio of OR_{cases} divided by $OR_{controls}$)

Figure 2. Proportion of cases and controls whose mothers used antidepressants in the 6 months before and during pregnancy

Figure 3. Patterns of maternal antidepressant (AD) use in the 6 months before and during pregnancy among cases and controls whose mothers used one type of AD during pregnancy (N=8,969) when we define the risk period as the first 3 months of pregnancy and gestational months 5-7 as the reference period; (a) mothers with AD use in both the risk and reference periods; (b) mothers with no AD use neither in the risk nor the reference periods; (c) mothers with AD use in the risk period but not in the reference period; and (d) mothers with AD use in the reference period but not in the risk period.

Figure 4. Patterns of maternal antidepressant (AD) use in the 6 months before and during pregnancy among cases and controls whose mothers used one type of AD during pregnancy (N=8,969) when we define the risk period as the first 3 months of pregnancy and 4-6 months before pregnancy as the reference period; (a) mothers with AD use in both the risk and reference periods; (b) mothers with no AD use neither in the risk nor the reference periods; (c) mothers with AD use in the risk period but not in the reference period; and (d) mothers with AD use in the reference period but not in the risk period.