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Maternal Smoking, Passive Tobacco Smoke, and Neural Tube Defects

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Abstract

BACKGROUND—Although cigarette smoke is a well-established toxin and harmful to the developing embryo, the evidence for an independent effect on the occurrence of neural tube defects (NTDs) is mixed. In this study, we examined the relation between NTDs and maternal exposures to cigarette smoke, including passive smoke exposure.

METHODS—We used cases and controls from the large, multistate, population-based National Birth Defects Prevention Study. A total of 1041 NTD cases and 5862 live birth controls, delivered during 1997 to 2004, were available for analyses. Mothers were interviewed by telephone between 6 weeks and 24 months after delivery. Participation rates were 71% for NTD case mothers and 69% for control mothers.

RESULTS—Compared with nonsmokers (and also not exposed to passive cigarette smoke), mothers exposed only to passive smoke had an increased NTD odds ratio (OR, 1.7; 95% confidence interval [CI], 1.4–2.0), adjusted for race–ethnicity, and study center. There was no increased OR for mothers who actively smoked 24 or fewer cigarettes per day. Mothers who smoked 25 or more cigarettes per day had an elevated OR (OR, 1.6; 95% CI, 0.9–3.0), but the OR adjusted for race–ethnicity, and center was compatible with the null.

CONCLUSION—Results suggest that maternal exposure to passive smoke is associated with NTDs. Women who plan on becoming pregnant should minimize their exposure to passive smoke and refrain from smoking.

Keywords

neural tube defects; cigarette smoke; passive cigarette smoke

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INTRODUCTION

Although cigarette smoke is a well-established toxin and is harmful to developing embryos, the evidence for an independent effect on the occurrence of neural tube defects (NTDs) is mixed. Many studies have not demonstrated an increased risk of NTDs (including spina bifida, anencephaly, and the broader category of central nervous system malformations) in the offspring of mothers who smoked cigarettes during pregnancy (Christianson, 1980; Shiono et al., 1986; Malloy et al., 1989; Shaw et al., 1996, 2009; Van den Eeden et al., 1990; Wasserman et al., 1996; Kallen, 1998; Grewal et al., 2008). However, other studies have shown that mothers who smoked cigarettes during the periconceptional period or early pregnancy had slightly elevated risks of NTDs or central nervous system malformations in offspring (Kelsey et al., 1978; Ericson et al., 1979; Evans et al., 1979; Hemminki et al., 1983; Seidman et al., 1990; McDonald et al., 1992). Reported exposure odds ratios (OR) from these case-control studies ranged from 1.3 to 1.8 for amounts of cigarette smoking that varied from any daily amount to more than 20 cigarettes per day. Only one of these studies was sufficiently large to demonstrate a statistically significant effect (relative risk = 1.8 for heavy smoking) of active smoking on NTDs (Evans et al., 1979). A shortcoming of these past studies was the inclusion of mothers who had passive exposure to cigarette smoke in the nonsmoking group; this misclassification among the referent group might have obscured or attenuated the risks of mothers who smoked.

Two recent studies have accounted for and reported increased and independent NTD risk associated with passive smoke exposure (Li et al., 2008; Suarez et al., 2008). In the Shanxi province of China, using 515 case and 682 controls, investigators reported a near doubling of risk in offspring among mothers exposed to passive smoke (OR, 1.84; 95% confidence interval [CI], 1.39–2.44) compared with those that were not exposed (Li et al., 2008). Risk estimates for active cigarette smoking were not reported in the Chinese study, because such behavior is rare among Chinese mothers (<2%; Li et al., 2006). Among Mexican American women living on the Texas–Mexico border, nonsmoking mothers exposed to passive smoke during the first trimester had an OR of 2.6 (95% CI, 1.6–4.0) for delivery of a child with an NTD (Suarez et al., 2008). Reported ORs for mothers who smoked were 2.2 for <10 cigarettes per day and 3.4 for 10 or more cigarettes per day. An earlier study by Wasserman et al. (1996) showed a weak and nonsignificant elevation in NTD risk for nonsmoking mothers exposed to passive smoke (OR, 1.2). Given the suggestive findings for passive smoke exposure, it is important that in all studies of smoking, the referent group be individuals who neither actively smoked nor were exposed to passive smoke.

We report on a national study examining the relation between maternal exposures to cigarette smoke and the occurrence of NTDs in offspring. Effects of active cigarette smoking were estimated separately from those of passive smoke. We used cases and controls from the large, multistate, population-based National Birth Defects Prevention Study (NBDPS), which provided us with the largest number of NTD cases of any study to date.

MATERIALS AND METHODS

Data Source and Collection

The NBDPS is an ongoing, population-based, case-control project designed to identify environmental and genetic factors associated with more than 30 different major birth defects. Detailed methods of the NBDPS were previously published (Yoon et al., 2001; Cogswell et al., 2009). The NBDPS is composed of ten Centers for Birth Defects Research and Prevention, located in Arkansas, California, Atlanta (at the Centers for Disease Control and Prevention [CDC]), Iowa, Massachusetts, North Carolina, New Jersey, New York, Texas, and Utah. The study methods and protocols were approved by the institutional review boards of each participating center and the CDC.

The NBDPS includes birth defects cases, which are live births or stillborn deliveries of >20 weeks' gestation or 500 gm, or prenatally diagnosed and terminated fetuses of any gestational age or weight. These cases are identified from the surveillance system in each participating center. Cases with single-gene or chromosome disorders are excluded from the NBDPS. In addition to individual centers' clinical reviews of the diagnostic information to determine eligibility, the cases were reviewed further and classified by selected clinical geneticists. For this study, NTD cases included mothers of infants with anencephaly (including craniorachischisis), spina bifida, and encephalocele. Anencephaly cases that co-occurred with spina bifida or encephalocele were included only in the anencephaly category. Controls were randomly selected from live birth certificates (IA, MA, NC, NJ, and UT) or birth hospitals (CA, NY, and TX). Georgia and Arkansas randomly selected controls by hospital at the start of the study and switched to selection from birth certificates in 2000. A randomly selected control was ineligible for inclusion if the infant had a major birth defect, was not a resident of the participating center's surveillance catchment area, was adopted, was in foster care, had a deceased mother, or had a mother who spoke neither Spanish nor English.

Interview data were gathered from participating centers using standardized 1-hour questionnaires. Mothers of cases and controls were contacted, consented, and interviewed in English or Spanish by telephone. The interviews were conducted between 6 weeks and 24 months after the estimated date of delivery. We included NBDPS data on deliveries from October 1997 to December 2004. Study participation rates were 71% for NTD case mothers and 69% for controls.

Initially, mothers were asked whether they smoked cigarettes at any time during the 3 months prior to pregnancy to the delivery date. If a mother responded yes, information on active cigarette smoking was collected monthly for the 3 months before conception and the first 3 months of pregnancy and by trimester for the remainder of pregnancy. Reported numbers of cigarette smoked in each time period were categorized as: fewer than 1, 1, 2 to 4, 5 to 14, 15 to 24, 25 to 34, and 35 or more per day. Mothers were also queried about their exposure to passive smoke at their home, work place, or school (Did anyone in your household smoke cigarettes in your home between 3 months before conception (B3) and Date of Index Birth (DOIB)? Did anyone smoke cigarettes near you at workplace or school you may have attended during that year?). They were also asked "during which months did

someone smoke in your home” and “during which months did someone smoke near you at work/school?” Information on the amount of passive smoke exposure was not collected.

Data Analysis

To estimate risks associated with cigarette smoking, we focused on the period from 1 month before to 1 month after conception, because this window of recalled cigarette smoking would be relevant to the formation of the NTD. An analysis of the distribution of cases and controls showed that active smoking levels were virtually the same between this period and the prior two-month period. Within the two-month period, cigarette smoking in either month was considered as exposure. This defined window of exposure was the same for passive smoke exposure. For analyses of active smoking, we grouped response categories of cigarettes smoked into three levels: light (<15 cigarettes per day), moderate (15–24 cigarettes per day), and heavy (≥ 25 cigarettes per day). We derived these categories based on narrower contiguous categories that had similarly sized odds ratios, precision considerations, and a prior NBDPS study (Honein et al., 2007). For passive smoke exposures, we combined exposures at home, work, and school, because the ORs for each source of exposure were of similar magnitude, and one fifth of study women reported exposures at both. To examine the effects of active and passive smoke exposure, we categorized women as (1) nonsmokers not exposed to passive smoke (the referent group); (2) nonsmokers exposed to passive smoke; and (3) active cigarette smokers, regardless of exposure to passive smoke.

Using logistic regression, we calculated ORs and 95% CIs for categories of cigarette smoke exposure. We calculated ORs separately for spina bifida and anencephaly; however, because the ORs for these NTD subtypes were similar, we tabulated results only for NTDs combined. We examined effect modification by calculating ORs for cigarette smoke exposures stratified by race–ethnicity and study site (center).

We screened for confounding from variables examined in previous studies (Shaw et al., 1996; Suarez et al., 2008; Shaw et al., 2009). These variables included maternal age, race–ethnicity, education, use of supplements containing folic acid (1 month before or after conception), intake of dietary folate equivalents, body mass index, and study center. Intake of dietary folate equivalents was measured through a food frequency questionnaire and based on the year preceding conception. Dietary folate equivalents were calculated by multiplying the amount of synthetic folic acid in fortified foods by 1.7 and then adding the amount of natural folate in foods. Body mass index was calculated by dividing self-reported maternal weight before pregnancy (kilograms) by maternal height² (meters²). We used logistic regression models to identify confounders by comparing ORs for maternal smoking exposure categories (active and passive) from a model consisting of all potential confounding variables to the ORs of a model in which the confounder of interest had been removed. This comparison was repeated for each potential confounding variable. We included the variable in the final model, as a confounder, when the ORs of the two models differed by 10% or more at any level of exposure. For all ORs we used nonsmokers (exposed to neither active nor passive smoke) as the referent group. The final model for the association between active and passive cigarette smoke exposure and NTDs was adjusted for

maternal race–ethnicity and study center. We tested differences in maternal characteristics between cases and controls using the chi-square test.

RESULTS

For this study, we had 1041 of 1055 case and 5862 of 5958 control mothers with complete information on active and passive cigarette smoke exposures, race–ethnicity, and center. More than half of case and control mothers were non-Hispanic white (52% of cases and 60% of controls), and Hispanic mothers were a larger proportion of cases than controls (32 vs 23%; $p < 0.05$) (Table 1). Fewer case mothers (49%) than control mothers (58%) completed 12 years of schooling ($p < 0.05$). A slightly smaller proportion of case mothers than controls smoked during 1 month before to 1 month after conception (17 vs. 19%; $p = 0.07$). More case mothers were exposed to passive cigarette smoke than were control mothers (21% vs 14%; $p < 0.05$).

Table 2 shows the association between cigarette smoke exposure and the occurrence of NTDs. Compared with nonsmokers who were not exposed to passive cigarette smoke around the time of conception, mothers who smoked 24 or fewer cigarettes per day did not show an increased OR. An elevated OR (1.6; 95% CI, 0.9–3.0) was observed for mothers who smoked 25 or more cigarettes per day, but the OR, adjusted for race–ethnicity and center was compatible with the null. Mothers exposed only to passive smoke had an increased NTD OR (1.7; 95% CI, 1.4–2.0). Adjustment for race–ethnicity and center did not materially affect the initial crude ORs (Table 2).

There was no marked difference in estimated ORs for passive smoking between spina bifida (OR, 1.5; 95% CI, 1.2–1.9) and anencephaly (OR, 1.7; 95% CI, 1.3–2.3) birth outcomes. ORs for passive smoke were similar for whites (OR, 1.6; 95% CI, 1.2–2.0), Hispanics (OR, 1.8; 95% CI, 1.3–2.4), and blacks (OR, 1.6; 95% CI, 1.0–2.5). When examining ORs by center, we found that passive smoking risk estimates were largest for Utah (OR, 3.0; 95% CI, 1.0–9.2), North Carolina (OR, 2.9; 95% CI, 1.4–6.3), Texas (OR, 2.2; 95% CI, 1.5–3.4), New York (OR, 2.2; 95% CI, 1.1–4.3), New Jersey (OR, 2.0; 95% CI, 1.1–3.5), and Iowa (OR, 1.8; 95% CI, 1.1–3.0). The effect was not as evident for Georgia (OR, 1.4; 95% CI, 0.8–2.3), Massachusetts (OR, 1.3; 95% CI, 0.6–2.9), California (OR, 1.3; 95% CI, 0.8–2.1), and Arkansas (OR, 1.0; 95% CI, 0.6–1.7). A statistical test for heterogeneity among center ORs was not statistically significant ($p = 0.21$). The number of mothers who smoked 25 or more cigarettes per day was too sparse across race–ethnicity categories and centers to fully examine effect modification.

DISCUSSION

Consistent with two other studies that reported an approximate doubling of risk (1.8 and 2.6; Li et al., 2006; Suarez et al., 2008), we observed an increased NTD OR for nonsmoking mothers exposed to passive smoke (OR, 1.7; 95% CI, 1.4–2.0) compared with those not exposed. Contradicting this finding was the result of no association between a moderate amount of maternal cigarette smoking (15–24 cigarettes per day) and the occurrence of NTDs in offspring. Mothers who smoked more than this amount (25 or more cigarettes)

during the periconceptional period had a modest OR (1.6; 95% CI, 0.9–3.0), which was indistinguishable from the null. For the results on passive and active smoking to be congruent, nonsmoking mothers would have to have been exposed to levels of passive smoke higher than 25 cigarettes per day. Risk effect estimates of active smoking from other studies at similar levels (20 or more cigarettes per day) ranged from no effect (Christianson, 1980; Shaw et al., 1996; Wasserman et al., 1996) to some effect (1.4–1.8; Kelsey et al., 1978; Evans et al., 1979; McDonald et al., 1992).

This study was based on a large population-based series of NTD cases, thoroughly reviewed and classified by qualified clinical geneticists. Participation of eligible subjects was relatively good and comparable between case and control mothers (71 vs. 69%). The controls were generally representative of unaffected births in the United States regarding attributes such as maternal age and maternal smoking during pregnancy (Cogswell et al., 2009). The proportion of control mothers who had smoked during pregnancy was similar to the proportion in the source populations (9.9 vs. 9.5%; Cogswell et al., 2009). However, the prevalence of cigarette smoking around the time of conception among controls in this study (19%) was slightly lower than national estimates of current cigarette smoking among similarly aged women during the same period (22%).

The fact that estimated ORs for passive smoking were higher than for active cigarette smoking prompts a consideration of recall bias or other types of bias. The recall of cigarette smoking exposures by mothers interviewed between 6 weeks and 24 months after the estimated date of delivery is subject to error, hopefully to the same extent as in case and control mothers. This type of misclassification would have attenuated ORs estimated for active cigarette smoking. It is also possible that case and control mothers may differentially report passive smoking exposures due to socioeconomic attitudes towards smoking or other factors. If for example, case mothers tended to overreport exposure to passive smoking, the ORs would be inflated. We believe that it is more likely that passive smoke exposure was nondifferentially misclassified. Recent studies show that women underestimate their level of exposure to environmental smoke when compared with cotinine levels (DeLorenze et al., 2002; George et al., 2006b). Examination of the passive smoking information shows that ORs for work (1.5), home (1.7), and both sources of exposure (2.0) are in line with what can be surmised about intensity (work vs. home) and duration (both home and work). The results for heavy active smoking were limited because of the low number of women who smoked 25 cigarettes or more a day; the majority (70%) of smokers in our study were light smokers. Finally, if the effect of active cigarette smoking exposures is on an early loss of fetuses with NTDs, this would have limited our ability to observe it. A recent study has shown that active smoking and passive exposure to cigarette smoke increases the risk of spontaneous abortion (George et al., 2006a). By protocol, the NBDPS excludes fetal deaths at <20 weeks' gestation.

One mechanism by which exposure to cigarette smoke could increase NTD risk in offspring is through elevated serum homocysteine, which has been linked with NTD-affected pregnancies (Steeegers-Theunissen et al., 1994; Mills et al., 1995; Zhao et al., 2006; Gaber et al., 2007). Exposure to cigarette smoke has been associated with elevated homocysteine in both animal (Davis et al., 2004) and human studies (Ganji and Kafai, 2003; Chrysohoou et

al., 2004; Kim et al., 2010). It is possible that cigarette smoking is merely a confounder of poor diet (Trobs et al., 2002; Chrysohoou et al., 2004; Kim et al., 2010). However, high serum homocysteine levels have been linked with NTD-affected pregnancies, even when dietary intake is adequate as indicated by serum B₁₂, red blood cell, or serum folate levels (Felkner et al., 2009). Furthermore, homocysteine levels seem to be positively correlated with smoking exposure in nonsmokers, independent of nutrient levels (Kim et al., 2010).

In conclusion, results from this large, population-based, case-control study suggest that maternal exposure to passive smoke might be a risk factor for NTDs. Given the growing evidence of the deleterious effects of cigarette smoke on pregnancy outcomes, women who are planning to become pregnant should minimize exposure to passive smoke and refrain from smoking.

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References

- Christianson RE. The relationship between maternal smoking and the incidence of congenital anomalies. *Am J Epidemiol.* 1980; 112:684–695. [PubMed: 7435494]
- Chrysohoou C, Panagiotakos DB, Pitsavos C, et al. The associations between smoking, physical activity, dietary habits and plasma homocysteine levels in cardiovascular disease-free people: the ‘ATTICA’ study. *Vasc Med.* 2004; 9:117–123. [PubMed: 15521701]
- Cogswell ME, Bitsko RH, Anderka M, et al. Control selection and participation in an ongoing, population-based, case-control study of birth defects. *Am J Epidemiol.* 2009; 170:975–985. [PubMed: 19736223]
- Davis JA, Brown AT, Chen H, et al. Cigarette smoke increases intimal hyperplasia and homocysteine in a rat carotid endarterectomy. *J Surg Res.* 2004; 121:69–75. [PubMed: 15313378]
- DeLorenze GN, Kharrazi M, Kaufman FL, et al. Exposure to environmental tobacco smoke in pregnant women: the association between self-report and serum cotinine. *Environ Res.* 2002; 90:21–32. [PubMed: 12359187]
- Ericson A, Kallen B, Westerholm P. Cigarette smoking as an etiologic factor in cleft lip and palate. *Am J Obstet Gynecol.* 1979; 135:348–351. [PubMed: 484624]
- Evans DR, Newcombe RG, Campbell H. Maternal smoking habits and congenital malformations: a population study. *BMJ.* 1979; 2:171–173. [PubMed: 466337]
- Felkner M, Suarez L, Canfield MA, et al. Maternal serum homocysteine and risk for neural tube defects in a Texas-Mexico border population. *Birth Defects Res A Clin Mol Teratol.* 2009; 85:574–581. [PubMed: 19180649]
- Gaber KR, Farag MK, Soliman SE, et al. Maternal vitamin B12 and the risk of fetal neural tube defects in Egyptian patients. *Clin Lab.* 2007; 53:69–75. [PubMed: 17323828]
- Ganji V, Kafai MR. Demographic, health, lifestyle, and blood vitamin determinants of serum total homocysteine concentrations in the third National Health and Nutrition Examination Survey, 1988–1994. *Am J Clin Nutr.* 2003; 77:826–833. [PubMed: 12663279]
- George L, Granath F, Johansson AL, et al. Environmental tobacco smoke and risk of spontaneous abortion. *Epidemiology.* 2006a; 17:500–505. [PubMed: 16837826]

- George L, Granath F, Johansson ALV, et al. Self-reported nicotine exposure and plasma levels of cotinine in early and late pregnancy. *Acta Obstetrica et Gynecologica*. 2006b; 85:1331–1337.
- Grewal J, Carmichael SL, Ma C, et al. Maternal periconceptional smoking and alcohol consumption and risk for select congenital anomalies. *Birth Defects Res A Clin Mol Teratol*. 2008; 82:519–526. [PubMed: 18481814]
- Hemminki K, Mutanen P, Saloniemä I, et al. Smoking and the occurrence of congenital malformations and spontaneous abortions: multivariate analysis. *Am J Obstet Gynecol*. 1983; 145:61–66. [PubMed: 6849345]
- Honein MA, Rasmussen SA, Reefhuis J, et al. Maternal smoking and environmental tobacco smoke exposure and the risk of orofacial clefts. *Epidemiology*. 2007; 18:226–233. [PubMed: 17202867]
- Kallen K. Maternal smoking, body mass index, and neural tube defects. *Am J Epidemiol*. 1998; 147:1103–1111. [PubMed: 9645788]
- Kelsey JL, Dwyer T, Holford TR, et al. Maternal smoking and congenital malformations: an epidemiological study. *J Epidemiol Commun Health*. 1978; 32:102–107.
- Kim DB, Oh YS, Yoo KD, et al. Passive smoking in never-smokers is associated with increased plasma homocysteine levels. *Int Heart J*. 2010; 51:183–187. [PubMed: 20558908]
- Li Z, Ren A, Zhang L, et al. A population-based case-control study of risk factors for neural tube defects in four high-prevalence areas of Shanxi province, China. *Paediatr Perinat Epidemiol*. 2006; 20:43–53.
- Li ZW, Liu JM, Ren A, et al. Maternal passive smoking and the risk of neural tube defects: a case-control study in Shanxi province, China. *Zhonghua Liu Xing Bing Xue Za Zhi*. 2008; 29:417–420. [PubMed: 18956669]
- Malloy MH, Kleinman JC, Bakewell JM, et al. Maternal smoking during pregnancy: no association with congenital malformations in Missouri 1980–83. *Am J Public Health*. 1989; 79:1243–1246. [PubMed: 2764201]
- McDonald AD, Armstrong BG, Sloan M. Cigarette, alcohol, and coffee consumption and congenital defects. *Am J Public Health*. 1992; 82:91–93. [PubMed: 1536342]
- Mills JL, McPartlin JM, Kirke PN, et al. Homocysteine metabolism in pregnancies complicated by neural-tube defects. *Lancet*. 1995; 345:149–151. [PubMed: 7741859]
- Seidman DS, Ever-Hadani P, Gale R. Effect of maternal smoking and age on congenital anomalies. *Obstet Gynecol*. 1990; 76:1046–1050. [PubMed: 2234712]
- Shaw GM, Carmichael SL, Vollset SE, et al. Mid-pregnancy cotinine and risks of orofacial clefts and neural tube defects. *J Pediatr*. 2009; 154:17–19. [PubMed: 18990410]
- Shaw GM, Velie EM, Morland KB. Parental recreational drug use and risk for neural tube defects. *Am J Epidemiol*. 1996; 144:1155–1160. [PubMed: 8956628]
- Shiono PH, Klebanoff MA, Berendes HW. Congenital malformations and maternal smoking during pregnancy. *Teratology*. 1986; 34:65–71. [PubMed: 3764779]
- Stegers-Theunissen RP, Boers GH, Trijbels FJ, et al. Maternal hyperhomocysteinemia: a risk factor for neural-tube defects? *Metabolism*. 1994; 43:1475–1480. [PubMed: 7990699]
- Suarez L, Felkner M, Brender JD, et al. Maternal exposures to cigarette smoke, alcohol, and street drugs and neural tube defect occurrence in offspring. *Matern Child Health J*. 2008; 12:394–401. [PubMed: 17641961]
- Trobs M, Renner T, Scherer G, et al. Nutrition, antioxidants, and risk factor profile of nonsmokers, passive smokers and smokers of the Prevention Education Program (PEP) in Nuremberg, Germany. *Prev Med*. 2002; 34:600–607. [PubMed: 12052020]
- Van den Eeden SK, Karagas MR, Daling JR, et al. A case-control study of maternal smoking and congenital malformations. *Paediatr Perinat Epidemiol*. 1990; 4:147–155. [PubMed: 2362871]
- Wasserman CR, Shaw GM, O'Malley CD, et al. Parental cigarette smoking and risk for congenital anomalies of the heart, neural tube, or limb. *Teratology*. 1996; 53:261–267. [PubMed: 8864168]
- Yoon PW, Rasmussen SA, Lynberg MC, et al. The national birth defects prevention study. *Public Health Reports*. 2001; 116:32–40.

Zhao W, Mosley BS, Cleves MA, et al. Neural tube defects and maternal biomarkers of folate, homocysteine, and glutathione metabolism. *Birth Defects Res A Clin Mol Teratol.* 2006; 76:230–236. [PubMed: 16575882]

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Table 1

Maternal Characteristics among Neural Tube Defect Cases and Controls in the National Birth Defects Prevention Study, 1997–2004

	Cases (%), n = 1041	Controls (%), n = 5862
Race-ethnicity ¹		
Non-Hispanic white	544 (52.3)	3527 (60.2)
Non-Hispanic black	100 (9.6)	669 (11.4)
Hispanic	334 (32.1)	1322 (22.6)
Asian/Pacific Islanders	18 (1.7)	174 (3.0)
Others	45 (4.3)	170 (2.9)
Age at conception (years) ¹		
<20	154 (14.8)	823 (14.0)
20–24	230 (22.1)	1365 (23.3)
25–29	331 (31.8)	1571 (26.8)
30–34	203 (19.5)	1435 (24.5)
>35	123 (11.8)	668 (11.4)
Education (years) ^{1,2}		
<12	221 (21.2)	989 (16.9)
12	305 (29.3)	1462 (24.9)
>12	513 (49.3)	3396 (57.9)
Body mass index ^{1,3}		
Normal or underweight	546 (55.4)	3480 (61.8)
Overweight	216 (21.9)	1254 (22.3)
Obese	224 (22.7)	897 (15.9)
Smoked cigarettes ⁴		
Yes	172 (16.5)	1108 (18.9)
No	869 (83.5)	4754 (81.1)
Tobacco exposure ¹		
Smoked ⁵	172 (16.5)	1108 (18.9)
Passive smoke only	218 (20.9)	814 (13.9)
Not exposed ⁶	651 (62.5)	3940 (67.2)
Study Center ¹		
Arkansas	137 (13.2)	711 (12.1)
California	213 (20.5)	789 (13.5)
Georgia	122 (11.7)	620 (10.6)
Iowa	130 (12.5)	659 (11.2)
Massachusetts	64 (6.2)	743 (12.7)
North Carolina	47 (4.5)	286 (4.9)
New Jersey	70 (6.7)	576 (9.8)
New York	62 (6.0)	527 (9.0)
Texas	149 (14.3)	693 (11.8)

	Cases (%), n = 1041	Controls (%), n = 5862
Utah	47 (4.5)	258 (4.4)

¹Statistically significant differences in distribution between cases and controls at $p < 0.05$.

²Two case mothers and 15 control mothers had missing values for education.

³Fifty-five case women and 231 control women had missing values for body mass index.

⁴During 1 month before or after conception.

⁵Whether or not exposed to passive smoke.

⁶Nonsmokers who were not exposed to passive smoke.

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Table 2

Maternal Cigarette Smoking Exposures during the Periconceptional Period¹ and Odds Ratios of Neural Tube Defects, National Birth Defects Prevention Study, 1997–2004

	No. of cases	No. of controls	Crude ORs (95% CI)	Adjusted ² ORs (95% CI)
Nonsmokers ³	651	3940	1.0 (referent)	1.0 (referent)
Passive exposure only	218	814	1.6 (1.4–1.9)	1.7 (1.4–2.0)
Active cigarette smoking ⁴	172	1108	0.9 (0.7–1.0)	0.9 (0.8–1.1)
1–14 cigarettes/day	123	773	1.0 (0.8–1.2)	1.0 (0.8–1.3)
15–24 cigarettes/day	36	277	0.8 (0.6–1.1)	0.9 (0.6–1.3)
25 cigarettes/day	13	58	1.4 (0.7–2.5)	1.6 (0.9–3.0)

¹The period from one month before to one month after conception.

²Odds ratios were adjusted for race-ethnicity and center.

³Nonsmokers who were not exposed to passive smoke.

⁴Active cigarette smokers whether or not exposed to passive smoke.

OR, odd ratio; CI, confidence interval.

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