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Maternal Smoking and Congenital Heart Defects in the Baltimore-Washington Infant Study

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KEY WORDS
maternal smoking, birth defects, heart defects, case-control study, epidemiology, odds ratio

ABBREVIATIONS
CHD—congenital heart defect
TGA—transposition of the great arteries
NBDPS—National Birth Defects Prevention Study
RVOTO—right ventricular outflow tract obstruction
AVSD—atrioventricular septal defect
BWIS—Baltimore-Washington Infant Study
OR—odds ratio
CI—confidence interval
l-TGA—levo-transposition of the great arteries

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WHAT'S KNOWN ON THIS SUBJECT: Maternal smoking during pregnancy has been implicated as a possible risk factor for birth defects, but the evidence is mixed, and when identified as a risk factor, the magnitude of the estimates has been typically modest.

WHAT THIS STUDY ADDS: Results of this study, based on a population-based design with high-quality case ascertainment and defect classification, add to the existing body of evidence that implicates first-trimester maternal cigarette smoking as a modest risk factor for select congenital heart defect phenotypes.

abstract

OBJECTIVE: We investigated associations between maternal cigarette smoking during the first trimester and the risk of congenital heart defects (CHDs) among the infants.

METHODS: The Baltimore-Washington Infant Study was the first population-based case-control study of CHDs conducted in the United States. Case and control infants were enrolled during the period 1981–1989. We excluded mothers with overt pregestational diabetes and case mothers whose infants had noncardiac anomalies (with the exception of atrioventricular septal defects with Down syndrome) from the analysis, which resulted in 2525 case and 3435 control infants. Self-reported first-trimester maternal cigarette consumption was ascertained via an in-person interview after delivery. Associations for 26 different groups of CHDs with maternal cigarette consumption were estimated by using logistic regression models. Odds ratios (ORs) corresponded to a 20-cigarette-per-day increase in consumption.

RESULTS: We observed statistically significant positive associations between self-reported first-trimester maternal cigarette consumption and the risk of secundum-type atrial septal defects (OR: 1.36 [95% confidence interval (CI): 1.04–1.78]), right ventricular outflow tract defects (OR: 1.32 [95% CI: 1.06–1.65]), pulmonary valve stenosis (OR: 1.35 [95% CI: 1.05–1.74]), truncus arteriosus (OR: 1.90 [95% CI: 1.04–3.45]), and levo-transposition of the great arteries (OR: 1.79 [95% CI: 1.04–3.10]). A suggestive association was observed for atrioventricular septal defects among infants without Down syndrome (OR: 1.50 [95% CI: 0.99–2.29]).

CONCLUSIONS: These findings add to the existing body of evidence that implicates first-trimester maternal cigarette smoking as a modest risk factor for select CHD phenotypes. *Pediatrics* 2011;127:e647–e653

Congenital heart defects (CHDs) are the most common type of birth defect among newborns (80 cases per 10 000 live births)[1–4] and are a leading cause of mortality from birth defects.[5–8] Although there has been substantial progress in recent years in understanding genetic and chromosomal risk factors, there remain relatively few recognized noninherited, modifiable risk factors for CHDs. Consistent associations have been reported between CHDs and relatively uncommon maternal conditions during pregnancy, such as rubella infection and pregestational diabetes mellitus; associations with more prevalent modifiable risk factors, such as maternal cigarette smoking, also have been reported.[9–14]

With respect to maternal smoking, in a retrospective analysis of data from the Swedish Child Cardiology Registry and the Swedish Medical Birth Registry, Källén[11] found evidence for associations between any first-trimester maternal smoking and risk of conotruncal defects, transposition of the great arteries (TGA), atrial septal defects, and patent ductus arteriosus (among term infants). More recently, an analysis of data from the National Birth Defects Prevention Study (NBDPS), a multistate population-based case-control study, revealed that self-reported maternal periconceptional smoking was associated with right ventricular outflow tract obstruction defects (RVOTOs) (particularly pulmonary valve stenosis), membranous ventricular septal defects, secundum-type atrial septal defects, and atrioventricular septal defects (AVSDs) (without Down syndrome).[14] We further examined associations between self-reported maternal smoking and specific CHD phenotypes by using data from the Baltimore-Washington Infant Study (BWIS), a population-based case-control study of CHDs conducted in Maryland, Washington, DC, and adjacent counties of northern Virginia during the period 1981–1989.[1,15]

METHODS

The BWIS, the first population-based etiologic study of CHDs in the United States, captured data from case and control infants within a population of ~890 000 live births. Case infants were live-born infants with a CHD, actively ascertained from 6 pediatric centers and 53 hospitals that serve the area. CHDs were diagnosed and confirmed within 1 year of birth via echocardiography, cardiac catheterization, surgery, or autopsy. Preterm infants (infants born at <38 weeks' gestation) with patent ductus arteriosus were excluded. Each case infant was given a primary cardiac diagnosis based on the malformation component considered to represent the earliest embryologic disturbance. Population-based control infants were selected randomly from the live-birth logs of regional hospitals.[1,15]

Maternal smoking was assessed via an in-person, postdelivery interview. Respondents reported smoking behavior during 5 time periods: 4 to 6 months before conception; 1 to 3 months before conception; and the first, second, and third trimesters of pregnancy. Response levels per time period were grouped as 0, 1 to 10, 11 to 20, 21 to 39, or ≥40 cigarettes per day. Our analyses focused on reported smoking during the first trimester only.

We restricted our analyses to singleton infants with a CHD who did not have any other organ-system defects, including chromosomal or syndrome-related birth defects, except for infants with an AVSD with Down syndrome. We analyzed AVSDs separately for infants with and without Down syndrome. We also excluded case and control infants whose mothers reported pregestational diabetes mellitus.

To estimate the association between first-trimester smoking and CHDs, we used multiple logistic regression, adjusting for the following covariates: family history of CHDs (for a parent or a full or half-sibling), infant gender, infant race (black, white, or other), maternal age, and prepregnancy BMI. We used both linear and quadratic terms for maternal age and BMI in the models. We modeled the main effect of first-trimester maternal smoking 2 ways: (1) using an ordinal variable with levels of smoking coded as 0 for 0 cigarettes per day, 0.5 for 1 to 10 cigarettes per day, 1 for 11 to 20 cigarettes per day, 2 for 21 to 39 cigarettes per day, and 3 for ≥40 cigarettes per day; and (2) using indicator variables for 3 levels of smoking (1–10, 11–20, and ≥21 vs 0 cigarettes per day). All analyses were performed by using SAS 9.1 (SAS Institute, Inc, Cary, NC).

RESULTS

Beginning with 4390 case and 3572 control infants, we restricted our case group to singleton live births with a CHD but without any other birth defects, except for the inclusion of case infants with AVSD and Down syndrome. We restricted analyses to case and control infants with maternal interviews and those whose mothers did not report overt pregestational diabetes mellitus. The final sample size comprised 2525 case and 3435 control infants.

Characteristics for case infants with a CHD and control infants are presented in Table 1. A family history of CHDs was strongly associated with case status, and infants with a CHD tended to be born at earlier gestational ages and have lower birth weights. Infants with a CHD were less likely to be white and more likely to be delivered by a mother with gestational diabetes.

TABLE 1 Characteristics of Case Infants With a CHD and Control Infants: BWIS, 1981–1989[a]

Characteristic	Case Infants, *n* (%)	Control Infants, *n* (%)	*P*
Total[a]	2525	3435	—
Gender			
Female	1260 (49.9)	1694 (49.3)	—
Male	1265 (50.1)	1741 (50.7)	.655
Gestational age, wk			
<37	250 (9.9)	189 (5.5)	—
37–40	1757 (69.7)	2390 (69.6)	—
≥41	514 (20.4)	853 (24.9)	<.001
Birth weight, g			
≥2500	2182 (86.6)	3209 (93.5)	—
<2500	339 (13.4)	224 (6.5)	<.001
Parity			
Primiparous	1246 (49.3)	1668 (48.6)	—
Multiparous	1279 (50.7)	1767 (51.4)	.548
Infant race			
White	1624 (64.3)	2279 (66.3)	—
Black	806 (31.9)	1063 (30.9)	—
Other	95 (3.8)	93 (2.7)	.039
Maternal education, y			
<12	461 (18.3)	637 (18.6)	—
12	949 (37.6)	1221 (35.6)	—
≥13	1112 (44.1)	1575 (45.9)	.248
Prepregnancy BMI			
<18.5	225 (8.9)	350 (10.2)	—
18.5 to <25	1775 (70.4)	2344 (68.4)	—
25 to <30	346 (13.7)	486 (14.2)	—
≥30	174 (6.9)	248 (7.2)	.286
Family history of CHD			
No	2427 (96.1)	3395 (98.8)	—
Yes	98 (3.9)	40 (1.2)	<.001
Gestational diabetes mellitus			
No	2410 (95.4)	3321 (96.7)	—
Yes	115 (4.6)	114 (3.3)	.014

[a] Case and control infants were restricted to maternally interviewed, singleton live births in the absence of overt pregestational diabetes. Case infants were further restricted to those with no extracardiac defects, with the exception of cases with AVSD and Down syndrome.

Patterns of smoking before conception and during pregnancy for case and control mothers are presented in Table 2. Approximately 64% of interviewed mothers reported no smoking before pregnancy, and this proportion increased to >70% during pregnancy. Among the mothers who did smoke, the vast majority of them reported smoking ≤20 cigarettes per day.

When we modeled first-trimester smoking as an ordinal variable, we observed statistically significant elevated associations with truncus arteriosus (odds ratio [OR]: 1.90 [95% confidence interval (CI): 1.04–3.45]), levo-transposition of the great arteries (l-TGA) (congenitally corrected TGA) (OR: 1.79 [95% CI: 1.04–3.10]), RVOTO defects (OR: 1.32 [95% CI: 1.06–1.65]), pulmonary valve stenosis (a subgroup of RVOTO defects) (OR: 1.35 [95% CI: 1.05–1.74]), and secundum-type atrial septal defect (OR: 1.36 [95% CI: 1.04–1.78]) (Table 3). Many of these associations were supported by the indicator variables model as well, although because of the small number of exposed case infants at the highest exposure levels, many estimates from this model had wide 95% CIs. For example, a secundum-type atrial septal defect displayed a positive dose-response relationship with increasing cigarette consumption, although all 3 of the 95% CIs from the indicator variables model included the null value. Conversely, the association with cigarette consumption and l-TGA seemed to be driven predominantly by the association at the highest exposure level. This pattern was similar for laterality and looping defects (of which l-TGA is a subtype). We also observed a suggestive dose-response pattern for AVSDs without Down syndrome, although the CI from the ordinal model contained the null value (OR: 1.50 [95% CI: 0.99–2.29]).

DISCUSSION

The BWIS had several strengths, including the use of an extensive regional grid of hospitals and clinics to ensure that all cases of CHDs among live-born infants were identified.[15]

TABLE 2 Reported Maternal Smoking Patterns Among Case and Control Mothers According to Periconceptional Period: BWIS, 1981–1989[a]

Smoking level, Cigarettes per d	1–3 mo Before Pregnancy, *n* (%)		First Trimester, *n* (%)		Second Trimester, *n* (%)		Third Trimester, *n* (%)	
	Cases	Controls	Cases	Controls	Cases	Controls	Cases	Controls
0	1610 (63.8)	2217 (64.5)	1773 (70.2)	2475 (72.1)	1908 (75.6)	2627 (76.5)	1914 (75.8)	2645 (77.0)
1–10	404 (16.0)	556 (16.2)	422 (16.7)	539 (15.7)	357 (14.1)	480 (14.0)	363 (14.4)	468 (13.6)
11–20	368 (14.6)	505 (14.7)	250 (9.9)	314 (9.1)	213 (8.4)	249 (7.2)	200 (7.9)	237 (6.9)
21–39	101 (4.0)	125 (3.6)	55 (2.2)	83 (2.4)	33 (1.3)	58 (1.7)	33 (1.3)	66 (1.9)
≥40	42 (1.7)	32 (0.9)	25 (1.0)	24 (0.7)	14 (0.6)	21 (0.6)	15 (0.6)	19 (0.6)

[a] Case and control infants were restricted to maternally interviewed, singleton live births in the absence of overt pregestational diabetes. Case infants were further restricted to those with no extracardiac defects, with the exception of cases with AVSD and Down syndrome.

TABLE 3 Adjusted ORs and 95% CIs for Associations Between Selected CHDs and Reported Maternal Smoking: BWIS, 1981–1989

CHD	N_{total}	Adjusted $OR_{ordinal}$ (95% CI)	$n_{1–10}$	Adjusted $OR_{1–10\ cig/d}$ (95% CI)	$n_{11–20}$	Adjusted $OR_{11–20\ cig/d}$ (95% CI)	$n_{\geq 21}$	Adjusted $OR_{\geq 21\ cig/d}$ (95% CI)
Controls	3435		539		314		107	
Any CHD	2525	1.09 (0.98–1.21)	422	1.11 (0.96–1.28)	250	1.13 (0.95–1.36)	80	1.07 (0.80–1.45)
Conotruncal defects	392	0.99 (0.79–1.24)	50	0.83 (0.60–1.15)	40	1.15 (0.80–1.64)	11	0.91 (0.48–1.72)
Dextro-TGA	186	0.94 (0.68–1.30)	22	0.82 (0.51–1.30)	14	0.81 (0.46–1.43)	7	1.12 (0.51–2.47)
Dextro-TGA with ventricular septal defects	56	1.39 (0.89–2.18)	5	0.70 (0.27–1.80)	4	0.84 (0.30–2.39)	5	2.86 (1.09–7.48)[a]
Dextro-TGA with double-outlet right ventricle	19	0.41 (0.08–2.02)	2	0.68 (0.15–3.12)	1	0.50 (0.06–3.91)	0	NA
Normally related great arteries defects	211	1.05 (0.78–1.41)	31	0.95 (0.63–1.44)	26	1.47 (0.95–2.28)	4	0.68 (0.25–1.88)
Tetralogy of Fallot	165	0.82 (0.56–1.20)	23	0.84 (0.52–1.35)	17	1.17 (0.69–1.98)	1	0.21 (0.03–1.49)
Truncus arteriosus	20	1.90 (1.04–3.45)[a]	1	0.43 (0.05–3.36)	5	3.41 (1.15–10.17)[a]	2	4.00 (0.86–18.73)
Laterality and looping defects	40	1.29 (0.74–2.25)	5	0.76 (0.29–2.00)	2	0.53 (0.12–2.24)	4	3.19 (1.08–9.43)[a]
I-TGA	24	1.79 (1.04–3.10)[a]	4	1.24 (0.40–3.88)	2	0.93 (0.21–4.17)	4	5.25 (1.66–16.61)
AVSD with Down syndrome	187	0.98 (0.71–1.36)	28	1.14 (0.74–1.75)	17	1.06 (0.62–1.82)	4	0.76 (0.28–2.11)
AVSD without Down syndrome	57	1.50 (0.99–2.29)	10	1.44 (0.70–2.97)	7	1.57 (0.68–3.59)	4	2.00 (0.60–6.71)
Total anomalous pulmonary return	41	0.60 (0.24–1.46)	6	0.92 (0.38–2.27)	1	0.24 (0.03–1.77)	1	0.70 (0.09–5.23)
Left ventricular outflow tract obstruction defects	250	0.95 (0.72–1.25)	50	1.42 (1.01–1.99)[a]	14	0.60 (0.34–1.06)	8	1.00 (0.48–2.11)
Hypoplastic left heart syndrome	117	0.94 (0.62–1.41)	27	1.53 (0.97–2.42)	7	0.67 (0.30–1.47)	3	0.90 (0.28–2.91)
Coarctation of the aorta	79	1.18 (0.78–1.80)	14	1.33 (0.72–2.45)	5	0.69 (0.27–1.75)	4	1.65 (0.58–4.68)
Aortic valve stenosis	54	0.67 (0.33–1.36)	9	1.33 (0.63–2.81)	2	0.38 (0.09–1.62)	1	0.47 (0.06–3.52)
RVOTO defects	270	1.32 (1.06–1.65)[a]	49	1.20 (0.86–1.69)	27	1.25 (0.81–1.91)	12	1.71 (0.92–3.18)
Pulmonary valve stenosis	205	1.35 (1.05–1.74)[a]	45	1.53 (1.06–2.19)[a]	18	1.15 (0.69–1.92)	9	1.79 (0.88–3.64)
Pulmonary atresia with intact ventricular septum	39	1.28 (0.73–2.25)	4	0.73 (0.25–2.14)	8	2.43 (1.06–5.53)[a]	1	0.88 (0.12–6.62)
Septal defects	844	1.10 (0.94–1.28)	149	1.14 (0.93–1.41)	88	1.19 (0.92–1.54)	25	1.07 (0.68–1.67)
Membranous-type ventricular septal defect	477	1.11 (0.92–1.35)	93	1.24 (0.96–1.60)	48	1.13 (0.81–1.58)	15	1.15 (0.66–2.00)
Muscular-type ventricular septal defect	139	0.61 (0.38–0.98)	13	0.54 (0.30–0.97)	10	0.67 (0.34–1.29)	2	0.40 (0.10–1.63)
Secundum-type atrial septal defect	186	1.36 (1.04–1.78)[a]	37	1.41 (0.95–2.11)	22	1.59 (0.98–2.58)	7	1.64 (0.74–3.62)
Patent ductus arteriosus	46	1.20 (0.69–2.07)	4	0.53 (0.18–1.52)	8	1.93 (0.87–4.26)	1	0.75 (0.10–5.59)
Ebstein anomaly	32	0.83 (0.36–1.90)	4	0.86 (0.29–2.54)	2	0.67 (0.16–2.88)	1	0.94 (0.13–7.07)

ORs were adjusted for family history of CHD, infant gender, infant race, maternal age (linear and quadratic), and maternal BMI (linear and quadratic). Smoking refers to reported maternal smoking during the first trimester. cig indicates cigarettes.

[a] Significant results.

Case confirmation by a team of pediatric cardiologists involved intensive, direct clinical review, which minimized the likelihood and extent of misclassification. The sophisticated case-classification approach used in the BWIS continues to influence epidemiologic studies of CHDs; the classification of case infants with a CHD in the ongoing NBDPS relies heavily on the approach developed by BWIS investigators.[16] Results from both our study and the NBDPS provide evidence that maternal periconceptional cigarette smoking is associated with 4 cardiac phenotypes.[14] Specifically, in the recent study from the NBDPS, investigators observed associations of periconceptional maternal smoking with secundum-type atrial septal defects, RVOTO, pulmonary valve stenosis, and AVSDs (without Down syndrome).[14]

Our findings were not entirely consistent with those of previous studies. In a retrospective analysis by Källén[11] of data from the Swedish Child Cardiology Registry and the Swedish Medical Birth Registry on associations between maternal cigarette smoking and CHD phenotypes, a positive association was observed with atrial septal defects (type not specified), but no associations were observed with endocardial cushion defects (presence or absence of Down syndrome was not specified) or pulmonary or aortic valve abnormalities. Findings were not reported separately for pulmonary valve stenosis or for RVOTO defects. In addition, conotruncal defects (particularly TGA) and patent ductus arteriosus (among term infants) were associated with maternal cigarette smoking.[11] A case-control study from California of birth defects that examined possible interactions of maternal use of periconceptional vitamins with selected factors revealed a positive association between maternal smoking and conotruncal defects only among offspring of mothers who did not use vitamins during the periconceptional period.[17] Neither our study nor the NBDPS found any evidence of an association between maternal smoking and conotruncal defects or patent ductus arteriosus.[14]

In our analyses, we also observed evidence for associations with truncus arteriosus (1 type of conotruncal defect) and I-TGA. Neither of these defects was investigated in the NBDPS, presumably because of small case counts. The Swedish study did not reveal evidence for an association with

"asplenia-polysplenia-situs inversus with any heart malformation," an outcome group that included I-TGA.[11] Findings for truncus arteriosus or I-TGA as individual defects were not reported.

There has been variability in exposure definitions and data-collection methods among studies in this area. Smoking in the BWIS was defined as 1 to 10, 11 to 20, 21 to 39, and ≥40 cigarettes per day during the first trimester of pregnancy, and data were collected by using a retrospective maternal interview after delivery. Likewise, the NBDPS obtained smoking information via maternal interview after delivery, although the time period of interest was the 1 month before conception through the end of the first trimester, and smoking was categorized as light (1–14 cigarettes per day), medium (15–25 cigarettes per day), and heavy (>25 cigarettes per day).[14] The Swedish study considered only any smoking versus no smoking; however, the data were reported by mothers prospectively during their first prenatal visit at 10 to 12 weeks' gestation.[11] Similarly, the California study considered any smoking versus no smoking during the periconceptional period, but the data were collected from retrospective maternal interviews.[17] In light of these differences in the classification of exposures (as well as in the definitions of cardiac phenotypes and groups), it is not surprising that results were not entirely consistent across the studies. Differences in time period and geography might have contributed to the variability in results as well.

The associations of maternal smoking with secundum-type atrial septal defects, pulmonary valve stenosis, and AVSDs without Down syndrome in our study and in the NBDPS suggested that these associations likely were not a result of chance. Recall bias also was not a likely explanation, given that case-control differences in maternal smoking were not noted for other CHD phenotypes. In our analyses, we accounted for several recognized CHD risk factors (eg, family history, pregestational diabetes), which reduced the possibility of confounding by such factors. We selected the first trimester of pregnancy as the exposure window of interest, because this period of gestation has been included as the relevant exposure window in other studies of CHDs and possible risk factors.[9] However, it is possible that exposures later during gestation (eg, subclinical viral infections or undiagnosed hyperglycemia) might have resulted in disturbances in morphogenesis and given rise to certain lesions, such as atrial septal defects and pulmonary valve stenosis, so that some of the associations we observed with maternal smoking could have reflected associations with such factors later during gestation.

Possible mechanisms by which smoking might result in CHDs remain to be defined. However, given the complexity of the development of the cardiovascular system, such mechanisms are likely to involve a number of gene-gene, gene-environment, or environment-environment interactions, or a combination thereof. Results of studies in which the interaction of maternal smoking with polymorphisms in biotransformational enzymes and the risk of CHDs among offspring were investigated have suggested that various types of interactions might be involved. Hobbs et al[18] suggested a link between CHDs, smoking, and the 677 C⟶T polymorphism related to folate metabolism, and McDonald et al[19] reported an interaction between methylenetetrahydrofolate reductase gene activity and tobacco exposure on serum folate levels, which suggests an antagonistic effect of smoking on serum folate levels. Other studies of interactions have provided findings consistent with the hypothesis of smoking-mediated reductions in serum folate levels.[17,20,21] A number of other mechanisms have been proposed for adverse effects of smoking on organogenesis, including fetal hypoxia caused by carbon monoxide, impaired uteroplacental circulation with resultant reduced supply of essential nutrients for embryonic tissues, and DNA damage from polycyclic aromatic hydrocarbons.[22–24] There is a need for further work to elucidate the extent to which these or other mechanisms involving the complex mixture of chemicals in cigarette smoke could be involved in the development of atrial septal defects, pulmonary atresia, and AVSDs without Down syndrome and not other CHD phenotypes.

The release of a 1980 US Surgeon General's report on the health consequences of smoking for women marked the beginning of efforts to actively reduce smoking during pregnancy.[25] The BWIS began data collection 1 year later. Arguably, self-reported maternal smoking might have been more accurate and reliable in the BWIS relative to studies conducted more recently. In recent years, women might have been more likely to misreport their smoking behaviors as smoking-cessation efforts have become more common and as knowledge of the dangers associated with smoking during pregnancy has become more widespread. The prevalence of smoking during pregnancy has been decreasing since the 1980s, and awareness of the benefits of smoking cessation (especially during pregnancy) has increased.[26–28] Mothers now might be more reluctant to admit to smoking during pregnancy, and among those who do admit smoking, they might underreport the number of cigarettes smoked.[27,29] The effect of this misclassification is unpredictable,

especially if it is differential with respect to case-control status.

Considering data from the 1990s and 2000s from the Pregnancy Risk Assessment Monitoring System (PRAMS), together with our analysis of BWIS control mothers (1981–1989), women have been increasingly less likely to smoke 1 to 3 months before pregnancy, less likely to smoke during the third trimester, and more likely to cease smoking by the third trimester.[28,30] We note that smoking cessation in the PRAMS refers to the cessation of smoking by the third trimester by women who reported smoking 3 months before pregnancy; the conventional risks of maternal smoking in this context relate to low birth weight and prematurity. If maternal smoking is a valid first-trimester risk factor for birth defects, then birth defect–specific smoking cessation must focus on cessation during or before the first trimester.

CONCLUSIONS

In our study, we observed 3 positive associations and 1 borderline association that were consistent with previous findings from the NBDPS: secundum-type atrial septal defects; RVOTO defects; pulmonary valve stenosis (a subgroup of RVOTO defects); and AVSDs without Down syndrome.[14] The association with atrial septal defects also was observed in a previous analysis of Swedish registry data.[11] Taken together, these findings suggest that maternal smoking during the first trimester of pregnancy might present a modest risk for selected CHDs. Although we cannot discount random error as an alternative explanation for our observed results, if the associations we observed are causal, then they suggest the possibility of primary prevention via targeted smoking-cessation interventions. Successful cessation or reduction of maternal smoking during pregnancy also might yield reductions in other adverse pregnancy outcomes for which there are known associations, including preterm delivery, low birth weight, and oral clefts.[31–36]

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