

GSK Medicine: Paroxetine
Study No.: WEUSRTP2280
Title: First Trimester Paroxetine Use and the Prevalence of Congenital, Specifically Cardiac, Malformations: Systematic Review and Meta-Analysis of Epidemiological Data
Rationale: This study met a regulatory request and provides a summary of existing data on paroxetine and congenital malformations.
Objectives: The objective was to conduct a systematic review with critical meta-analysis of all available relevant epidemiological data regarding first trimester paroxetine use and the prevalence of congenital, including cardiac, malformations.
Indication: Major depressive disorder/Obsessive-compulsive disorder/Panic disorder/Social anxiety disorder/Generalized anxiety disorder/Post-traumatic stress disorder/Premenstrual dysphoric disorder
Study Investigators/Centers: GSK conducted in collaboration with University of North Carolina (UNC)-GSK Center of Excellence in Pharmacoepidemiology and Public Health
Research Methods:
Data Source: Existing literature and additional information obtained from publication authors
Study Design: Systematic review and meta-analysis
Study Population:
Identification of Studies: A systematic literature search was conducted initially for original research published in English from 1992 through February 15, 2007 and subsequently updated through October 15, 2007. The search was further updated based on data available through 30 September 2008 (with author contacts through 30 November 2008). Secondary references were also searched to find additional studies.
Inclusion Criteria: In order to be included in the meta-analysis, a publication must have been published in English and have included human subjects and a control or comparison group. Data from all studies using an overall category of congenital malformations such as "total," "any" or "all" congenital malformations/anomalies/birth defects were included in the meta-analysis for this outcome. Data from studies using an overall category of cardiac defects combined such as "any cardiac" or "congenital heart defects" were included in the meta-analysis for this outcome.
Exclusion Criteria: Data from case reports, case series, non-human data, neonatal consequences from breast-milk exposure, third trimester only exposure and neonatal complications unrelated to congenital defects were excluded. Review articles and meta-analyses were retained for secondary references and/or if they contained original data not contained elsewhere. Both abstracts and full text manuscripts were reviewed for results pertaining to the prevalence of congenital defects, both cardiac and total, with paroxetine use.
Study Exposures, Outcomes:
Data Extraction: Data were extracted separately by two investigators using an abstraction form with pre-defined data fields and any discrepancies resolved. A sample of the studies was checked against the dataset by a third investigator who did not take part in the initial abstractions. The initial data entry was verified and then re-verified during analysis. Publication authors were contacted by two investigators to obtain specific information needed for data abstraction not included in published information, such as paroxetine-specific estimates for total and specific defects, as well as clarification on exposure definition and ascertainment, outcome ascertainment, definition and exclusions, control or comparison groups used, and confounders assessed.
Data Analysis Methods: Graphical and statistical analyses to assess funnel plot symmetry and consistency of results were performed. Funnel plot asymmetry was assessed by computation of p-values for Begg and Mazumdar's log rank test, the regression test of Egger et al. and Duval and Tweedie's trim and fill imputation method. Overall consistency of results was assessed by homogeneity tests using Cochran's Q statistic. Analysis of study characteristics was performed by both stratified and meta-regression methods. The stratified analyses consisted of the computation fixed-effect summary estimates (prevalence odds ratios (POR) and corresponding 95% CIs), homogeneity test p-values and meta-regression models within study characteristic categories containing at least two results. Sensitivity analyses were performed using five alternative continuity corrections where unadjusted effect estimates and standard errors had to be calculated. STATA Intercooled version 9.2 for Windows (Stata Corp., College Station, TX) was used to perform the meta-analyses at the University of North Carolina. Ancillary analyses and graphics were produced using SAS Release 8.2 (SAS, Cary, NC).
Limitations:
<ul style="list-style-type: none"> Data extracted from abstracts may be incomplete or change following subsequent peer-review process.

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- As a compilation of observational studies, this meta-analysis is subject to the limitations associated with each individual study. Associations that were not addressed in each of the studies could not be assessed by the meta-analysis.
- The meta-analysis was limited by the study characteristics that were reported by each individual study. Only characteristics that were reported by more than four studies could be assessed in order for a stratified analysis to contain two studies per stratum.
- Study characteristics were analyzed individually. Due to the size of the literature, the inclusion of more than one study characteristic in a meta-regression model could not be performed. Thus unmeasured meta-confounding, where other study characteristics are influencing a relationship between the outcome and a study characteristic, is possible.

Study Results: While subject to limitations, this meta-analysis suggests an increased prevalence of both cardiac malformations [1.46 (95% CI 1.17-1.82)] and total malformations [1.24 (95% CI 1.08-1.43)] in association with paroxetine use during the first trimester. There was little evidence of funnel plot asymmetry and overall heterogeneity, although some of the study characteristics may be associated with the relationship between paroxetine and cardiac malformations as well as total malformations.

Tables

Table 1: Selected Details of Included and Excluded Studies and Author Contacts

First Author	Year	Data Source	Comparison Group	Type	Author Response and/or Reason for exclusion
Study included and author provided information					Author Response
Simon	2002	AD	No SSRI ^{a, 1}	Journal Article	Provided paroxetine specific outcomes
Casper	2003	Clinic	Depressed ^{b,1}	Journal Article	Provided paroxetine specific outcomes
Vial	2006	TIS	Controls from TIS ^{c,3}	Abstract	Provided clarification of methods, paroxetine specific outcomes, adjusted odds ratios and individual defects
Kallen	2007	PBR	General Population ⁴	Journal Article	Provided clarification of methods, paroxetine specific outcomes, adjusted odds ratios and individual defects
Chambers	2007	TIS	Controls from TIS ^{c,1}	Unpublished	Contributed specific malformations and larger paroxetine sample
Wen	2006	AD	No SSRI ^{a,1}	Journal Article	Provided paroxetine specific outcomes and adjusted odds ratio
Bakker	2006	PBR	No SSRI ^{a,3}	Abstract	Provided clarification of methods
Nash	2007	AD	No SSRI ^{a, 1}	Abstract	Provided clarification on methods and paroxetine specific outcomes as well as unadjusted odds ratios
Davis	2007	AD	No SSRI ^{a, 3}	Journal Article	Provided clarification of methods
Maschi	2008	TIS	Controls from TIS ^{c,1}	Journal Article	Provided paroxetine specific outcomes and clarification of methods
Study included and author not contacted for further information					
Berard	2007	PBR	Depressed ^{d, 5}	Journal Article	Full information in paper
Cole	2007	AD	Depressed ^{d, 2}	Journal Article	Full information in paper
Alwan	2007	CC	No SSRI ^{e, 3}	Journal Article	Full information in paper

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Louik	2006	CC	No SSRI ^{e, 1}	Abstract/Poster	Abstract contained estimate for total malformations outcome
Louik	2007	CC	No SSRI ^{e, 1}	Journal Article	Paper contained estimates for cardiac malformation outcomes
Bar-Oz	2007	Meta-analysis	NA	Journal Article	Provided results for Kulin and Malm which could not be obtained from their publications
Diav-Citrin	2008	TIS	Controls from TIS _{c, 3}	Journal Article	Full information in paper
Study included and author did not provide additional information				Author Response	
Kulin	1998	TIS	Controls from TIS _{c, 3}	Journal Article	No response: article retained for study characteristic information
Malm	2005	PBR	No SSRI ^{a, 3}	Journal Article	Contributed data to another meta-analysis: article retained for study characteristic information
Schloemp	2006	TIS	Controls from TIS _{c, 3}	Abstract	No response
Oberlander	2008	PBR	Non Depressed, non medicated	Journal Article	Could not provide additional specific data due to data use agreement
Study excluded and author did not provide additional information				Author response	
Wichman	2007	Clinic	All births in clinic	Abstract	Author could not contribute data in time frame
Einarson	2007	TIS	Controls from TIS _c	Abstract	Author did not provide additional data because study was unpublished
Wogelius	2006	PBR	No SSRI ^a	Journal Article	Could not get paroxetine specific information within time frame
Di Gianantoni o	2006	TIS	Controls from TIS _c	Abstract	Author verified that report was about venlafaxine not paroxetine
Einarson	2008	TIS	Controls from TIS _c	Journal Article	Did not provide additional data because group already performed meta-analysis
Einarson	2008	TIS	Controls from TIS _c	Abstract	Did not provide additional data because group already performed meta-analysis
Study excluded and author not contacted				Exclusion reason	
Hendrick	2003	TIS	No Comparison	Journal Article	Case Series-did not provide internal control group
McElhatton	1996	TIS	No Comparison	Journal Article	Case Series-did not provide internal control group
Bianca	2005	Clinic	No Comparison	Abstract	Case Series-did not provide internal control group
Study excluded: more recent publication included					
Unfred	2001	TIS	Controls from TIS _c	Abstract	Same cohort as Chambers (2007) unpublished
Hallberg	2005	PBR	General population	Journal Article	Same cohort as Kallen (2007)
Ericson	1999	PBR	General population	Journal Article	Same cohort as Kallen (2007)
Kallen	2006	PBR	General population	Letter to the editor	Same cohort as Kallen (2007)
Cole	2006	AD	Depressed ^d	Abstract	Same cohort as Cole (2007)
Alwan	2005	CC	No SSRI ^e	Abstract	Same cohort as Alwan (2007)

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Study No.: WEUSRTP2280								
Diav-Citrin	2005	TIS	Controls from TIS _{c,3}	Abstract	Same cohort as Diav-Citrin (2008)			
Oberlander	2007	PBR	Non Depressed, non medicated	Abstract	Same cohort as Oberlander (2008)			
TIS: Teratogen Information Service AD: Administrative database PBR: Population based registry linked with medication data CC: Case-control surveillance program								
a: No SSRI: No SSRI during first trimester as recorded by prescription data b: Depressed: Untreated depressed population c: Controls from TIS: Controls from TIS population (exposed to agents deemed not teratogenic) d: Depressed: Treated with other antidepressants e: No SSRI: No SSRI during first trimester as recorded by maternal report								
1.Paroxetine alone compared to women unexposed to any SSRI 2.Paroxetine alone compared to women exposed to OTHER SSRIs 3.Paroxetine alone or in combination with other SSRIs compared to women unexposed to any SSRI 4.,Paroxetine alone compared to general population (SSRI exposure unknown) 5. Paroxetine alone or in combination with other SSRIs compared to women exposed to other antidepressants								
Table 2: First Trimester Paroxetine Use and Total Congenital Malformations (n=17)								
Study First Author	Year	OR	95% CI	Inverse-variance weight (% of total)	PEM	PENM	UM	UNM
Cohort Studies								
Casper ^a	2003	2.40*	(0.12-46.39)*	0.4	1	5	1	12
Malm ^c	2005	0.95*	(0.34-2.67)*	3.6	4	145	50	1721
Cole ^a	2007	1.89	(1.20-2.98)	18.6	29	786	83	4115
Schloemp ^b	2006	0.76	(0.18-2.53)	2.2	3	85	25	532
Vial ^b	2006	1.40	(0.60-3.30)	5.3	12	523	10	621
Wen ^c	2006	1.29	(0.58-2.53)	7.1	8	117	76	3802
Kallen ^d	2007	0.98	(0.72-1.34)	39.8	42	866	41233	832643
Chambers ^b	Unpublished	5.10*	(1.54-16.84)*	2.7	9	132	4	299
Simon ^c	2002	0.74*	(0.04-13.52)*	0.5	0	12	9	176
Kulin ^b	1997	1.77*	(0.57-5.45)*	3.0	5	71	9	226
Davis ^c	2007	1.03	(0.73-1.48)	30.8	26	156	6805	42849
Oberlander ^c	2008	0.93*	(0.64-1.35)*	27.9	29	964	3369	103951
Maschi ^b	2008	1.24*	(0.15-10.52)*	0.8	1	46	6	342
Diav-Citrin ^b	2008	2.13*	(1.19-3.81)*	11.3	18	330	34	1325
Case-Control Studies								
Louik ^c	2006	1.38	(0.85-2.26)	16.1	62	30	9429	5830
Berard ^a	2007	1.32	(0.79-2.20)	14.7	43	499	58	803
Alwan ^c	2007	1.60	(0.92-2.77)	12.7	70	18	9552	4074

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PEM- Paroxetine exposed malformations PENM- Paroxetine exposed non-malformed UM- Unexposed malformations UNM- Unexposed non-malformed
Comparison Groups Used a: Treated or untreated depressed population b: Controls from TIS population (exposed to agents deemed not teratogenic) c: No SSRI during first trimester as recorded by prescription data or maternal report d: General Population
* OR and 95% CI calculated from reported numbers
Figure 1: First Trimester Paroxetine Use and the Prevalence of Total Congenital Malformations: Forest Plot

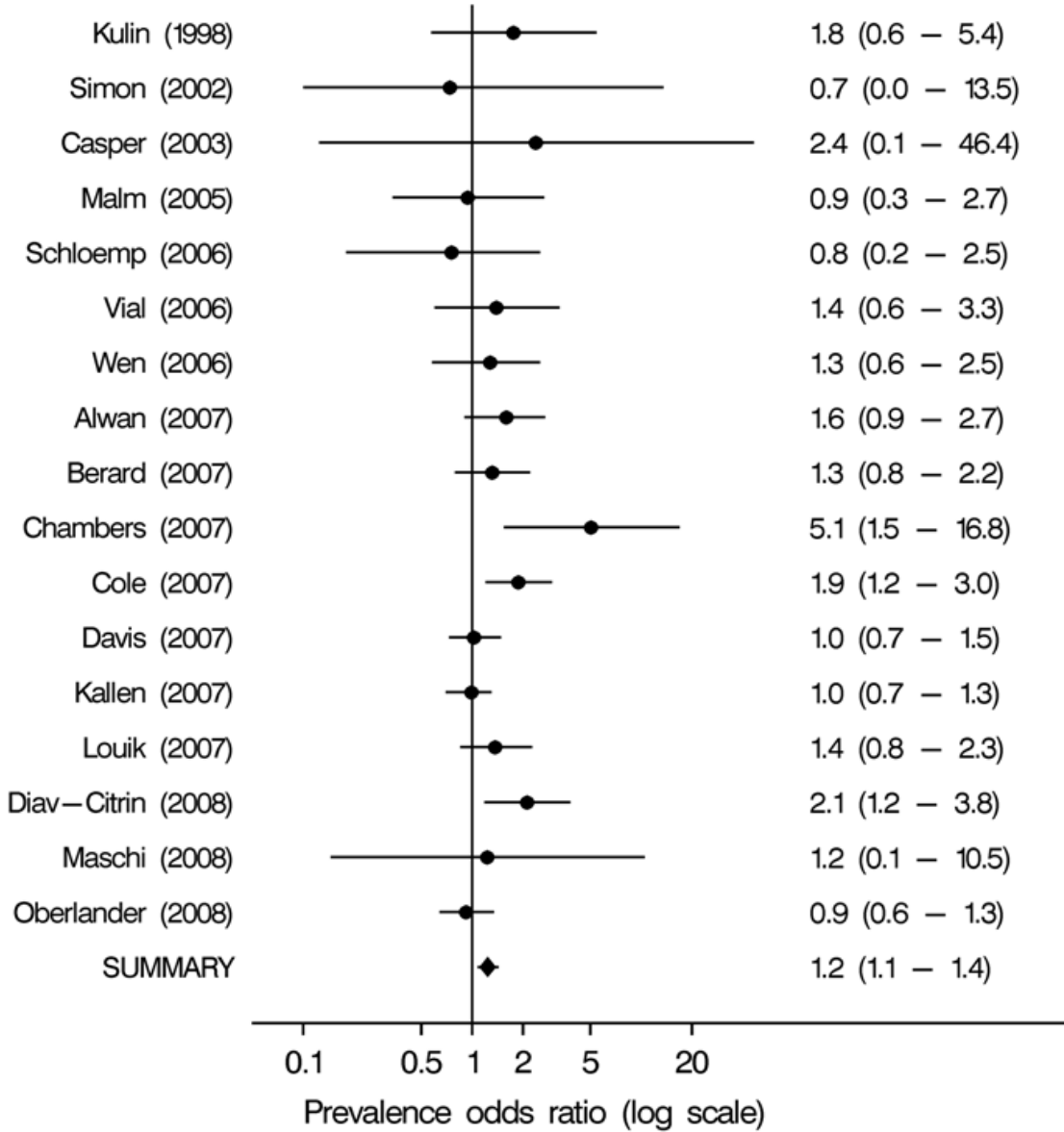


Table 3: First Trimester Paroxetine Use and Total Congenital Malformations: Analyses of Overall Homogeneity and Funnel Plot Symmetry

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Analysis	Number of results	Homogeneity P-value	Funnel plot symmetry P-values		Number of results imputed by trim and fill method	Fixed-effect summary POR (95% CI)	
			Begg	Egger		Without imputed results	With imputed results
Paroxetine and total malformations	17	0.2	0.5	0.2	2	1.24 (1.08-1.43)	1.22 (1.06-1.40)

Table 4: First Trimester Paroxetine Use and Total Congenital Malformations: Study Characteristic Analyses

Study characteristic	Level	Number of results	Homogeneity P-value ^a	Fixed-effect summary OR (95% CI)	Ratio of odds ratios (95% CI) ^a
Design	Case-control	3	0.9	1.42 (1.06, 1.91)	1.
	Cohort	14	0.1	1.20 (1.02, 1.40)	0.89 (0.58, 1.35)
Publication type	Article	13	0.3	1.21 (1.04, 1.40)	1.
	Abstract	3	0.7	1.31 (0.87-1.96)	1.03 (0.61, 1.71)
	Unpublished	1	Na	Na	Na
Data source	Medication-linked population based database	5	0.8	1.03 (0.84, 1.26)	1.
	TIS or Drug and Health Information Centre	6	0.4	1.88 (1.27, 2.77)	1.82 (1.17, 2.83)
	Administrative data base	3	0.1	1.29 (0.98, 1.70)	1.25 (0.89, 1.76)
	Clinic or case-control surveillance	3	0.9	1.48 (1.03, 2.13)	1.44 (0.95, 2.18)
Continent	Europe	7	0.4	1.16 (0.91, 1.48)	1.
	North America	10	0.1	1.29 (1.09, 1.52)	1.10 (0.74, 1.65)
First trimester definition	0-14 weeks post-conception	6	0.1	1.06 (0.87-1.31)	1.
	3-13 weeks post LMP	2	0.4	1.86 (1.15, 3.01)	1.70 (0.97, 2.96)
	Not specified	4	0.8	1.30 (0.75, 2.25)	1.16 (0.62, 2.16)
	30 days pre-conception to end of first trimester	2	0.7	1.47 (1.02-2.12)	1.35 (0.85, 2.14)
	First trimester (0-13 weeks) based on EDD	3	0.1	1.29 (0.98-1.70)	1.20 (0.81, 1.78)

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Paroxetine use and comparison definition	Paroxetine w/o other SSRI use compared to no exposure to any SSRI	7	0.2	1.19 (0.92, 1.55)	0.95 (0.63, 1.43)
	Paroxetine w or w/o other SSRI use compared to no exposure to any SSRI	3	0.8	1.07 (0.78-1.45)	0.82 (0.51, 1.31)
	Paroxetine w/o other SSRI use compared to women exposed to other SSRIs	1	Na	Na	Na
	Paroxetine or comparison group not specified	6	0.2	1.25 (1.01, 1.55)	1.
General malformation definition	Unspecified	6	0.9	1.40 (1.00, 1.97)	1.18 (0.78, 1.80)
	ICD-8/9 740-759, ICD-10 Q00-Q99	8	0.06	1.15 (0.98, 1.35)	1.
	Significant structural, functional anomalies	3	0.7	1.85 (1.19, 2.87)	1.56 (0.94, 2.59)
Time period for malformation ascertainment	Birth to 7 days	2	0.6	1.20 (0.62, 2.31)	0.89 (0.41, 1.93)
	Birth, 1 year and beyond	10	0.3	1.25 (1.05, 1.49)	1.
	Unspecified	5	0.1	1.23 (0.96, 1.58)	0.99 (0.65, 1.51)
Malformation ascertainment	Medical record verified claims, discharge data	11	0.4	1.17 (1.01, 1.36)	1.
	Maternal or physician report from a TIS or congenital defects register	5	0.5	2.05 (1.36, 3.08)	1.72 (1.08, 2.74)
	Unspecified	1	Na	Na	Na
Malformation excluded	None or unspecified	8	0.4	1.08 (0.87, 1.33)	1.04 (0.75, 1.44)
	Minor anomalies	4	0.5	1.12 (0.87, 1.43)	1.
	Genetic anomalies	4	0.9	1.75 (1.24, 2.46)	1.62 (1.08, 2.43)
	Minor and genetic anomalies	1	Na	Na	Na
Exclusion of infants exposed to potential teratogens	Unspecified	8	0.6	1.50 (1.11, 2.02)	1.
	Yes	5	0.2	1.25 (0.99, 1.59)	0.85 (0.54, 1.34)
	No (with or without adjustment)	4	0.1	1.13 (0.91, 1.39)	0.79 (0.50, 1.24)

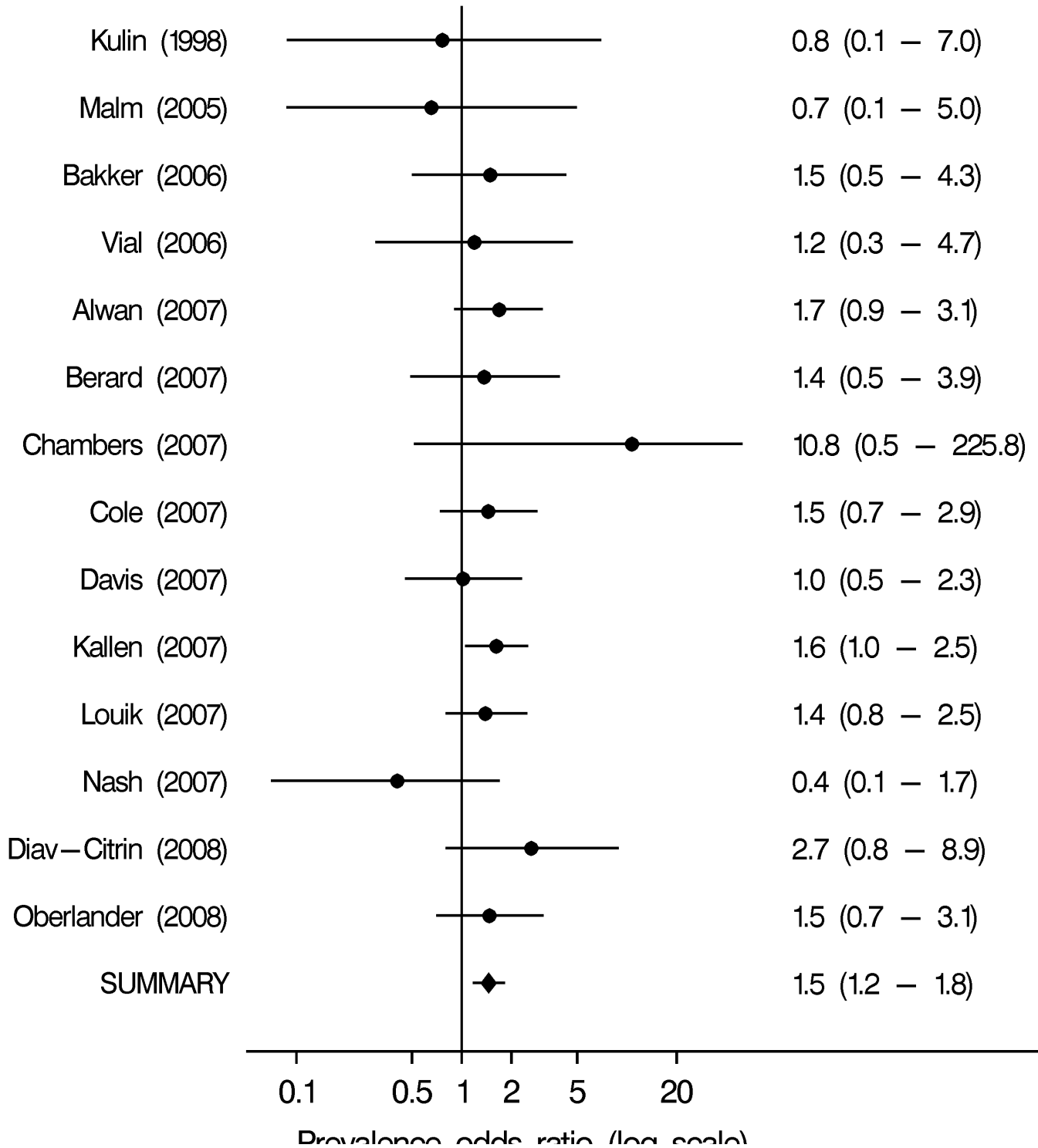
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Paroxetine ascertainment	Prescription data base/ Patient medical record	7	0.3	1.17 (0.97, 1.42)	1.
	Maternal /physician report in 1st trimester to a TIS	2	0.3	1.24 (0.53, 2.92)	1.03 (0.40, 2.66)
	Multiple maternal interviews & medical record: TIS	2	0.1	2.16 (1.08, 4.33)	1.87 (0.83, 4.19)
	Maternal interview at end of first trimester, after delivery or unspecified time	6	0.2	1.27 (1.02, 1.58)	1.15 (0.76, 1.73)
Study comparison group	No SSRI prescriptions	7	0.7	1.12 (0.92, 1.37)	1.
	Depressed women (treated with other antidepressants or untreated)	3	0.6	1.62 (1.16, 2.27)	1.44 (0.98, 2.13)
	Women exposed to other medications deemed non-teratogenic who called information service	6	0.4	1.88 (1.27, 2.77)	1.67 (1.08, 2.59)
	General Population	1	Na	Na	Na
Adjustment for parity	Unspecified	9	0.04	1.29 (1.07, 1.55)	1.
	Considered but did not adjust	3	0.9	1.70 (0.66, 4.37)	1.25 (0.45, 3.47)
	Adjusted	5	0.5	1.16 (0.93, 1.45)	0.89 (0.60, 1.33)
Adjustment for maternal age	Unspecified	1	Na	Na	1.
	Considered but did not adjust	7	0.9	1.10 (0.82, 1.49)	0.22 (0.06, 0.82)
	Adjusted	9	0.1	1.25 (1.07, 1.47)	0.26 (0.07, 0.90)
Adjustment for tobacco and alcohol	Unspecified	9	0.1	1.22 (1.02, 1.48)	1.
	Considered but did not adjust	3	0.8	1.65 (0.62, 4.45)	1.28 (0.44, 3.75)
	Adjusted	5	0.2	1.25 (1.01, 1.55)	1.04 (0.70, 1.54)
Adjustment for pregnancy outcome history	Unspecified	14	0.2	1.31 (1.11, 1.55)	1.
	Considered but did not adjust	1	Na	Na	Na
	Adjusted	2	0.3	1.06 (0.81, 1.39)	0.80 (0.52, 1.24)
Adjustment for other diagnoses	Unspecified	11	0.2	1.18 (0.98, 1.43)	1.
	Considered but did not adjust	1	Na	Na	Na
	Adjusted	5	0.2	1.32 (1.07, 1.62)	1.06 (0.72, 1.56)
Adjustment for family history of malformations	Unspecified	16	0.2	1.23 (1.06, 1.42)	1.
	Adjusted	1	Na	Na	Na
Adjustment for BMI	Unspecified	15	0.2	1.21 (1.04, 1.40)	1.
	Adjusted	2	0.7	1.47 (1.02-2.12)	1.16 (0.71, 1.90)

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Adjustment for vitamin use	Unspecified	15	0.2	1.21 (1.04, 1.40)	1.
	Adjusted	2	0.7	1.47 (1.02-2.12)	1.16 (0.71, 1.90)
Adjustment for other medications	Unspecified	11	0.4	1.19 (0.99, 1.42)	1.
	Considered but did not adjust	1	Na	Na	Na
	Adjusted	5	0.1	1.34 (1.07, 1.68)	1.09 (0.74, 1.60)
Adjustment for any of 9 potential confounders	Adjusted for at least 1	16	0.5	1.22 (1.06, 1.40)	1.
	Adjusted for none	1	Na	Na	Na
How potential confounders were assessed	Unspecified	1	Na	Na	Na
	Group differences assessed, no adjustment	4	0.7	1.07 (0.77, 1.48)	0.84 (0.52, 1.36)
	Adjustment	9	0.1	1.25 (1.07, 1.47)	1.
	Cases and controls matched, no adjustment	3	0.9	1.32 (0.62, 2.83)	1.01 (0.43, 2.33)

Table 5: First Trimester Paroxetine Use and Cardiac Malformations (n=14)

Study First Author	Year	OR	95% CI	Inverse-variance weight (% of total)	PEM	PENM	UM	UNM
Cohort Studies								
Cole ^b	2007	1.46	(0.74-2.88)	8.3	12	803	40	4158
Vial ^a	2006	1.20	(0.30-4.70)	2.0	4	531	4	627
Kallen ^c	2007	1.63	(1.05-2.53)	19.9	20	888	11367	862509
Chambers ^a	Unpublished	10.77*	(0.51-225.84)*	0.4	2	139	0	303
Davis ^d	2007	1.03*	(0.45-2.32)*	5.8	3	179	503	49151
Kulin ^a	1998	0.77*	(0.09-7.00)*	0.8	1	75	4	231
Malm ^a	2005	0.66*	(0.09-4.96)*	0.9	1	148	18	1753
Nash ^d	Unpublished	0.41	(0.07-1.70)	1.5	2	141	1913	54038
Diav-Citrin ^a	2008	2.66	(0.8-8.9)	2.7	7	341	8	1351
Oberlander ^d	2008	1.48*	(0.7-3.1)*	6.9	7	986	512	106808
Case-Control Studies								
Louik ^d	2007	1.40	(0.79-2.47)	11.8	25	30	3699	5830
Bakker ^d	2006	1.50	(0.50-4.30)	3.3	18	NR	504	NR
Berard ^b	2007	1.38	(0.49-3.92)	3.6	10	499	14	803
Alwan ^d	2007	1.70	(0.92-3.16)	10.1	32	18	4236	4074
PEM- Paroxetine exposed malformations PENM- Paroxetine exposed non-malformed UM- Unexposed malformation UNM- Unexposed non-malformed								
Comparison Groups Used a Controls from TIS population (exposed to agents deemed not teratogenic)								

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b Treated depressed population c General Population d No SSRI during first trimester as recorded by prescription data or maternal report
NR=Not reported
*OR and 95% CI calculated from reported numbers
Figure 2: First Trimester Paroxetine Use and the Prevalence of Cardiac Malformations: Forest Plot



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Table 6: First Trimester Paroxetine Use and Cardiac Malformations: Main and Sensitivity Analyses of Overall Homogeneity and Funnel Plot Symmetry

			Funnel plot symmetry P-values		Number of results imputed by trim and fill method	Fixed-effect summary POR (95% CI)	
Analysis	Number of results	Homogeneity P-value	Begg	Egger		Without imputed results	With imputed results
Paroxetine and cardiac malformations	GSK Medicine: Paroxetine Study No.: WEUSRTP2280	0.9	0.4	0.5	3	1.46 (1.17-1.82)	1.52 (1.23-1.89)

The analysis of paroxetine and cardiac malformations used the standard continuity correction of 0.5 for each cell.

Table 7: First Trimester Paroxetine Use and Cardiac Malformations: Study Characteristic Analyses (n=14)

Study characteristic	Level	Number of results	Homogeneity P-value ^a	Fixed-effect summary OR (95% CI)	Ratio of odds ratios (95% CI) ^a
Design	Case-control	4	1.0	1.51 (1.05, 2.17)	1.
	Cohort	10	0.6	1.43 (1.08, 1.90)	0.95 (0.60, 1.51)
Publication type	Article	10	1.0	1.49 (1.18, 1.88)	1.
	Abstract	2	0.8	1.38 (0.59, 3.22)	0.92 (0.54, 1.58)
	Unpublished	2	0.1	0.83 (0.20, 3.41)	0.55 (0.13, 2.31)
Data source	Medication-linked population based database	6	0.7	1.44 (1.04, 2.00)	1.
	TIS	4	0.5	1.89 (0.84, 4.23)	1.31 (0.55, 3.13)
	Administrative data base	2	0.5	1.26 (0.75, 2.13)	0.88 (0.47, 1.62)
	Clinic or case-control surveillance	2	0.7	1.53 (1.01, 2.33)	1.06 (0.62, 1.81)
Continent	Europe	5	0.8	1.60 (1.11, 2.31)	1.
	North America	9	0.7	1.38 (1.05, 1.83)	0.86 (0.54, 1.36)
First trimester definition	0-14 weeks post-conception	5	0.7	1.56 (1.10, 2.22)	1.
	3-10 weeks post LMP	3	0.2	1.30 (0.59, 2.85)	0.83 (0.35, 1.96)
	Not specified	2	0.6	1.31 (0.50, 3.46)	0.84 (0.30, 2.35)
	30 days pre-conception to end of first trimester	2	0.7	1.53 (1.01, 2.33)	0.98 (0.57, 1.69)
	First trimester (0-13 weeks) based on EDD	2	0.5	1.26 (0.75, 2.13)	0.81 (0.43, 1.51)
Paroxetine use and comparison definition	Paroxetine w/o other SSRI use compared to no exposure to any SSRI	4	0.3	1.36 (0.88, 2.09)	0.83 (0.49, 1.41)
	Paroxetine w or w/o other SSRI use compared to no exposure to any SSRI	3	0.9	1.02 (0.52, 1.97)	0.62(0.30, 1.29)
	Paroxetine w/o other SSRI use compared to women exposed to other SSRIs	1	Na	Na	Na
	Paroxetine or comparison group not specified	6	0.9	1.64 (1.20, 2.23)	1.
Cardiac malformation definition	Unspecified	5	0.7	1.42 (0.90, 2.24)	0.99 (0.58, 1.69)
	ICD-9 745-747, ICD-10 Q20-Q28	8	0.7	1.43 (1.09, 1.89)	1.
	Contruncal, septal, Right ventricular outflow tract obstruction, Left ventricular outflow tract				

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