

Use of selective serotonin-reuptake inhibitors in the first trimester and risk of cardiovascular-related malformations: a meta-analysis of cohort studies

Tie-Ning Zhang¹, Shan-Yan Gao², Zi-Qi Shen³, Da Li³, Cai-Xia Liu³, Hai-Chen Lv⁴, Yuan Zhang⁵, Ting-Ting Gong³, Xin Xu², Chao Ji², Qi-Jun

Wu^{2,*}

Supplementary Table S1. Characteristics of cohort studies in the meta-analysis

First author (ref), year, location	No. of cohort/cases	Study period	Outcomes	Risk estimates (95% CI)	Adjusted factors
Furu et al ³⁰ , 2015, Europe	2,303,647	1996-2010		Odds Ratio	Maternal age, year of birth, birth order, smoking, maternal diabetes, country, and use of other prescribed drugs.
	27,309		Any cardiac defect	1.15 (1.05-1.26)	
	17,879		ASD and VSD	1.17 (1.05-1.31)	
	1,095		Atrioventricular septal defect	1.22 (0.77-1.91)	
	2,261		Conotruncal and major arch Anomalies	0.95 (0.67-1.35)	
	2,641		Left ventricular outflow tract Obstruction	1.09 (0.80-1.49)	
	2,778		Right ventricular outflow tract Obstruction	1.48 (1.15-1.89)	
	657		Situs anomalies and looping defect	1.00 (0.52-1.90)	
Berard et al ³¹ , 2015, North America	18,493	1998-2010		Risk Ratio	Maternal age, welfare status, diabetes, . hypertension,asthma,and other medication use
	405		Cardiac malformations	1.10 (0.82-1.48)	
	322		ASD/VSD	1.30 (0.99-1.70)	

Supplementary Table S1. Continued

First author (ref), year, location	No. of cohort/cases	Study period	Outcomes	Risk estimates (95% CI)	Adjusted factors
Ban et al ³² , 2014, Europe	349,127	1990-2009	Specific heart anomalies	Odds Ratio 1.14 (0.89-1.45)	Maternal age at the end of pregnancy, year of childbirth,townsend deprivation quintile, maternal smoking history,BMI before pregnancy, and maternal diabetes,hypertension, asthma, and epilepsy in the year before conception or during pregnancy.
	2,512		Septal defect	0.89(0.63-1.27)	
	N/A		ASD	1.68 (0.98-2.91)	
	N/A		VSD	0.63(0.38-1.03)	
	N/A		LVOTD	1.05 (0.20-11.24)	
	N/A		RVOTD	2.22 (0.98-5.03)	
Huybrechts et al ³³ , 2014, North America	949,504	2000-2007	Cardiac malformations	Odds Ratio 1.25 (1.13-1.38)	N/A
	6,819		VSD	1.20 (1.04-1.39)	
	3,413		Right ventricular outflow tract obstruction	1.12 (0.87-1.45)	
	1,106		Other cardiac defect	1.34 (1.17-1.54)	
	3,458				

Supplementary Table S1. Continued

First author (ref), year, location	No. of cohort/cases	Study period	Outcomes	Risk estimates (95% CI)	Adjusted factors
Knudsen et al ³⁴ , 2014, Europe	72,280	1995-2008		Odds Ratio	Maternal age, year of conception, use of antiepileptics and/or insulin during first trimester.
	546		CHD	1.64 (0.89-3.00)	
	129		Severe CHD	4.03 (1.75-9.26)	
	97		ASD	2.82 (0.88-9.04)	
	333		VSD	0.94 (0.35-2.53)	
54	Pulmonary valve stenosis	3.47 (0.83-14.5)			
Vasilakis- Scaramozza et al ³⁵ , 2013, Europe	9,893	1991-2002		Relative Risk	Prepregnancy BMI, maternal age, cigarette smoking status, history of DM, insulin use, exposure to a teratogen during the first trimester, history of infertility, and premature delivery.
35	Cardiovascular anomalies	0.80 (0.40-1.90)			
Margulis et al ³⁶ , 2013, Europe	149,464	1996-2010		Odds Ratio	Year of delivery, maternal age at delivery, prepregnancy marital status, index of multiple deprivation at the practice level, family history of congenital malformations, prepregnancy body mass, prepregnancy diabetes, cigarette smoking, alcohol intake, diagnosis of depression in baseline year, diagnosis of other mental conditions in baseline year or contact with or referral to a psychiatrist, number of health care encounters in baseline year and number of nonantidepressant drugs prescribed in baseline year.
	721		Cardiac malformations	1.09 (0.66-1.79)	
	N/A		Septal defects	1.12 (0.60-2.09)	

Supplementary Table S1. Continued

First author (ref), year, location	No. of cohort/cases	Study period	Outcomes	Risk estimates (95% CI)	Adjusted factors
Nordeng et al ³⁸ , 2012, Europe	63,395	1999-2009	Cardiovascular anomalies	Odds Ratio 1.51 (0.67-3.43)	Maternal depression, maternal age at delivery, parity, and use of psychotropic drugs during pregnancy.
	547		ASD/VSD	1.57 (0.64-3.87)	
Jimenez- Solem et al ³⁹ , 2012, Europe	848,786	1997-2009	Congenital malformation of heart	Odds Ratio 2.01 (1.60-2.53)	Mother's age, parity, income, education, smoking, And year of conception.
	7,832		ASD	2.60 (1.84-3.68)	
	2,524		Atrioventricular septal defect	1.25 (0.31-5.02)	
	N/A		VSD	1.62 (1.05-2.50)	
	2,824		Septal defect	2.04 (1.53-2.72)	
Colvin et al ²¹ , 2011, other regions	123,405	2002-2005	Cardiovascular anomalies	Odds Ratio 1.60 (1.10-2.31)	N/A
	691		Ostium secundum type ASD	2.73 (1.26-5.89)	
	97		VSD	0.99 (0.44-2.23)	
	218				

Supplementary Table S1. Continued

First author (ref), year, location	No. of cohort/cases	Study period	Outcomes	Risk estimates (95% CI)	Adjusted factors
	382		Bulbus cordis anomalies and anomalies of cardiac septal closure	1.23 (0.71-2.15)	
	250		Other congenital anomaly of heart	1.77 (0.99-3.16)	
Malm et al ³⁷ , 2011, Europe	635,583 8,253	1996-2006	All major cardiovascular anomalies	Odds Ratio 1.09 (0.90-1.32)	Age at the end of pregnancy, parity, year of pregnancy ending, smoking during pregnancy, purchase of other reimbursed psychiatric drugs during the first trimester, and maternal prepregnancy diabetes.
	1,297		ASD	1.04 (0.64-1.69)	
	5,550		VSD	1.20 (0.96-1.50)	
	437		Conotruncal heart defect	0.46 (0.14-1.46)	
	476		Left ventricular outflow tract defects	0.93 (0.40-2.13)	
	423		Right ventricular outflow tract defects	1.74 (0.85-3.57)	
	240		Transposition of great arteries	0.60 (0.15-2.52)	

Supplementary Table S1. Continued

First author (ref), year, location	No. of cohort/cases	Study period	Outcomes	Risk estimates (95% CI)	Adjusted factors
Kornum et al ⁴⁰ , 2010, Europe	216,042 1,429	1991-2007	Cardiac malformations	Odds Ratio 1.70 (1.10-2.50)	Maternal smoking status, maternal age, birth order, and birth year.
Merlob et al ²⁰ , 2009, Other regions	N/A 67,871 1,091	2000-2007	Septal heart defect Congenital heart malformation	Relative Risk 2.17 (1.07-4.39)	N/A
Pedersen et al ¹⁹ , 2009, Europe	493,113 4,004	1996-2003	Major cardiac malformations	Odds Ratio 1.44 (0.86-2.40)	Age, calendar year, income, marriage status, tobacco smoking.
Oberlander et al ²² , 2008, North America	2,327 11,957 529 81 225	1998-2001	Septal heart defects Cardiovascular congenital defects ASD VSD	1.99 (1.13-3.53) Odds Ratio 1.36 (0.84-2.21) 3.28 (1.42-7.53) 1.12 (0.50-2.52)	N/A

Supplementary Table S1. Continued

First author (ref), year, location	No. of cohort/cases	Study period	Outcomes	Risk estimates (95% CI)	Adjusted factors
Davis et al ⁴¹ , 2007, North America	87,407 682	1996-2000	Bulbus cordis anomalies and anomalies of cardiac septal closure	Relative Risk 0.93 (0.50-1.73)	Health system, maternal age, and birth season.
	506		Other congenital anomalies of heart	0.88 (0.42-1.86)	
Kallen et al ⁴² , 2007, Europe	880,431 11,445 7,213 1,218	1995-2004	Any cardiac defect VSD and/or ASD Unspecified cardiac defect	Odds Ratio 0.97 (0.77-1.21) 1.10 (0.84-1.44) 1.04 (0.42-2.15)	Year of birth, maternal age, parity, smoking, and ≥ 3 Previous miscarriages.
Kulin et al ⁴³ , 1998, North America	534 6		Cardiac malformations	Relative Risk 0.53 (0.10-2.86)	N/A

Abbreviations: ASD, atrial septal defect; BMI, body mass index; CHD, congenital heart defect; DM, diabetes mellitus; LVOTD, left ventricular outflow tract defect; N/A, not available; RVOTD, right ventricular outflow tract defect; VSD, ventricular septal defect.

Supplementary Table S2. Methodological quality of cohort studies included in the meta-analysis^a

First author (reference), publication year	Representativeness of the exposed cohort	Selection of the unexposed cohort	Ascertainment of exposure	Outcome of interest not present at start of study	Control for important factor or additional factor ^b	Assessment of outcome	Follow-up long enough for outcomes to occur ^c	Adequacy of follow-up of cohorts ^d
Furu et al ³⁰ , 2015	*	*	*	*	**	*	*	*
Berard et al ³¹ , 2015	*	*	*	*	*	*	*	*
Ban et al ³² , 2014	*	*	*	*	**	*	-	-
Huybrechts et al ³³ , 2014	*	*	*	*	-	*	*	*
Knudsen et al ³⁴ , 2014	*	*	*	*	*	*	*	*
Vasilakis- Scaramozza et al ³⁵ , 2013	*	*	*	*	**	*	*	*
Margulis et al ³⁶ , 2013	*	*	*	*	**	*	*	*
Nordeng et al ³⁸ , 2012	*	*	*	*	*	*	-	-
Jimenez- Sole et al ³⁹ , 2012	*	*	*	*	**	*	*	*
Colvin et al ²¹ , 2011	*	*	*	*	-	*	*	*
Malm et al ³⁷ , 2011	*	*	*	*	**	*	-	-
Kornum et al ⁴⁰ , 2010	*	*	*	*	**	*	*	*
Merlob et al ²⁰ , 2009	*	*	*	*	-	*	*	*
Pedersen et al ¹⁹ , 2009	*	*	*	*	**	*	*	*
Oberlander et al ²² , 2008	*	*	*	*	-	*	-	-
Davis et al ⁴¹ , 2007	*	*	*	*	*	*	*	*
Kallen et al ⁴² , 2007	*	*	*	*	**	*	-	-
Kulin et al ⁴³ , 1998	*	*	*	*	-	*	-	-

- ^a A study could be awarded a maximum of one star for each item except for the item Control for important factor or additional factor. The definition/explanation of each column of the Newcastle-Ottawa Scale is available from (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp).
- ^b A maximum of 2 stars could be awarded for this item. Studies that controlled for age received one star, whereas studies that controlled for other important confounders such as smoking and/or alcohol using received an additional star.
- ^c A cohort study with a follow-up time >9 months was assigned one star.
- ^d A cohort study with a follow-up rate >75% was assigned one star.

