Maternal Smoking and Congenital Heart Defects, National Birth Defects Prevention Study, 1997–2011

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Abstract

Objectives: To assess associations between maternal smoking and congenital heart defects (CHDs) in offspring.

Study design: We performed a retrospective case-control study using data for cases of CHD (n=8,339) and non-malformed controls (n=11,020) children from all years (1997–2011) of the National Birth Defects Prevention Study. Maternal self-reported smoking one month before through three months after conception was evaluated as a binary (none, any) and categorical (light, medium, heavy) exposure. Multivariable logistic regression was used to estimate adjusted odds ratios (aOR) and 95% confidence intervals. Stratified analyses were performed for septal defects according to maternal age, pre-pregnancy body mass index, and maternal race/ethnicity.

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Results: Multiple CHDs displayed modest associations with any level of maternal periconceptional smoking independent of potential confounders; the strongest associations were for aggregated septal defects (OR 1.5 [1.3–1.7]), tricuspid atresia (OR 1.7 [1.0–2.7]), and double outlet right ventricle (DORV) (1.5 [1.1–2.1]). TA and DORV also displayed dose-response relationships. Among heavy smokers, the highest odds were again observed for TA (aOR 3.0 [1.5–6.1]) and DORV (aOR 1.5 [1.1–2.2]). Heavy smokers   35 years old more frequently had a child with a septal defect when compared with similarly aged non-smokers (aOR 2.3 [1.4–3.9]).

Conclusions: Maternal periconceptional smoking is most strongly associated with septal defects, TA and DORV; the risk for septal defects is modified by maternal age.

Keywords

tobacco; pregnancy; congenital heart disease

In the United States, approximately 10% of women smoke during pregnancy and subsequently give birth to live infants; this equates to >30,000 children born to mothers who smoke every year.[1] Previous studies have demonstrated that maternal smoking is associated with increased risk for cleft lip/palate, intrauterine growth restriction, prematurity, sudden unexpected infant death, and other adverse birth outcomes.[2–6] In contrast, the relationship between maternal periconceptional smoking and risk of congenital heart defects (CHDs) in offspring is less clear. Understanding modifiable risk factors for CHDs is particularly important given their frequency and impact on individuals and the community: CHDs affect about 1 in 100 babies, are one of the leading causes of infant mortality due to birth defects, and CHD-associated hospitalizations cost more than $5 billion annually in the US (>15% of costs for all pediatric hospitalizations).[7, 8]

Three large case-control studies have investigated associations between maternal smoking during pregnancy and risk of CHDs in offspring: the National Birth Defects Prevention Study (NBDPS),[9] the Baltimore-Washington Infant Study,[10] and a study using records from the Washington State Department of Health.[11] Findings suggested that maternal smoking is associated with modest risks of specific CHDs, although there was considerable variability in their study methodologies and results.

The NBDPS was the only study with participants from multiple sites across the United States. The current study updates a previous analysis of NBDPS data by Malik et al, re-assessing associations between maternal smoking and CHDs in offspring with nine additional years of data, including more than twice as many case children as were in the original report.[9]

Methods

The NBDPS was a population-based case-control study that included pregnancies ending from October 1997 through December 2011.[12] There were 10 study sites (centers) that contributed data to the study, each located in a different state. Case children had at least one NBDPS-eligible birth defect ascertained from existing population-based birth defect surveillance systems. Pregnancies that ended in elective termination, stillbirth, or

live-birth were ascertained, although not all study sites included all pregnancy outcomes during the entire study period. Case children with an identified genetic syndrome were excluded. Control children were live-births with no major birth defects delivered during the study period and selected from birth certificates or birth hospital logs from the same catchment area as case children. The NBDPS included 47,382 eligible case and 18,272 eligible control children, of which interviews were completed with mothers of case children [32,187 (68%)] and mothers of control children [11,814 (65%)].[12] After informed consent, mothers answered questionnaires via a computer-assisted telephone interview about their demographics, health, and exposures.[13] In order to complete the questionnaire, mothers had to speak English or Spanish. Questionnaires were completed between 6 weeks and 24 months after the estimated due date.

For the present study, the process by which case and control children were selected from the NBDPS is displayed in the Figure; this was the same process used by Malik et al.[9] Only singleton pregnancies were included for case and control children. Additionally, there were small numbers of terminations (n = 20) and stillbirths (n = 55) among potential case children; we excluded these because of the previously reported discordances between pre- and postnatal diagnoses of CHDs (postnatal diagnostic modalities are considered more reliable).[14] Case children with extracardiac anomalies and those whose mothers were diagnosed with preconceptional diabetes were also excluded. Isolated muscular ventricular septal defects (VSDs) were only enrolled in the first 15 months of the NBDPS, and these were therefore excluded. Additionally, one center enrolled case children with pulmonary valve stenosis for only a portion of the study, and participants from that center with pulmonary valve stenosis were excluded. After exclusions, there were 8,339 case children and 11,020 control children in the final analysis. Among participants included in our analysis, the median time between estimated due date and administration of the computer-assisted telephone interview was 315 days (interquartile range: 213–448 days) for mothers of case children and 227 days (interquartile range: 151–351 days) for mothers of control children.

Phenotypes of CHDs were ascertained and adjudicated by two or more pediatric cardiologists who reviewed reports from transthoracic echocardiography, cardiac catheterization, autopsy, and/or surgery, all of which had to have been performed in the first year of life in order for the case child to be eligible.[15] Some lesions comprised constellations of defects that are generally recognized to be a single entity (e.g. tetralogy of Fallot). Certain phenotypes were categorized into larger groups based on the anatomic site of the lesion including septal defects (VSDs [except muscular, conotruncal and malaligned types] and secundum-type atrial septal defects [ASDs], but not atrioventricular septal defects [AVSDs]); right-sided obstructive lesions (pulmonary valve stenosis, pulmonary atresia, tricuspid atresia [TA], and Ebstein anomaly); left-sided obstructive lesions (aortic valve stenosis, hypoplastic left heart syndrome, coarctation of the aorta, and interrupted aortic arch type A and type C); and conotruncal defects (transposition of the great arteries, tetralogy of Fallot, truncus arteriosus, double outlet right ventricle [DORV], interrupted aortic arch type B, and malaligned VSDs, which generally occur in the setting of conotruncal-type defects).[16]

AVSDs were analyzed separately from isolated ASDs and VSDs, as the unifying phenotypic hallmark of AVSDs is a common atrioventricular junction (ie, concomitant deficiency of septa and atrioventricular valve leaflets at the crux of the heart), whereas isolated ASD or isolated VSD represent deficiencies of septa alone.[17]

Maternal smoking was assessed for the periconceptional period, an interval defined as one month prior to conception through three months after conception. During the computer-assisted telephone interview, mothers were asked the following question about each of the four months in the periconceptional period: During (month in question) about how many cigarettes did you smoke a day? Mothers were asked to select from the following amounts of cigarettes smoked per day : <1 cigarette, 1 cigarette, 2–4 cigarettes, ½ pack (5–14 cigarettes), 1 pack (15–24 cigarettes), 1½ packs (25–34 cigarettes), 2 packs (35–44), or >2 packs. Smoking was stratified into the following categories: light (1–4 cigarettes/day), medium (5–14 cigarettes/day), and heavy (15 cigarettes/day). Maternal periconceptional cigarette smoking was assessed by obtaining the highest level of self-reported smoking. Although there are no standard definitions for daily smoking levels, some authors have used similar strata in recent reports.[18, 19] Our definition of smoking categories was more granular in the lower end of the exposure range compared with the categories used by Malik et al, in which smoking levels were categorized as follows: light (1–14 cigarettes/day), medium (15–24 cigarettes/day), and heavy (25 cigarettes/day).[9]

Categorical variables were expressed as counts and percentages; continuous variables were expressed as medians with interquartile ranges given that all variables violated normality assumptions. Comparisons between case and control children were made using Chi-Square, Fisher exact, and Wilcoxon Rank Sum tests. Unconditional multivariable logistic regression analysis was used to estimate adjusted odds ratios (aORs) and 95% confidence intervals (CIs) between maternal smoking and CHDs while adjusting for covariates. Separate regression models were created to assess smoking as a binary variable (yes, no) and with three levels of stratification among women who smoked (light, medium, heavy). Both sets of models used women who did not smoke as the reference category. Models were adjusted for ten covariates: infant sex (female, male), maternal age at delivery (<20 years, 20–34 years, 35 years), race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other race/ethnicity), category of pre-pregnancy body mass index (<18.5 kg/m^2, 18.5-<25.0 kg/m^2, 25.0-<30.0 kg/m^2, 30 kg/m^2), periconceptional alcohol consumption (yes, no), folic acid intake from one month prior to conception to two months after conception (yes, no), energy adjusted dietary folate intake (in dietary folate equivalents), periconceptional caffeine intake (yes, no), family history of CHDs (in a first-degree relative of the case or control child), and site; these were the same ten covariates used in the models reported by Malik et al.[9] To support including NBDPS case and control children from 1997–2002 in our analyses of all NBDPS children (1997–2011), we initially conducted separate analyses of data from 1997 through 2002 (the study years used by Malik et al) and from 1997 through 2011.

Additional analyses were performed to examine the relationship between smoking and septal defects stratified by age at delivery, maternal race/ethnicity, and pre-pregnancy body mass index. aORs and 95% CIs were estimated for all associations; the comparator was women who did not smoke in the same stratum (i.e. women who smoked and were 35 years old

at delivery were compared with women who did not smoke and were 35 years old at delivery).

All statistical analyses were performed using SAS version 9.4 (SAS Institute).

Results

The characteristics of case and control children and mothers are summarized in Table 1. In the final analytic sample, there were 19,359 subjects, of whom 8,339 were case children and 11,020 were control children without a CHD from all years (1997–2011) of the National Birth Defects Prevention Study. Case children were more frequently male and were more likely to have a family history of a CHD when compared with control children. Compared with control mothers, case mothers more frequently smoked during the periconceptional period, tended to be of older age at delivery, be of non-Hispanic white or black race/ethnicity, have a higher pre-pregnancy body mass index, have lower levels of dietary folate intake, less frequently used alcohol, and had higher caffeine intake in the periconceptional period.

Table 2 presents aORs and 95% CIs for the association between any maternal periconceptional cigarette smoking and CHDs in offspring. In decreasing order of the strength of the association, women who reported any smoking were more likely to have a child with secundum ASD (aOR=1.7 [95% CI: 1.5–2.0]), TA (aOR=1.7 [95% CI: 1.0–2.7]), any septal defect (aOR=1.5 [95% CI: 1.3–1.7]), DORV (aOR=1.5 [95% CI: 1.1–2.2]), perimembranous VSD (aOR=1.3 [95% CI 1.1–1.5]), AVSD (aOR= 1.3 [95% CI 1.0–1.9]), right-sided obstructive lesion (aOR=1.2 [95% CI 1.0–1.4]), pulmonary valve stenosis (aOR=1.2 [95% CI 1.0–1.4]), truncus arteriosus (aOR=1.2 [95% CI 0.7–2.1]), and Ebstein anomaly (aOR=1.1 [95% CI 0.7–1.8]).

In analyses that assessed amount of daily smoking (Table II), the strongest association was observed between heavy smoking and TA (aOR= 3.1 [95% CI 1.5–6.2]), followed by DORV (aOR = 2.0 [1.1–3.4]). Additionally, suggestions of dose-response relationships were observed for TA, DORV, and perimembranous VSD.

In comparing analyses between data from the initial study by Malik et al (1997–2002) and the full dataset (1997–2011), we observed general agreement in results between the two study periods, using the same consistent categories of smoking (i.e., light >1–4 cigarettes/day, moderate 5–14 cigarettes/day, and heavy 15 cigarettes/day; Table 3: available at www.jpeds.com). Because of the general agreement, we included subjects from all NBDPS years (1997–2011). Analyses were also performed using the daily smoking categorizations employed by Malik et al and were compared with the categorizations used in the current analysis; again, there was general agreement for associations between the two systems of classifying daily smoking (Table 4; available at www.jpeds.com).

Table 5 focuses on septal defects and displays results stratified by selected maternal characteristics. Results were mostly consistent across strata. The largest variation for any stratum was observed for those 35 years old with heavy smoking, who were 2.3 times more likely to have offspring with a septal defect (95% CI: 1.4–3.9) compared with non-smokers

35 years old, although a weaker but still statistically significant association was observed for smokers <35 years old (OR: 1.5 [95% CI: 1.2–1.8]). Otherwise, there was not notable variation in the aORs for maternal race/ethnicity or maternal body mass index, nor was a dose response relationship observed for maternal body mass index.

Discussion

In the last 20 years, three groups have published case-control studies investigating the association between maternal smoking around the time of conception and CHDs: Malik et al in 2008 (using the NBDPS, 1997–2002),[9] Alverson et al in 2011 (using the Baltimore Washington Infant Study, 1981–1989),[10] and Sullivan et al in 2015 (using birth records from the Washington Department of Health, 1989–2011).[11] Malik et al reported that smoking was associated with aggregated septal defects (ASDs and VSDs) and right-sided obstructive lesions.[9] We updated results from that publication by using all years of the NBDPS (1997–2011). We also modified the categorization of daily smoking to be more consistent with contemporary classifications; specifically, we defined daily smoking as light (<1–4 cigarettes/day), medium (5–14 cigarettes/day), and heavy (15 cigarettes/day).[18, 19]

The original report of Malik et al and our update showed associations between maternal periconceptional smoking and septal defects in offspring. Compared with those observed by Malik et al, our study identified novel associations with TA and DORV, and attenuated associations with right ventricular outflow tract lesions.

Our results were also consistent with those reported by Alverson et al from the Baltimore-Washington Infant Study, in which maternal smoking in the first trimester was associated with secundum ASDs and right ventricular outflow tract lesions.[10] Additionally, they observed associations with truncus arteriosus and levo-transposition of the great arteries, neither of which were observed in our study. The methods used in our study and those used by Alverson et al were similar in that case children were classified by cardiologists through review of echocardiography, cardiac catheterization, surgery, and/or autopsy reports, and exposure to maternal smoking was assessed via a post-delivery interview. Additionally, both studies excluded children with extracardiac anomalies. The studies differed, however, in the timing of the exposure, the number of cases (the present study had more than twice as many), and the covariates included in multivariable models.

Finally, our results were similar to the retrospective case-control study by Sullivan et al using Washington State birth certificates, in which the authors observed modest associations between maternal first trimester smoking and secundum ASDs and right-side obstructive lesions.[11] Their methods differed from those in our study in several ways. The amount of daily smoking was ascertained from birth certificates, which may be less accurate in identifying and quantifying daily smoking when compared with a post-delivery questionnaire.[20] Also, the timing of the exposure was somewhat different (first trimester as opposed to periconceptional period). Finally, cardiac phenotypes were determined using only International Classifications of Diseases, Ninth Edition codes (rather than review by several cardiologists), and case children were not excluded if they had an extracardiac anomaly.

One consistent finding across the aforementioned studies and the present study is an association between maternal smoking and secundum ASDs. As opposed to the other investigated lesions, ASDs, especially smaller ones, can be difficult to identify on physical examination, and are not detected on screening with pulse oximetry.[21, 22] For these reasons, ASDs frequently go undiagnosed until adulthood.[23] Nevertheless, ASDs can be important clinically, as late diagnosis of ASD (i.e. after 25 years of age) is associated with increased risk of pulmonary vascular obstructive disease, which in turn is associated with higher postoperative mortality.[24] Further research may help determine if routine transthoracic echocardiography is warranted to screen for ASDs in children born to mothers who smoke.

Although the association with ASDs was a consistent finding across studies, we observed several novel associations (for TA and DORV), whereas other previously reported associations were either attenuated (right-sided obstructive lesions) or not observed (truncus arteriosus) in our study. There may be several explanations for these discrepancies. First, as previously noted, the study methods varied. Second, some of the studied lesions exhibit considerable anatomic heterogeneity, and may have been classified differently across studies; the definition of DORV, for example, continues to be debated among cardiologists, surgeons, and anatomists.[25] Third, for the aggregated groups of lesions (e.g. right-sided obstructive lesions), there may have been different distributions of lesion subtypes, leading to different results. Finally, given the weak and/or modest associations observed in this study and other studies, chance is likely also to explain noted discrepancies.

Among selected maternal characteristics (race/ethnicity, age, and body mass index), the combination of maternal age ≥ 35 years and smoking ≥ 15 cigarettes per day was associated with the highest odds of having a child with a septal defect. These findings are consistent with those reported by Sullivan et al, in which maternal age modified the risk of having a child with any CHD.[11] CHD screening recommendations for children born to older mothers who smoke could be informed by future research.

An important negative finding in the present data was absent effect modification according to maternal race and pre-pregnancy BMI. Among smokers, Black race is known to be associated with more severe adverse outcomes even when adjusting for other variables.[26] And higher pre-pregnancy body mass index has been associated with increased risk of several CHDs, including ASDs.[27] The present study may have been underpowered to show effect modification based on these subgroups, and further investigation may be warranted.

Although the present study did not investigate a mechanism for the association between maternal smoking and CHDs in offspring, it is notable that the three most commonly associated lesions (septal defects, DORV and TA) are presumed to arise from somewhat disparate perturbations in cardiogenesis. Previous studies investigating links between smoking and CHDs have also reported significant heterogeneity among associated lesions.[9–11] It may be that smoking exerts teratogenic effects on multiple pathways involved in cardiac development (e.g., neural crest cell migration, septation, looping).[28, 29] Gene-environment interactions likely mediate many of these associations; for example, a polymorphism in the gene coding for methylenetetrahydrofolate reductase was observed to confer increased risk of having a child with a CHD among women who smoke.[30]

There were several potential limitations of our study. All possible confounders were not included in models: for example, we did not adjust for several social determinants of health that have previously been shown to be associated with CHDs, including maternal poverty, maternal education level, and household income.[31] There were several reasons, however, that we did not adjust for all of these social determinants of health. The present study was conceived as a replication of the study performed by Malik et al, and we used the same 10 covariates employed in that study, of which three variables were socially/demographically-mediated (maternal age at delivery, maternal race/ethnicity, and site).[9] Other covariates in our models have elsewhere been associated with socioeconomic status (i.e. body mass index, folic acid intake, and alcohol consumption).[32–34] In so doing, we hoped to capture as many confounders associated with CHDs as possible, many of which were socially-mediated, without overfitting the models. Additionally, other studies have indicated that the risk of CHDs in offspring may be associated (albeit weakly) with environmental toxins other than smoking; these contaminants include ozone, vehicle exhaust, second hand smoke, and disinfectant byproducts.[35–38] Many of those investigations came from the NBDPS, and we elected to not repeat those analyses. Another limitation was that mothers were asked to recall events that took place up to two years in the past, and they may not have accurately reported the exact number of cigarettes. Alternatively, some mothers may have stopped smoking just prior to the periconceptional period, but mistakenly reported smoking in the periconceptional period, which would have led to misclassification of the exposure. Social desirability bias may have occurred as maternal self-reports of a behavior (such as smoking) known to be harmful to an unborn child may be underreported.[39] Conversely, recall bias could have resulted in a systematic bias if mothers of children with CHDs were more likely to recall smoking. Another possible limitation was that the exclusion of stillbirths and terminations may have caused selection bias. Also, the NBDPS (as well as the Baltimore Washington Infant Study and Washington health records) does not report the size of secundum-type ASD, or necessarily differentiate from patent foramen ovale; this is a limitation, as the severity of secundum-type ASD is largely predicated on its size.[40] Finally, many associations were tested, and some positive associations may be attributable to chance.

This study adds several CHDs to the list of adverse pregnancy outcomes associated with smoking, and further highlights the importance of providing cessation therapies to women of reproductive age.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

Abbreviations and Acronyms:

aOR	adjusted odds ratio
ASD	atrial septal defect
AVSD	atrioventricular septal defect
CI	confidence interval
CHD	congenital heart defect
DORV	double outlet right ventricle
NBDPS	National Birth Defects Prevention Study
US	United States
VSD	ventricular septal defect

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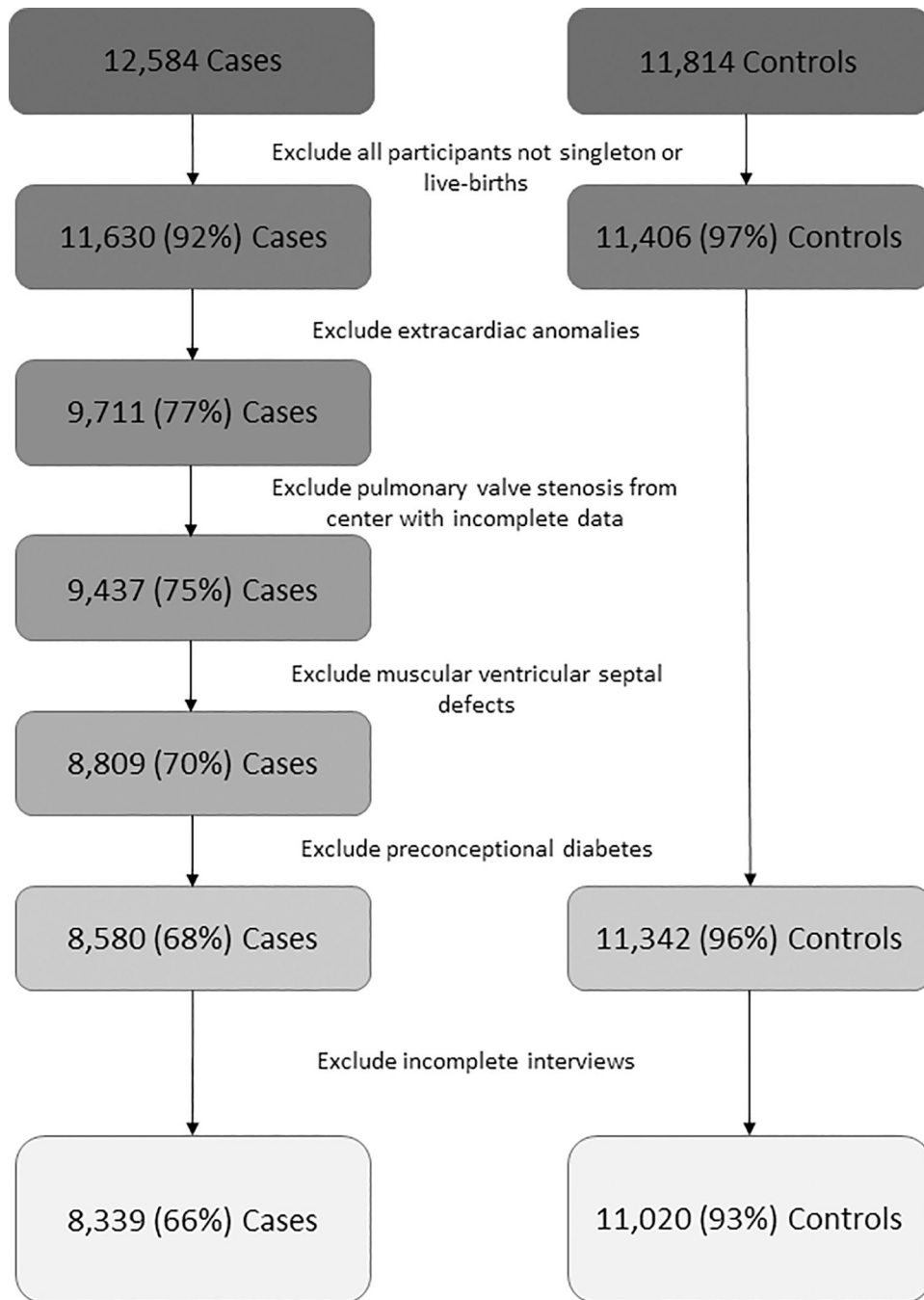
Figure.

Exclusion of case and control participants, National Birth Defects Prevention Study, 1997–2011.

Table 1.

Characteristics of Case and Control Children, National Birth Defects Prevention Study, 1997–2011

Variable	Cases, n (%)	Controls, n (%)	p-value
Sex			<0.001
Female	3762 (45.1)	5406 (49.1)	
Male	4573 (54.8)	5604 (50.9)	
Missing	4 (0.1)	10 (0.1)	
Maternal age			0.006
<20 y	725 (8.7)	1077 (9.8)	
20–34 y	6365 (76.3)	8416 (76.4)	
35 y	1249 (15.0)	1527 (13.9)	
Maternal race/ethnicity			<0.001
White, non-Hispanic	5061 (60.7)	6412 (58.2)	
Black, non-Hispanic	942 (11.3)	1202 (10.9)	
Hispanic	1789 (21.5)	2686 (24.4)	
Other	547 (6.6)	718 (6.5)	
Missing	0 (0.0)	2 (<0.1)	
Maternal body mass index, kg/m			<0.001
Underweight (<18.5)	430 (5.2)	564 (5.1)	
Normal (18.5 to <25.0)	4034 (48.4)	5696 (51.7)	
Overweight (25.0 to <30.0)	1906 (22.9)	2400 (21.8)	
Obese (30.0)	1636 (19.6)	1911 (17.3)	
Missing	333 (4.0)	449 (4.1)	
Family history of CHD			<0.001
Yes	322 (3.9)	128 (1.2)	
No	8017 (96.1)	10892 (98.8)	
Periconceptional[a] smoking			0.001
None	6655 (79.8)	9040 (82.0)	
Light Smoking	477 (5.7)	596 (5.4)	
Medium Smoking	716 (8.6)	812 (7.4)	
Heavy Smoking	478 (5.7)	556 (5.1)	
Missing	13 (0.2)	16 (0.2)	
Folic acid intake one month prior to conception to two months after conception			0.654
Yes	6332 (75.9)	8337 (75.7)	
No	2007 (24.1)	2683 (24.4)	
Dietary folate intake, μg/day			<0.001
Median (IQR)	423.3 (281.3–618.9)	442.7 (297.6–647.6)	
Range	0.0–6715.0	0.0–8120.5	

Variable	Cases, n (%)	Controls, n (%)	p-value
Periconceptional[a] alcohol use			0.026
Yes	2967 (35.6)	4098 (37.2)	
No	5332 (63.9)	6886 (62.5)	
Missing	40 (0.5)	36 (0.3)	
Periconceptional[a] caffeine intake, mg/d			0.016
Median (IQR)	86.3 (20.4–182.9)	80.7 (17.1–179.0)	
Range	0.0–1313.0	0.0–1308.4	

[a] The periconceptional period was one month prior to conception to three months after conception.

CHD = congenital heart defect, mg = milligrams, IQR = interquartile range

Table 2.

Adjusted odds for associations between maternal periconceptional smoking and congenital heart defects in offspring, National Birth Defects Prevention Study, 1997–2011

CHD Subtype	Any Smoking		Light Smoking (1–4 cigarettes/day)		Medium Smoking (5–14 cigarettes/day)		Heavy Smoking (≥15 cigarettes/day)	
	Numbers of Cases/Controls	aOR (95% CI)	Numbers of Cases/Controls	aOR (95% CI)	Numbers of Cases/Controls	aOR (95% CI)	Numbers of Cases/Controls	aOR (95% CI)
Aggregated septal defects [a] (not including atrioventricular septal defect)	640/1964	1.5 (1.3–1.7)	189/596	1.5 (1.2–1.7)	266/812	1.5 (1.3–1.7)	185/556	1.6 (1.3–1.9)
- Ventricular septal defect (perimembranous)	248/1964	1.3 (1.1–1.5)	68/596	1.1 (0.9–1.5)	103/812	1.2 (1.0–1.6)	77/556	1.4 (1.1–1.9)
- Atrial septal defect (secundum)	351/1964	1.7 (1.5–2.0)	101/596	1.7 (1.3–2.1)	149/812	1.7 (1.4–2.1)	101/556	1.7 (1.3–2.2)
Atrioventricular septal defect	64/1964	1.3 (1.0–1.9)	16/596	1.2 (0.7–2.0)	30/812	1.5 (1.0–2.2)	18/556	1.3 (0.8–2.2)
Right-sided obstructive lesions	319/1964	1.2 (1.0–1.4)	78/596	1.0 (0.8–1.3)	143/812	1.3 (1.0–1.5)	98/556	1.3 (1.0–1.7)
- Pulmonary valve stenosis [b]	240/1901	1.2 (1.0–1.4)	59/567	1.0 (0.7–1.3)	106/792	1.2 (0.9–1.5)	75/542	1.3 (1.0–1.7)
- Ebstein anomaly	25/1964	1.1 (0.7–1.8)	7/596	1.0 (0.5–2.3)	11/812	1.1 (0.6–2.2)	7/556	1.1 (0.5–2.5)
- Pulmonary atresia with intact ventricular septum	35/1964	1.0 (0.7–1.5)	10/596	0.9 (0.5–1.8)	16/812	1.1 (0.6–1.8)	9/556	1.0 (0.5–2.1)
- Tricuspid atresia	28/1964	1.7 (1.0–2.7)	4/596	0.7 (0.3–2.0)	13/812	1.8 (1.0–3.4)	11/556	3.1 (1.5–6.2)
Left-sided obstructive lesions	270/1964	0.9 (0.8–1.1)	77/596	0.9 (0.7–1.2)	125/812	1.0 (0.8–1.3)	68/556	0.8 (0.6–1.0)
- Hypoplastic left heart syndrome	91/1964	1.0 (0.8–1.3)	24/596	0.9 (0.6–1.4)	44/812	1.1 (0.8–1.6)	23/556	0.8 (0.5–1.4)
- Coarctation of the aorta	104/1964	0.7 (0.6–0.9)	35/596	0.9 (0.6–1.3)	40/812	0.7 (0.5–1.0)	29/556	0.7 (0.4–1.0)
- Aortic valve stenosis	77/1964	1.0 (0.8–1.3)	19/596	0.9 (0.6–1.5)	40/812	1.3 (0.9–1.8)	18/556	0.7 (0.4–1.2)
Conotruncal defects	363/1964	1.0 (0.8–1.1)	115/596	1.0 (0.8–1.3)	153/812	1.0 (0.8–1.2)	95/556	0.9 (0.7–1.1)
- Tetralogy of Fallot	143/1964	0.9 (0.7–1.1)	56/596	1.1 (0.8–1.5)	54/812	0.8 (0.6–1.0)	33/556	0.7 (0.5–1.0)
- d-Transposition of the great arteries	123/1964	0.9 (0.7–1.2)	31/596	0.8 (0.6–1.2)	57/812	1.0 (0.8–1.4)	35/556	0.9 (0.6–1.3)
- Double outlet right ventricle	56/1964	1.5 (1.1–2.2)	15/596	1.1 (0.6–2.1)	22/812	1.6 (1.0–2.6)	19/556	2.0 (1.1–3.4)
- Truncus arteriosus	17/1964	1.2 (0.7–2.1)	6/596	1.4 (0.6–3.3)	8/812	1.3 (0.6–2.8)	3/556	0.7 (0.2–2.5)
Anomalous pulmonary venous return	55/1964	1.0 (0.7–1.4)	13/596	0.8 (0.5–1.5)	23/812	1.1 (0.7–1.7)	19/556	1.1 (0.7–1.9)
- Total anomalous pulmonary venous return	44/1964	1.0 (0.7–1.5)	12/596	1.0 (0.5–1.7)	17/812	1.0 (0.6–1.7)	15/556	1.1 (0.6–2.1)

[a] Aggregated septal defects were all perimembranous ventricular septal defects, ventricular septal defects not otherwise specified, secundum atrial septal defects, and atrial septal defects not otherwise specified.

[b] The number of control infants was lower for pulmonary valve stenosis because one center enrolled children with pulmonary valve stenosis for only a portion of the study; case and control children from that center were excluded for analysis of pulmonary valve stenosis.

aOR = odds ratio, CI = confidence interval

Table 3: online only.

Comparisons of time periods for associations between maternal periconceptional smoking and congenital heart defects in offspring, National Birth Defects Prevention Study, 1997–2011

Outcome	(1997–2002)[a]	All years (1997–2011)[a]
Septal defects[b]	- Light smoking aOR 1.4, CI: 1.2–1.8 - Medium smoking aOR 1.5, CI: 1.1–2.0 - Heavy smoking aOR 2.1, CI: 1.2–3.5	- Light smoking aOR 1.5, CI: 1.2–1.7 - Medium smoking aOR 1.5, CI: 1.3–1.7 - Heavy smoking aOR 1.6, CI: 1.3–1.9
Ventricular septal defect	No significant associations	Heavy smoking aOR 1.4, CI: 1.1–1.9
Atrial septal defects	- Light smoking aOR 2.0, CI: 1.5–2.8 - Medium smoking aOR 1.8, CI: 1.1–3.0	- Light smoking aOR 1.7, CI: 1.3–2.1 - Medium smoking aOR 1.7, CI: 1.4–2.1 - Heavy smoking aOR 1.7, CI: 1.3–2.2
Atrioventricular septal defects	No significant associations	Any smoking aOR 1.3, CI: 1.0–1.9
Defects of the right ventricular outflow tract	Heavy smoking aOR 2.4, CI: 1.2–4.5	Heavy smoking aOR 1.3, CI: 1.0–1.7
Pulmonary valve stenosis	Heavy smoking aOR 2.3, CI 1.1–4.8	Heavy smoking aOR 1.3, CI: 1.0–1.7
Defects of the left ventricular outflow tract	No significant associations	No significant associations
Hypoplastic left heart syndrome	No significant associations	No significant associations
Coarctation of the aorta	No significant associations	No significant associations
Aortic valve stenosis	No significant associations	No significant associations
Conotruncal defects	No significant associations	No significant associations
Tetralogy of Fallot	No significant associations	No significant associations
d-Transposition of the great arteries	No significant associations	No significant associations
Double outlet right ventricle	No significant associations	Any smoking aOR 1.5, CI: 1.1–2.1 Heavy smoking aOR 2.0, CI: 1.1–3.4
Anomalous pulmonary venous return	No significant associations	No significant associations
Total anomalous pulmonary venous return	No significant associations	No significant associations

[a]Levels of smoking for both time periods (1997–2002 and 1997–2011) were calculated for the following levels: light >1–4 cigarettes/day, moderate 5–15 cigarettes/day, and heavy >15 cigarettes/day.

[b]Aggregated septal defects were all perimembranous ventricular septal defects, ventricular septal defects not otherwise specified, secundum atrial septal defects, and atrial septal defects not otherwise specified.

aOR = adjusted odds ratio, CI = 95% confidence interval.

Table 4: online only.

Adjusted odds for associations between maternal periconceptional smoking and congenital heart defects in offspring using previous criteria employed by Malik et al. for daily smoking amounts, National Birth Defects Prevention Study, 1997–2011

CHD Subtype	Any Smoking		Light Smoking (≤ 1–14 cigarettes/day)		Medium Smoking (15–24 cigarettes/day)		Heavy Smoking (≥ 25 cigarettes/day)	
	Numbers of Cases/Controls	aOR (95% CI)	Numbers of Cases/Controls	aOR (95% CI)	Numbers of Cases/Controls	aOR (95% CI)	Numbers of Cases/Controls	aOR (95% CI)
Aggregated septal defects [a]	640/1964	1.5 (1.3–1.7)	455/1408	1.5 (1.3–1.7)	153/458	1.6 (1.3–1.9)	32/98	1.5 (1.0–2.3)
- Ventricular septal defect (perimembranous)	248/1964	1.3 (1.1–1.5)	171/1408	1.2 (1.0–1.4)	64/458	1.4 (1.1–1.9)	13/98	1.4 (0.8–2.5)
- Atrial septal defect (secundum)	351/1964	1.7 (1.5–2.0)	250/1408	1.7 (1.4–2.0)	86/458	1.8 (1.4–2.3)	15/98	1.5 (0.8–2.6)
Atrioventricular septal defect	64/1964	1.3 (1.0–1.9)	46/1408	1.4 (1.0–1.9)	16/458	1.4 (0.8–2.4)	2/98	0.9 (0.2–3.7)
Right-sided obstructive lesions	319/1964	1.2 (1.0–1.4)	221/1408	1.1 (1.0–1.3)	79/458	1.3 (1.0–1.7)	19/98	1.5 (0.9–2.5)
- Pulmonary valve stenosis	240/1901	1.2 (1.0–1.4)	165/1359	1.1 (0.9–1.4)	61/445	1.3 (1.0–1.7)	14/97	1.4 (0.8–2.5)
- Ebstein anomaly	25/1964	1.1 (0.7–1.8)	18/1408	1.1 (0.6–1.9)	3/458	0.6 (0.2–1.9)	4/98	3.6 (1.2–10.6)
- Pulmonary atresia with intact ventricular septum	35/1964	1.0 (0.7–1.5)	26/1408	1.0 (0.6–1.6)	9/458	1.2 (0.6–2.4)	0/98	N/A
- Tricuspid atresia	28/1964	1.7 (1.0–2.7)	17/1408	1.3 (0.7–2.3)	10/458	3.3 (1.6–6.7)	1/98	1.7 (0.2–12.9)
Left-sided obstructive lesions	270/1964	0.9 (0.8–1.1)	202/1408	1.0 (0.8–1.2)	53/458	0.7 (0.5–1.0)	15/98	1.1 (0.6–1.9)
- Hypoplastic left heart syndrome	91/1964	1.0 (0.8–1.3)	68/1408	1.0 (0.8–1.4)	15/458	0.7 (0.4–1.2)	8/98	1.9 (0.9–4.0)
- Coarctation of the aorta	104/1964	0.7 (0.6–0.9)	75/1408	0.8 (0.6–1.0)	23/458	0.6 (0.4–1.0)	6/98	0.9 (0.4–2.0)
- Aortic valve stenosis	77/1964	1.0 (0.8–1.3)	59/1408	1.1 (0.8–1.5)	17/458	0.8 (0.5–1.4)	1/98	0.2 (0.0–1.6)
Conotruncal defects	363/1964	1.0 (0.8–1.1)	268/1408	1.0 (0.9–1.2)	73/458	0.8 (0.6–1.1)	22/98	1.2 (0.7–1.9)
- Tetralogy of Fallot	143/1964	0.9 (0.7–1.1)	110/1408	0.9 (0.7–1.1)	26/458	0.7 (0.4–1.0)	7/98	0.9 (0.4–2.0)
- d-Transposition of the great arteries	123/1964	0.9 (0.7–1.2)	88/1408	1.0 (0.7–1.2)	26/458	0.8 (0.5–1.2)	9/98	1.2 (0.6–2.6)
- Double outlet right ventricle	56/1964	1.5 (1.1–2.2)	37/1408	1.4 (0.9–2.1)	15/458	1.9 (1.0–3.4)	4/98	2.4 (0.8–6.8)

[a] Aggregated septal defects were all perimembranous ventricular septal defects, ventricular septal defects not otherwise specified, secundum atrial septal defects, and atrial septal defects not otherwise specified.

aOR = adjusted odds ratio, N/A = not applicable.

Table 5.

Association between maternal periconceptional smoking and odds of aggregated septal defects[a] (not including AVSD) in offspring by selected maternal characteristics, National Birth Defects Prevention Study, 1997–2011

Subgroup	Numbers of Cases/ Controls	Any Smoking aOR (95% CI)	Light Smoking aOR (95% CI)	Medium Smoking aOR (95% CI)	Heavy Smoking aOR (95% CI)
Maternal race/ethnicity					
White, non-Hispanic	1484/6332	1.4 (1.2–1.6)	1.3 (1.1–1.7)	1.4 (1.2–1.7)	1.5 (1.2–1.9)
Black, non-Hispanic	358/1188	1.8 (1.3–2.4)	1.7 (1.2–2.6)	1.9 (1.3–2.9)	1.1 (0.4–3.0)
Hispanic	535/2261	1.5 (1.1–2.0)	1.5 (1.0–2.1)	1.5 (0.9–2.5)	1.4 (0.6–2.9)
Maternal age					
< 35 years	2142/8998	1.5 (1.3–1.6)	1.4 (1.2–1.7)	1.5 (1.2–1.7)	1.5 (1.2–1.8)
35 years	390/1476	1.8 (1.3–2.4)	1.6 (0.9–2.9)	1.6 (1.0–2.5)	2.3 (1.4–3.9)
Pre-pregnancy maternal body mass index					
Underweight [<18.5 kg/m^2]	158/560	1.6 (1.1–2.4)	1.6 (0.8–3.0)	1.9 (1.2–3.3)	1.3 (0.7–2.4)
Normal [18.5–24.9 kg/m^2]	1266/5646	1.6 (1.4–1.9)	1.6 (1.2–2.0)	1.5 (1.2–1.9)	1.9 (1.5–2.4)
Overweight or Obese [25 kg/m^2]	1108/4268	1.3 (1.1–1.6)	1.3 (1.0–1.8)	1.3 (1.1–1.7)	1.3 (1.0–1.7)

[a] Aggregated septal defects were all perimembranous ventricular septal defects, ventricular septal defects not otherwise specified, secundum atrial septal defects, and atrial septal defects not otherwise specified.

aOR = adjusted odds ratio, AVSD = atrioventricular septal defect, CI = confidence interval