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ORIGINAL ARTICLE

Maternal Smoking During Pregnancy and the Risk of Congenital Heart Defects in Offspring: A Systematic Review and Metaanalysis

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Abstract Although a previous metaanalysis indicated that maternal smoking during pregnancy increased the risk of congenital heart defects (CHD) in offspring, the effect of smoking on individual CHD subtypes was not determined. Because CHDs are anatomically, clinically, epidemiologically, and developmentally heterogeneous, the authors conducted a systematic review and metaanalysis of the association between maternal smoking during pregnancy and the risk of CHDs, including CHD subtypes among offspring. Two types of summary relative risk (RR) estimates (any smoking vs no smoking and increasing categories of smoking, i.e., light, medium, and heavy) were calculated for CHDs as a group and for a number of CHD subtypes using both fixed- and random-effects models. Random effects estimates were reported if there was evidence of heterogeneity among the studies. Consistent with the previous metaanalysis, the authors observed a positive association between maternal smoking during pregnancy and the risk of CHDs as a group (RR, 1.11; 95 % confidence interval [CI], 1.02–1.21; number of cases [n] = 18,282). Additionally, women who smoked during pregnancy were more likely to have a child with 12 (71 %) of 17 CHD subtypes analyzed compared with women who did not smoke. The highest risk was for septal defects as a group (RR, 1.44; 95 % CI, 1.16–1.79; n = 2977). The evidence of dose response was observed for septal defects as a group, atrial septal defects, and atrioventricular septal defects. This systematic review and metaanalysis suggests that maternal smoking is modestly associated with an increased risk of CHDs and some CHD subtypes.

Keywords Congenital heart defects · Metaanalysis · Pregnancy · Smoking

Introduction

Congenital heart defects (CHDs) are the most common group of congenital malformations in the United States, with a birth prevalence of ~1 in 100 [5, 6, 8]. Due to congenital malformations, CHDs also are the leading cause of infant mortality, and those children who survive often require lifelong medical treatments. They may experience physical, developmental, and cognitive problems as well as reduced survival rates into adulthood [15, 32].

Despite the prevalence and clinical importance of CHDs, the etiology for ~70 % of cases remains unknown [8, 20]. One maternal exposure, long a suspected risk factor for CHDs, is smoking. This is important because in the United States, ~22 % of women of reproductive age smoke, and an estimated 12 % of women continue to smoke during their pregnancies [42].

A study by Fedrick et al. [14] was one of the first to report the association between maternal smoking and CHDs. However, the evidence since then has been mixed, with some studies showing positive associations and others providing null results [2, 9, 27]. The inconsistency in

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findings across studies likely is due to variability in case ascertainment and exposure assessment. Additionally, many studies had small numbers of cases and failed to control for potential confounders.

Finally, because CHDs include several distinct subtypes (e.g., conotruncal defects, left ventricular outflow track defects), there is a potential for etiologic heterogeneity, which may obscure findings when subtypes are "lumped" into a common phenotype to increase study power [8].

The equivocal evidence in the existing literature calls for a systematic assessment of currently available studies evaluating the association between maternal cigarette smoking during pregnancy and the risk of CHDs in offspring. A previous metaanalysis by Hackshaw et al. [17] estimated the effects of maternal smoking across a spectrum of birth defects including heart defects. However, the study did not evaluate the effects of maternal smoking on CHD subtypes, and dose–response relationships (i.e., increasing levels of smoking) were not assessed. Therefore, this study aimed to calculate summary relative risk (RR) estimates assessing the association between maternal cigarette smoking during pregnancy and CHDs overall as well as CHD subtypes, to examine dose–response relationships (i.e., light, medium, and heavy smoking), and to evaluate evidence of heterogeneity across studies.

Methods

Search Strategy

We searched the US National Library of Medicine Medline database for published articles in English from 1947 to July 2011 using Ovid and PubMed. Regular search terms and the Medical Subject Headings (MeSH) were used. The selected search terms included "tobacco," "smoking," "nicotine," "periconceptional," "maternal," "mother," "pregnant," "gestation," "birth defect," "congenital," "congenital heart defect," "cardiovascular," "heart," "conotruncal," "arteriosus," "atrioventricular," "pulmonary," "ventricular," and "septal." The MeSH terms included: "tobacco," "smoking," "nicotine," "tobacco smoke pollution," "pregnancy complications," "pregnancy," "pregnancy outcome," "mothers," "congenital abnormalities," "heart defect (congenital)," "cardiovascular abnormalities," and "cardiovascular diseases." Some terms not specific to the exposure and subtypes were included to identify studies that had examined several adverse birth outcomes or exposures including CHDs and smoking but may not have mentioned them in their titles or abstracts. Reference lists of articles were reviewed to identify additional articles.

Eligibility Criteria

We selected articles that (1) were original epidemiologic studies (i.e., case–control, cohort, or cross-sectional studies), (2) were published in the English language, (3) examined the association between maternal cigarette smoking anytime during pregnancy and CHDs overall or any one of the CHD subtypes in infants, (4) reported RRs (i.e., risk ratios or odds ratios) and associated 95 % confidence intervals (CIs) or had raw data available, (5) defined CHDs or one of the CHD subtypes as an outcome, and (6) provided exposure information.

Studies that examined only the effects of paternal or environmental tobacco smoke (i.e., secondhand smoke) and studies that assessed the association of interest in certain subgroups (e.g., mothers with CHDs, mothers with diabetes, or infants with Down syndrome) were not included in the review. In the case of multiple publications using the same data, we selected the study that contained the most comprehensive information (e.g., longest study periods or most CHD subtypes analyzed).

Data Extraction

One study author (L.J.L.) first screened studies by title and by abstract and made exclusions based on the eligibility criteria. The studies meeting the inclusion criteria were independently reviewed by two authors (L.J.L., P.J.L) to retrieve information of interest including study characteristics (i.e., authors, year of publication, geographic region, periods of data collection, study design, case classification, control definition, sample size, source of exposure data, smoking status, levels of smoking, exposure period during pregnancy, and adjusted/matched variables) and to record reported effect estimates and associated 95 % CIs as well as raw data if effect estimates were not available. Discrepancies between the authors were resolved by discussion.

When available, RR estimates and 95 % CIs were extracted from each study for CHDs overall and CHD subtypes. We selected the main confounder-adjusted RRs whenever possible. Otherwise, unadjusted effect estimates were extracted from each study. We conducted metaanalyses for specific CHD subtypes (i.e., subanalyses) if at least two studies had available data. In some cases, multiple publications using the same data source were used if those publications reported RRs for different CHD subtypes [1, 36, 38–41, 46]. Specifically, three studies, namely, Adams et al. [1] (conotruncal defects), Botto et al. [7] (any CHDs), and Williams et al. [46] (septal defects) identified cases from the Atlanta birth defects registry in overlapping periods, but they analyzed different subtypes of heart defects. Thus, their effect estimates were entered separately for our CHD subtype analyses.

Furthermore, six published studies used the Finnish birth defects registry for overlapping periods. For those studies, the report by Tikkanen and Heinonen [37] was included in the main analysis (i.e., CHDs overall), and the remaining five studies were included separately for subanalyses because the CHD subtypes assessed were different across those studies [36, 38–41]. For our analysis of atrioventricular septal defects (AVSDs), we extracted AVSD cases without Down syndrome from the Alverson et al. [2] and Malik et al. [27] studies.

Most studies presented risk estimates and raw data for maternal smoking using a dichotomous definition of exposure (i.e., yes vs no) [1, 4, 7, 14, 18, 19, 21–25, 28, 31, 33, 34, 41, 43, 47, 48]. For those studies in which smokers were only separated into more than two categories (i.e., light, medium, and heavy) [2, 9, 13, 16, 27, 29, 30, 36–40, 45, 46], we combined the categories to calculate a summary RR for dichotomous exposure [9, 27, 29, 30, 38–40, 45, 46]. However, we also evaluated additional categories of smoking in our analysis (i.e., light, medium, and heavy) when this information was available to evaluate the dose–response relationship of maternal smoking to CHDs as a group and to CHD subtypes.

Statistical Analysis

Based on the exposure definitions reported, we computed two types of summary effect estimates: any cigarette smoking and increasing categories of cigarette smoking (i.e., light, medium, and heavy). We used nonsmokers as the reference category in all analyses. We calculated summary RR estimates and 95 % CIs using both fixed- and random-effects models for the CHDs overall and for the CHD subtypes.

We first tested for heterogeneity across studies using Cochran's Q-test [10]. If there was an evidence of heterogeneity ($P < 0.1$), we used a random-effects model, which provided a more appropriate summary effect estimate between heterogeneous study-specific estimates, applying the DerSimonian and Laird method [11]. If the Q-test showed no evidence of heterogeneity, we used a fixed-effects analysis, applying inverse variance weighting to calculate summary RR estimates.

All analyses pertaining to summary RR estimates were calculated using the Stata 12.0 (StataCorp, College Station, TX, USA) command "meta." Because this command required values for standard errors (SEs) and none of the studies reported SEs, we calculated SEs using the following formula:

$$[\ln(\text{upper } 95\,\%\text{ CI}) - \ln(\text{lower } 95\,\%\text{ CI})]/3.92.$$

Forest plots were constructed to show study-specific RR estimates and a summary RR estimate, with a different size of box representing the relative weight of an individual study in calculating the summary RR estimate. Additionally, the presence of publication bias was evaluated by Egger's test ($P < 0.05$) and by visual inspection of the symmetry in funnel plots (Stata "metabias" and "metafunnel" commands).

In the main analysis examining the association between maternal cigarette smoking and the risk of CHDs overall, we performed a sensitivity analysis by calculating a summary effect estimate for CHDs overall limited to the studies that examined the association between maternal periconceptional smoking (i.e., 3 months before pregnancy through the first trimester) and CHDs.

Results

The study selection process identified 33 studies published between 1971 and 2011 for the metaanalysis (Fig. 1). The main study characteristics of included studies are shown in Table 1. As shown, 17 studies were conducted in the United States, 14 in Europe, and 2 in other regions (Canada and China). There were 23 case–control studies [1, 2, 4, 7, 16, 19, 22–25, 27, 30, 31, 34, 36–41, 43, 45, 46], 5 cohort studies [9, 21, 33, 47, 48], and 5 cross-sectional studies [13, 14, 18, 28, 29].

The studies derived their cases from various birth defects registries [1, 2, 7, 21, 27, 30, 31, 36–41, 45, 46], and the control subjects were randomly selected from birth certificates or hospital records or matched to cases by birth region or birth month [1, 4, 7, 25, 46]. For some studies ($n = 11$), cases were derived from a sample of live-born infants, whereas for other studies ($n = 12$), cases also were identified from stillbirths, neonatal deaths, and elective termination [7, 9, 14, 16, 19, 36–41, 46]. Although CHDs were diagnosed mainly within the first year after birth, diagnoses of CHDs were performed up to 7 years of age in the Chinese study [25] via echocardiography, cardiac catheterization, surgery, or autopsy. The specific inclusion and exclusion criteria used to identify and classify cases in each study are listed in the Online Resource.

Some studies ($n = 6$) collected information on maternal smoking and other variables using self-administered questionnaires [13, 14, 18, 33, 34, 48], whereas others ($n = 23$) collected maternal exposure information via telephone or in-person interviews [1, 2, 7, 16, 19, 21–25, 27, 29–31, 36–41, 45–47] after delivery (the time between delivery and the interview ranged up to 4 years [30]). In three studies, exposure information was collected from birth certificates [4, 28, 43], whereas one study used records from prenatal visits [9].

A wide range of exposure periods was examined, with 15 studies reporting the mother's smoking status or level of smoking during the first trimester of pregnancy, including 1 to 3 months before conception [1, 2, 7, 16, 19, 22, 25, 27,

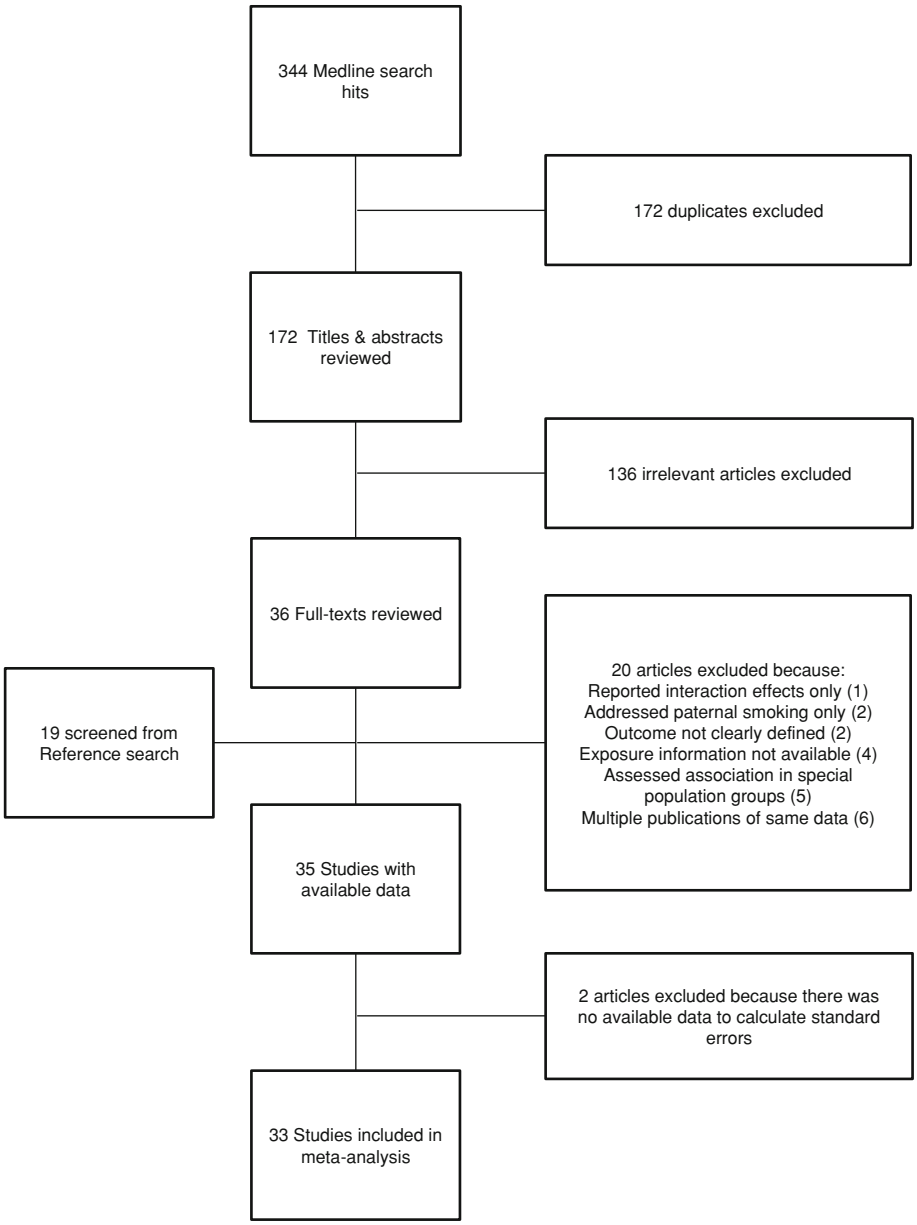

Fig. 1 Search strategy and study selection process used in the metaanalysis of the association between maternal cigarette smoking during pregnancy and the risk of congenital heart defects in offspring, 1945–2011

30, 31, 33, 36–41, 45, 46]. However, 14 studies did not specify the months of exposure during pregnancy.

Only one study examined the effects of maternal smoking during the late pregnancy period (months 4–10) [14]. Whereas 12 studies provided estimates on the association between maternal smoking and CHDs adjusted for a range of covariates [2, 19, 21–24, 27–30, 43, 47], 16 studies reported only unadjusted estimates (Table 1) [9, 13, 14, 16, 18, 31, 33, 34, 36–41, 45, 48].

Overall, 19 studies evaluated the association between maternal smoking during pregnancy and CHDs as a group in a total of 18,282 CHD cases (Table 2). There was evidence of heterogeneity across studies ($P < 0.001$) for CHDs overall. Thus, the random-effect estimate was reported. The summary RR estimate for CHDs overall was 1.11 (95 % CI, 1.02–1.21) among women who smoked during pregnancy compared with women who did not smoke during pregnancy (Table 2; Fig. 2).

We observed positive associations between maternal smoking during pregnancy and 12 (71 %) of 17 CHD subtypes analyzed. These positive associations ranged from 1.02 (fixed effects) for double-outlet right ventricle (95 % CI, 0.72–1.46; *n* cases = 179) to 1.44 (random effects) for septal defects as a group (95 % CI, 1.16–1.79; *n* cases = 2,977). There was no evidence of heterogeneity for most of the CHD subtypes evaluated ($n = 13$) (e.g., conotruncal defects, double-outlet right ventricle, hypoplastic left heart syndrome, and right ventricular outflow tract obstructions).

Table 1 Summary of the studies included in the metaanalysis, by publication year, 1971–2011

Author(s)	Publication year	Study location	Study period	Study design	No. of cases/controls[a]	Exposure assessment			Adjustment variables[b]
						Source	Period	Smoking categorization	
Fedrick et al. [14]	1971	England, Scotland, Wales (UK)	1958	CS	290/15,719	Self-administered questionnaire	P4–P10	Yes/no	No
Yerushalmy [48]	1973	USA	1960–1967	Cohort	115/14,616	Self-administered questionnaire	P	Yes/no	No
Himmelberger et al. [18]	1978	USA	NA	CS	163/10,360	Self-administered questionnaire	P	Yes/no	No
Evans et al. [13]	1979	Cardiff (UK)	1965–1976	CS	223/65,745	Self-administered questionnaire	P	Light (1–9 cigs/day) Medium (10–19) Heavy (21+)	No
Shiono et al. [33]	1986	California (USA)	1974–1977	Cohort	4624/28,8210	Self-administered questionnaire	P1–P3	Yes/no	No
Adams et al. [1]	1989	Atlanta (USA)	1976–1980	CC	83/1,303	Telephone interview	B1–P3	Yes/no	W
Malloy et al. [28]	1989	Missouri (USA)	1980–1983	CS	1,341/27,7844	Birth certificate	P	Yes/no	A, B, C, D, E
Van den Eeden et al. [43]	1990	Washington (USA)	1984–1986	CC	655/4,323	Birth certificate	P	Yes/no	A, E
Tikkanen and Heinonen [37]	1991a	Finland	1982–1984	CC	573/1,055	In-person interview	P1–P3	Light (1–14 cigs/day) Medium (15–29) Heavy (30+)	No
Tikkanen and Heinonen [36]	1991b	Finland	1982–1983	CC	150/756	In-person interview	P1–P3	Light (1–14 cigs/day) Medium (15–29)	No
McDonald et al. [29]	1992	Montreal (Canada)	1982–1984	CS	318/87,389	In-person interview	P	Light (1–9 cigs/day) Medium (10–19) Heavy (20+)	B, D, F, G
Shaw et al. [30]	1992	California (USA)	1981–1983	CC	141/176	Telephone interview	P1–P3	Light (<1/2 pk/day) Medium (1/2–1) Heavy (1+)	A, B, D
Tikkanen and Heinonen [38]	1992a	Finland	1982–1983	CC	50/756	In-person interview	P1–P3	Light (1–14 cigs/day) Medium (15–29)	No
Tikkanen and Heinonen [39]	1992b	Finland	1982–1983	CC	90/756	In-person interview	P1–P3	Light (1–14 cigs/day) Medium (15–29)	No
Tikkanen and Heinonen [40]	1993	Finland	1982–1983	CC	50/756	In-person interview	P1–P3	Light (1–14 cigs/day) Medium (15–29)	No
Tikkanen and Heinonen [41]	1994	Finland	1982–1983	CC	34/756	In-person interview	P1–P3	Yes/no	No
Wasserman et al. [45]	1996	California (USA)	1987–1988	CC	207/481	Telephone interview	B1–P3	Light (1–19 cigs/day) Medium (20+)	No
Kallen [21]	1999	Sweden	1983–1996	Cohort	3,384/1,413,811	In-person interview	P	Yes/no	A, D, E, H
Botto et al. [7]	2001	Atlanta (USA)	1968–1980	CC	905/3,029	Telephone interview	B1–P3	Yes/no	W
Woods and Raju [47]	2001	Cincinnati (USA)	1998–1999	Cohort	260	In-person interview	P	Yes/no	A, B, I
Williams et al. [46]	2004	Atlanta (USA)	1968–1980	CC	122/3,029	Telephone interview	B3–P3	Light (1–14 cigs/day) Medium (15–24) Heavy (25+)	W

Table 1 continued

Author(s)	Publication year	Study location	Study period	Study design	No. of cases/controls[a]	Exposure assessment			Adjustment variables[b]
						Source	Period	Smoking categorization	
Shaw et al. [31]	2005	California (USA)	1987–1988	CC	155/437	Telephone interview	B1–P2	Yes/no	No
Cedergren and Kallen [9]	2006	Sweden	1992–2001	Cohort	6,346/770,335	Antenatal visit records	P	Light (<10 cigs/day) Medium (10+)	No
Hobbs et al. [19]	2006	Arkansas (USA)	1998–2004	CC	275/118	Telephone interview	B1–P1	Yes/no	A, J, K
Batra et al. [4]	2007	Washington (USA)	1987–2003	CC	2,898/11,186	Birth certificate	P	Yes/no	W
Grewal et al. [16]	2008	California (USA)	1999–2003	CC	640/691	Telephone interview	P1	Light (1–5 cigs/day) Medium (5+)	No
Malik et al. [27]	2008	USA	1997–2002	CC	3,067/3,947	Telephone interview	B1–P3	Light (1–14 cigs/day) Medium (15–24) Heavy (25+)	A, B, F, G, K, L, M, N, O
Kuciene and Dulskiene [23]	2009	Kaunas (Lithuania)	1999–2005	CC	171/642	In-person/telephone interview	P	Yes/no	D, P, U
Liu et al. [25]	2009	Shandon Province (China)	2004–2005	CC	164/328	In-person interview	B1–P3	Yes/no	W
Smedts et al. [34]	2009	Netherlands	NA	CC	276/324	Self-administered questionnaire	P	Yes/no	No
Kuciene and Dulskiene [24]	2010	Kaunas (Lithuania)	1995–2005	CC	251/1,122	In-person/telephone interview	P	Yes/no	D
Alverson et al. [2]	2011	Baltimore, Washington DC, Virginia (USA)	1981–1989	CC	2,525/3,435	In-person interview	P1–P3	Light (1–10 cigs/day) Medium (11–20) Heavy (21+)	A, L, M, N, Q
Karatza et al. [22]	2011	Greece	2006–2009	CC	157/208	In-person interview	B1–P3	Yes/no	A, E, I, L, N, R, S, T, U

CS cross-sectional study, *CC* case–control study, *NA* not available, *B#* month before conception, *P#* month during pregnancy, *P* unspecified time during pregnancy

[a] Reported number of cases and control subjects with available exposure information

[b] Adjustment variables: *A* maternal age, *B* maternal race/ethnicity, *C* marital status, *D* maternal education, *E* parity, *F* alcohol consumption, *G* coffee consumption, *H* infant's year/month of birth, *I* maternal diabetes (pregestational or gestational), *J* interval between end of pregnancy and blood collection, homocysteine levels, *K* folic acid intake/dietary folate, *L* infant gender, *M* maternal body mass index, *N* family history of congenital heart defects, *O* maternal residence, *P* maternal occupation, *Q* infant race/ethnicity, *R* therapeutic drug use, *S* influenza-like illness, *T* paternal smoking, *U* maternal smoking before pregnancy, *V* prematurity, *W* cases and controls matched on birth hospital/geographic region, birth month/age, race, or sex

Table 2 Summary of relative risk (RR) for association between maternal smoking during pregnancy and congenital heart defects (CHDs)

Cardiac defects	No. of studies	No. of cases	Summary RR (95 % CI)	Heterogeneity *P* value	Egger's test *P* value[a]
All CHDs	19	18,282	1.11 (1.02–1.21)	<0.001	0.13
Conotruncal defects	8	2,561	1.09 (0.98–1.20)	0.31	0.12
Tetralogy of Fallot	5	885	0.93 (0.78–1.12)	0.68	0.14
Dextrotransposed great arteries	5	985	1.09 (0.84–1.42)	0.06	0.52
Double-outlet right ventricle	2	179	1.02 (0.72–1.46)	0.39	–
Left ventricular outflow tract obstructions	2	800	0.95 (0.80–1.13)	1.00	–
Hypoplastic left heart syndrome	4	433	1.03 (0.82–1.30)	0.89	0.23
Coarctation of the aorta	5	658	0.91 (0.75–1.10)	0.66	0.76
Aortic valve stenosis	2	160	0.89 (0.60–1.32)	0.35	–
Right ventricular outflow tract obstructions	2	817	1.20 (1.03–1.40)	0.23	–
Pulmonary valve stenosis	2	591	1.34 (1.12–1.60)	0.94	–
Septal defects	4	2,977	1.44 (1.16–1.79)	0.001	0.60
Ventricular septal defects	8	5,051	1.06 (0.91–1.23)	0.004	0.15
Atrial septal defects	6	806	1.34 (1.02–1.75)	0.04	0.24
Atrioventricular septal defects[b]	3	250	1.35 (1.01–1.81)	0.17	0.83
Anomalous pulmonary venous return	2	169	1.19 (0.83–1.71)	0.70	–
Total anomalous pulmonary venous return	2	128	0.98 (0.63–1.53)	0.22	–
Patent ductus arteriosus	4	684	1.21 (1.01–1.44)	0.77	0.11

CI confidence interval

[a] At least three studies are required for performance of Egger's test

[b] Atrioventricular septal defects without Down syndrome

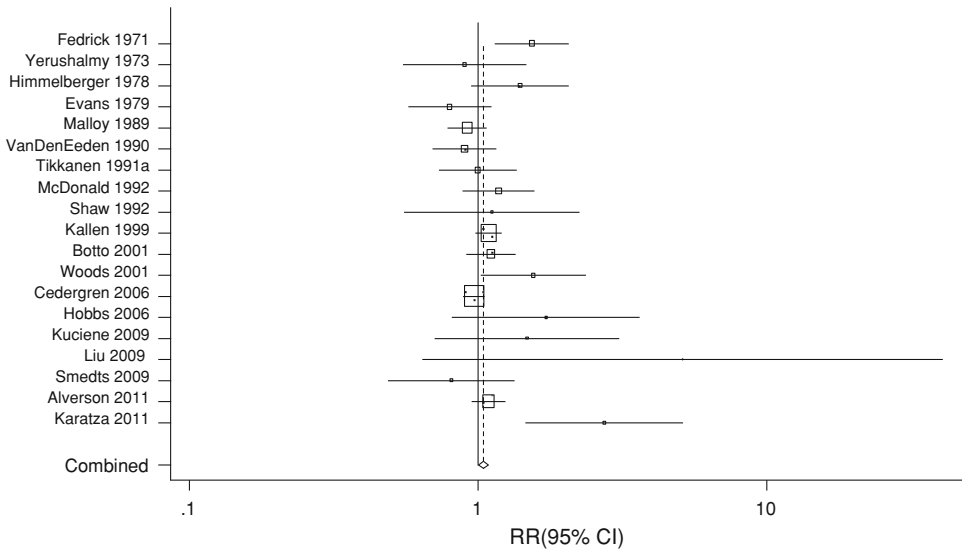

Fig. 2 Metaanalysis of studies on maternal cigarette smoking during pregnancy comparing mothers who reported smoking with mothers who did not reported smoking and all congenital heart defects (CHDs). Study-specific and summary relative risk and 95 % confidence intervals for 1971–2011 are shown

Based on the results of the Egger's test (Table 2) and funnel plot (data not shown) for CHDs overall, there was no evidence of publication bias. Additionally, Egger's test showed no evidence of publication bias for the CHD subtypes (Table 2). Funnel plots for the CHD subtypes also indicated that publication bias was not present (data not shown).

Summary RR estimates for CHDs overall and CHD subtypes were calculated by three different levels of smoking (light, medium, and heavy) (Table 3). The summary RR estimates for CHDs overall were 0.99 (95 % CI, 0.92–1.06; $n = 10{,}126$) for light smokers, 1.04 (95 % CI, 0.95–1.13; $n = 10{,}126$) for medium smokers, and 1.04 (95 % CI, 0.86–1.26; $n = 3207$) for heavy smokers compared with women who did not smoke during pregnancy.

Strong associations (RR, $\geq$1.99) were found for right ventricular outflow tract obstructions, pulmonary valve

Table 3 Summary of relative risk (RR) for association between maternal smoking during pregnancy and congenital heart defects (CHDs) by categories of smoking

Cardiac defects	No. of cases	Categorical exposure				
		Light Summary RR (95 % CI)	No. of cases	Medium Summary RR (95 % CI)	No. of Cases	Heavy Summary RR (95 % CI)
All CHDs	10,126	0.99 (0.92–1.06)	10,126	1.04 (0.95–1.13)	3,207	1.04 (0.86–1.26)
Conotruncal defects	1,758	1.02 (0.87–1.21)	1,758	0.98 (0.77–1.25)	1,141	0.93 (0.57–1.53)
Tetralogy of Fallot	742	1.07 (0.84–1.37)	742	0.84 (0.57–1.22)	480	0.65 (0.23–1.83)
Dextrotransposed great arteries	678	0.98 (0.76–1.28)	678	0.88 (0.60–1.28)	460	1.14 (0.61–2.16)
Left ventricular outflow tract obstructions	800	1.15 (0.93–1.44)	800	0.77 (0.54–1.09)	800	0.97 (0.55–1.72)
Hypoplastic left heart syndrome	306	1.29 (0.94–1.78)	306	0.81 (0.47–1.38)	306	1.17 (0.50–2.74)
Coarctation of the aorta	359	1.04 (0.76–1.44)	359	0.76 (0.44–1.31)	309	1.22 (0.48–3.06)
Aortic valve stenosis	160	1.00 (0.61–1.64)	160	0.71 (0.34–1.46)	160	0.49 (0.12–2.08)
Right ventricular outflow tract obstructions	817	1.23 (0.99–1.52)	817	1.09 (0.80–1.49)	817	1.99 (1.26–3.12)
Pulmonary valve stenosis	591	1.36 (1.07–1.73)	591	1.03 (0.71–1.49)	591	2.02 (1.22–3.37)
Septal defects	2,073	1.29 (1.11–1.49)	2,073	1.31 (1.08–1.60)	2,073	1.46 (0.77–2.77)
Ventricular septal defects	1,333	1.27 (1.08–1.49)	1,333	1.22 (0.97–1.52)	1,183	1.26 (0.84–1.91)
Atrial septal defects	574	1.42 (0.88–2.29)	574	1.63 (1.15–2.32)	524	1.91 (1.04–3.49)
Atrioventricular septal defects[a]	144	1.19 (0.73–1.94)	144	1.89 (1.09–3.28)	144	2.00 (0.78–5.15)
Total anomalous pulmonary venous return	128	1.00 (0.58–1.72)	128	0.79 (0.13–4.91)	144	0.91 (0.21–3.87)
Patent ductus arteriosus	504	1.26 (0.96–1.66)	128	1.35 (0.97–1.89)	46	–

CI confidence interval

[a] Atrioventricular septal defects without Down syndrome

stenosis, and AVSD in infants prenatally exposed to heavy smoking compared with no smoking. The increase in summary RR estimates in response to increasing levels of maternal smoking were observed for only three CHD subtypes (septal defects overall, atrial septal defects [ASDs], and AVSDs). The dose response did not increase monotonically for other subtypes of CHDs.

Discussion

Overall, there was evidence that maternal smoking during pregnancy modestly increased the risk of CHDs in offspring. Although the studies included in our analysis varied in terms of case definition, control selection, and exposure assessment, the associations were largely consistent in the subanalyses and sensitivity analyses. The effect of maternal smoking was observed for CHDs overall and for several CHD subtypes. The strongest association was seen for septal defects overall. Specifically, women who smoked during pregnancy were 44 % more likely to have a child with a septal defect than women who did not smoke during pregnancy.

There was no evidence of a dose response between maternal smoking and CHDs overall in offspring. This also was the case for most of the CHD subtypes (12 of 15 subtypes, 80 %). This may have been attributable to the small sample sizes in the high-exposure groups or to differences in how increasing smoking status was defined across studies. We extracted exposure categories as they were reported in each study, and the studies assigned exposure level using cutoffs based on the number or packs of cigarettes smoked per day. The only evidence of a dose–response effect was for septal defects overall, ASDs, and AVSDs.

The mechanisms by which smoking may result in CHDs still remain unknown. Findings have shown that maternal smoking has adverse effects on the developing fetus, including hypoxia caused by carbon monoxide, nicotine, and reduction in the supply of essential nutrients to the embryonic tissues [2, 44]. Additionally, polycyclic aromatic hydrocarbons, common components of cigarette smoke, are suspected teratogens in laboratory animals and humans [3, 26].

In the previous metaanalysis of smoking and birth defects, including heart defects [17], the effect estimate for CHDs overall (RR, 1.09; 95 % CI, 1.00–2.18; 19 studies) was similar to ours, but our study selection criteria differed. For example, some studies [1, 4, 16, 27, 33] that they included in their analysis of CHDs overall were included in our subanalyses. Moreover, they did not evaluate CHD subtypes. Additionally, our metaanalysis included findings

from the Baltimore-Washington Infant Study (BWIS), one of the a largest population-based case–control studies of CHDs, published in 2011 [2].

Our study must be considered in the light of certain limitations. For instance, our analysis was limited to studies published in English. However, we found no evidence of publication bias. Another limitation of our analysis was a lack of studies that examined effects of environmental tobacco smoke, which may have been an important component in the overall maternal smoking exposure during pregnancy. Furthermore, we derived most of our data from case–control studies, which may be more prone to information bias than cohort studies. However, the estimated effect of smoking was similar across different study designs (data not shown).

Our study had several strengths, including the large sample ($n = 18{,}282$) used to estimate the effect of maternal smoking on CHDs as a group. Additionally, due to the suspected heterogeneous etiologies, CHD subtypes were analyzed separately, and we were able to estimate a range of risks for CHD subtypes (RR, 1.02–1.44). We also evaluated increasing levels of smoking during pregnancy, and the evidence of dose response was observed for some CHD subtypes (i.e., septal defects overall, ASDs, and AVSDs).

Furthermore, we conducted a sensitivity analysis, restricting our analysis to studies with available information on exposure during the periconceptional period. Because heart anomalies develop during weeks 2–7 of gestation [35], we suspected that inclusion of studies that assessed exposure beyond the "critical period" may have biased our result toward the null. However, our sensitivity analysis showed no significant difference in the summary effect estimates (data not shown).

In conclusion, we found that mothers of offspring with CHDs were 11 % more likely to smoke during pregnancy than mothers of unaffected children. Although the effects were modest, smoking is a relatively common exposure among women of reproductive age and could have important public health consequences. Young women continue to smoke although the adverse effects of smoking on reproductive health are known, and more than a half of women smokers continue to smoke even after they learn that they are pregnant [12].

The demonstration of an association between smoking during pregnancy and CHDs can be used in the development of population-based prevention strategies to reduce the burden of CHDs and other birth defects. A decrease in maternal smoking during pregnancy would result in improved reproductive outcomes and may contribute to a reduction in infant mortality and morbidity.

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References

1. Adams MM, Mulinare J, Dooley K (1989) Risk factors for conotruncal cardiac defects in Atlanta. J Am Coll Cardiol 14: 432–442
2. Alverson CJ, Strickland MJ, Gilboa SM, Correa A (2011) Maternal smoking and congenital heart defects in the Baltimore-Washington Infant Study. Pediatrics 127:e647–e653
3. Barbieri O, Ognio E, Rossi O, Astigiano S, Rossi L (1986) Embryotoxicity of benzo(a)pyrene and some of its synthetic derivatives in Swiss mice. Cancer Res 46:94–98
4. Batra M, Heike CL, Phillips RC, Weiss NS (2007) Geographic and occupational risk factors for ventricular septal defects: Washington State, 1987–2003. Arch Pediatr Adolesc Med 161:89–95
5. Boneva RS, Botto LD, Moore CA, Yang Q, Correa A, Erickson JD (2001) Mortality associated with congenital heart defects in the United States: trends and racial disparities, 1979–1997. Circulation 103:2376–2381
6. Botto LD, Correa A, Erickson JD (2001) Racial and temporal variations in the prevalence of heart defects. Pediatrics 107:e32
7. Botto LD, Lynberg MC, Erickson JD (2001) Congenital heart defects, maternal febrile illness, and multivitamin use: a population-based study. Epidemiology 12:485–490
8. Botto LD, Lin AE, Riehle-Colarusso T, Malik S, Correa A (2007) Seeking causes: classifying and evaluating congenital heart defects in etiologic studies. Birth Defects Res A Clin Mol Teratol 79:714–727
9. Cedergren MI, Kallen BA (2006) Obstetric outcome of 6,346 pregnancies with infants affected by congenital heart defects. Eur J Obstet Gynecol Reprod Biol 125:211–216
10. Cochran WG (1954) The combination of estimates from different experiments. Biometrics 10:101–129
11. DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. Control Clin Trials 7:177–188
12. Ebrahim SH, Floyd RL, Merritt RK, Decoufle P, Holtzman D (2000) Trends in pregnancy-related smoking rates in the United States, 1987–1996. JAMA 283:361–366
13. Evans DR, Newcombe RG, Campbell H (1979) Maternal smoking habits and congenital malformations: a population study. BMJ 2:171–173
14. Fedrick J, Alberman ED, Goldstein H (1971) Possible teratogenic effect of cigarette smoking. Nature 231:529–530
15. Gilboa SM, Salemi JL, Nembhard WN, Fixler DE, Correa A (2010) Mortality resulting from congenital heart disease among children and adults in the United States, 1999 to 2006. Circulation 122:2254–2263
16. Grewal J, Carmichael SL, Ma C, Lammer EJ, Shaw GM (2008) Maternal periconceptional smoking and alcohol consumption and risk for select congenital anomalies. Birth Defects Res A Clin Mol Teratol 82:519–526
17. Hackshaw A, Rodeck C, Boniface S (2011) Maternal smoking in pregnancy and birth defects: a systematic review based on 173,687 malformed cases and 11.7 million controls. Hum Reprod Update 17:589–604
18. Himmelberger DU, Brown BW Jr, Cohen EN (1978) Cigarette smoking during pregnancy and the occurrence of spontaneous abortion and congenital abnormality. Am J Epidemiol 108: 470–479

19. Hobbs CA, James SJ, Jernigan S, Melnyk S, Lu Y, Malik S et al (2006) Congenital heart defects, maternal homocysteine, smoking, and the 677 C>T polymorphism in the methylenetetrahydrofolate reductase gene: evaluating gene–environment interactions. Am J Obstet Gynecol 194:218–224
20. Jenkins KJ, Correa A, Feinstein JA, Botto L, Britt AE, Daniels SR et al (2007) Noninherited risk factors and congenital cardiovascular defects: current knowledge: a scientific statement from the American Heart Association Council on Cardiovascular Disease in the Young: endorsed by the American Academy of Pediatrics. Circulation 115:2995–3014
21. Kallen K (1999) Maternal smoking and congenital heart defects. Eur J Epidemiol 15:731–737
22. Karatza AA, Giannakopoulos I, Dassios TG, Belavgenis G, Mantagos SP, Varvarigou AA (2011) Periconceptional tobacco smoking and isolated congenital heart defects in the neonatal period. Int J Cardiol 148:295–299
23. Kuciene R, Dulskiene V (2009) Maternal socioeconomic and lifestyle factors during pregnancy and the risk of congenital heart defects. Medicina Kaunas 45:904–909
24. Kuciene R, Dulskiene V (2010) Parental cigarette smoking and the risk of congenital heart septal defects. Medicina Kaunas 46: 635–641
25. Liu S, Liu J, Tang J, Ji J, Chen J, Liu C (2009) Environmental risk factors for congenital heart disease in the Shandong Peninsula, China: a hospital-based case–control study. J Epidemiol 19: 122–130
26. Lupo PJ, Langlois PH, Reefhuis J, Lawson CC, Symanski E, Desrosiers TA et al (2012) Maternal occupational exposure to polycyclic aromatic hydrocarbons and gastroschisis among offspring in the National Birth Defects Prevention Study. Environ Health Perspect 120:910–915
27. Malik S, Cleves MA, Honein MA, Romitti PA, Botto LD, Yang S et al (2008) Maternal smoking and congenital heart defects. Pediatrics 121:e810–e816
28. Malloy MH, Kleinman JC, Bakewell JM, Schramm WF, Land GH (1989) Maternal smoking during pregnancy: no association with congenital malformations in Missouri 1980–1983. Am J Public Health 79:1243–1246
29. McDonald AD, Armstrong BG, Sloan M (1992) Cigarette, alcohol, and coffee consumption and congenital defects. Am J Public Health 82:91–93
30. Shaw GM, Malcoe LH, Swan SH, Cummins SK, Schulman J (1992) Congenital cardiac anomalies relative to selected maternal exposures and conditions during early pregnancy. Eur J Epidemiol 8:757–760
31. Shaw GM, Iovannisci DM, Yang W, Finnell RH, Carmichael SL, Cheng S et al (2005) Risks of human conotruncal heart defects associated with 32 single nucleotide polymorphisms of selected cardiovascular disease-related genes. Am J Med Genet A 138A: 21–26
32. Shillingford AJ, Glanzman MM, Ittenbach RF, Clancy RR, Gaynor JW, Wernovsky G (2008) Inattention, hyperactivity, and school performance in a population of school-age children with complex congenital heart disease. Pediatrics 121:e759–e767
33. Shiono PH, Klebanoff MA, Berendes HW (1986) Congenital malformations and maternal smoking during pregnancy. Teratology 34:65–71
34. Smedts HP, de Vries JH, Rakhshandehroo M, Wildhagen MF, Verkleij-Hagoort AC, Steegers EA et al (2009) High maternal vitamin E intake by diet or supplements is associated with congenital heart defects in the offspring. BJOG 116:416–423
35. Srivastava D (2001) Genetic assembly of the heart: implications for congenital heart disease. Annu Rev Physiol 63:451
36. Tikkanen J, Heinonen OP (1991) Risk factors for ventricular septal defect in Finland. Public Health 105:99–112
37. Tikkanen J, Heinonen OP (1991) Maternal exposure to chemical and physical factors during pregnancy and cardiovascular malformations in the offspring. Teratology 43:591–600
38. Tikkanen J, Heinonen OP (1992) Risk factors for atrial septal defect. Eur J Epidemiol 8:509–515
39. Tikkanen J, Heinonen OP (1992) Risk factors for conal malformations of the heart. Eur J Epidemiol 8:48–57
40. Tikkanen J, Heinonen OP (1993) Risk factors for coarctation of the aorta. Teratology 47:565–572
41. Tikkanen J, Heinonen OP (1994) Risk factors for hypoplastic left heart syndrome. Teratology 50:112–117
42. Tong VT, Jones JR, Dietz PM, D'Angelo D, Bombard JM (2009) Trends in smoking before, during, and after pregnancy: pregnancy risk assessment monitoring system (PRAMS), United States, 31 Sites, 2000–2005. MMWR Surveill Summ 58:1–29
43. Van den Eeden SK, Karagas MR, Daling JR, Vaughan TL (1990) A case–control study of maternal smoking and congenital malformations. Paediatr Perinat Epidemiol 4:147–155
44. van Rooij IA, Wegerif MJ, Roelofs HM, Peters WH, Kuijpers-Jagtman AM, Zielhuis GA et al (2001) Smoking, genetic polymorphisms in biotransformation enzymes, and nonsyndromic oral clefting: a gene–environment interaction. Epidemiology 12:502–507
45. Wasserman CR, Shaw GM, O'Malley CD, Tolarova MM, Lammer EJ (1996) Parental cigarette smoking and risk for congenital anomalies of the heart, neural tube, or limb. Teratology 53: 261–267
46. Williams LJ, Correa A, Rasmussen S (2004) Maternal lifestyle factors and risk for ventricular septal defects. Birth Defects Res A Clin Mol Teratol 70:59–64
47. Woods SE, Raju U (2001) Maternal smoking and the risk of congenital birth defects: a cohort study. J Am Board Fam Pract 14:330–334
48. Yerushalmy J (1973) Congenital heart disease and maternal smoking habits. Nature 242:262–263