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Associations between maternal reports of periconceptional fever from miscellaneous causes and structural birth defects

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Abstract

Background: Associations between birth defects and fevers attributed to colds, influenza, and urinary tract infections (UTIs) have been observed in previous studies. Our aim was to study associations between birth defects and fevers attributed to other causes.

Methods: We analyzed data from 34,862 participants in the National Birth Defects Prevention Study, a multistate case–control study of major structural birth defects. Using multivariable logistic regression, we assessed the association between maternal report of fever during early pregnancy due to causes other than colds, influenza, or UTI and 36 categories of birth defects.

Results: Maternal reports of fever due to other causes were associated with significantly elevated odds ratios ranging from 1.93 to 10.60 for 8 of 36 birth defects, primarily involving the spine,

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

limbs, and heart (spina bifida, intestinal atresia, intercalary limb deficiency, transverse limb deficiency, congenital heart defect with heterotaxy, tetralogy of Fallot, pulmonary atresia and atrial septal defect, not otherwise specified).

Conclusion: Our data suggests fever itself or other physiologic changes associated with many infections are associated with some birth defects. Women who are pregnant or planning to become pregnant may want to consider speaking with their healthcare provider about the best ways to avoid infections that may cause fever and for guidance on how to treat fevers during pregnancy.

Keywords

atrial septal defect; birth defects; congenital heart defect (CHD) with heterotaxy; fever; intercalary limb deficiency; spina bifida; tetralogy of Fallot; transverse limb deficiency; intestinal atresia; pregnancy; pregnant women; pulmonary atresia

1 | INTRODUCTION

Hyperthermia (an increase in body temperature regardless of cause) is an established teratogen in animal models (Cawdell-Smith, Upfold, Edwards, & Smith, 1992; Finnell, Moon, Abbott, Golden, & Chernoff, 1986) and data also support its potential as a teratogen in humans (Dreier, Andersen, & Berg-Beckhoff, 2014; Edwards, Shiota, Smith, & Walsh, 1995; Luteijn, Brown, & Dolk, 2014; Moretti, Benjamin, Fried, & Koren, 2005; Shi et al., 2014). In clinical practice, most episodes of hyperthermia are due to fevers, typically linked with an infection or inflammatory process. Previous epidemiological studies of birth defects have examined the combined exposure of any maternal fevers occurring during early pregnancy, as well as fevers that were specifically attributed to colds, influenza, and/or urinary tract infections (UTIs) (Botto, Lynberg, & Erickson, 2001; Botto et al., 2014; Cleves, Malik, Tonia, & Carter, 2008; Hashmi et al., 2010; MacMahon & Yen, 1971; Paput, Czeizel, & Bánhidy, 2011; Waller et al., 2018). However, fever due to reasons other than colds, influenza, and UTIs may also be associated with birth defects. The National Birth Defects Prevention Study (NBDPS) asked mothers whether they experienced any fevers during their pregnancy that were not related to colds, influenza or UTIs. The aim of this analysis was to assess the association between maternal fever due to these miscellaneous causes and 36 categories of birth defects.

2 | MATERIALS AND METHODS

The NBDPS is a population-based, multistate, case–control study of risk factors for nonsyndromic structural malformations. It included clinical review of cases to establish study eligibility and to accurately classify birth defects, a maternal telephone interview and collection of buccal swabs for genetic studies. The study methods have been published in detail previously (Rasmussen et al., 2003; Reefhuis et al., 2015). The estimated dates of delivery for the cases and controls were between October 1, 1997 and December 31, 2011. Cases were identified from birth defects surveillance programs at 10 sites (located in all or part of Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, and Utah). Controls were live born infants without major birth defects,

selected from birth certificates or birth hospital logs to be representative of the population from which the cases were drawn.

Cases included live births, fetal deaths (≥20 weeks gestation), and pregnancy terminations (any gestational age). They were diagnosed by physical examination, imaging, autopsy, or pathology reports from surgical procedures. Clinical geneticists affiliated with the NBDPS aggregated the case infants across study sites and reviewed them according to established guidelines, classifying them as having isolated, multiple, or complex birth defects (Rasmussen et al., 2003; Reefhuis et al., 2015). Isolated birth defects were defined as cases having only one major birth defect, two or more major birth defects affecting only one organ system, or one major birth defect with a sequence of related defects (Rasmussen et al., 2003; Reefhuis et al., 2015). Cases with multiple birth defects had two or more major unrelated defects in different organ systems. Birth defects that were strongly suspected or known to have been caused by single-gene disorders or chromosomal abnormalities were excluded from the NBDPS.

For certain birth defects, it was necessary to adjust the number of controls used in our analyses, so that the controls would reflect the population from which the cases were ascertained. For hypospadias, a male-restricted birth defect, controls were restricted to pregnancies with male infants. For oral clefts, controls born in Utah before July 1, 2004 were excluded because Utah only ascertained cases of orofacial clefts on or after this date. For pulmonary valve stenosis, controls born in California before 2002 were excluded because California only ascertained cases of pulmonary valve stenosis beginning in 2002. For simple muscular ventricular septal defects, all controls born after 1999 were excluded, because the NBDPS only ascertained cases of simple muscular ventricular septal defects between 1998 and 1999.

2.1 | Exposure assessment

Maternal interviews were conducted using a standardized computer-assisted telephone interview, in either English or Spanish, between 6 weeks and 24 months after the estimated date of delivery. Interviews were completed an average of 11 months after the estimated date of delivery for case mothers and 9 months for control mothers. Participation rates were 67% for controls and 64% for cases.

A standard sequence of interview questions was used to obtain maternal histories of all maternal fevers in the 3 months before conception and during pregnancy. Mothers were first asked whether they had a fever from a “cold or flu,” and then asked whether they had a fever from a UTI or pelvic inflammatory disease (PID). Finally, they were asked whether they had “any fever not previously mentioned.” If they answered yes to this question, they were asked to report the cause of the fever, the months during which it occurred, and its duration.

We defined fever due to miscellaneous causes as maternal report of fever that the mother attributed to a cause other than having colds, influenza, UTIs, or PID. We included only those fevers reported to have occurred between 1 month before conception and 3 months after conception, the critical time period for causation of most birth defects. The unexposed

group was comprised of mothers who did not report a fever from any cause during this time period.

2.2 | Statistical analysis

The following participants were excluded from our analyses: (a) NBDPS cases where fewer than three mothers reported exposure to a miscellaneous fever during the critical period, (b) all case and control mothers who reported a fever from colds, influenza, UTIs, or PID during the critical time period, (c) mothers with missing information on fever due to miscellaneous causes or missing information for one or more of the covariates in the final model, and (d) case and control mothers with pre-existing Type I or Type II diabetes mellitus. This last category was excluded because prepregnancy diabetes is a strong risk factor for many categories of birth defects (Tinker et al., 2020).

Using unconditional logistic regression, we computed adjusted odds ratios (aOR) and 95% confidence intervals (CIs) for the association between maternal report of miscellaneous fever and 36 categories of NBDPS birth defects (21 noncardiac and 15 cardiac).

Initially, we identified the following nine a priori covariates as potential confounders for this analysis: maternal age (<18, 19–24, 25–29, 30–34, 35–39, and ≥40 years), maternal race and ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, and other race or ethnicity), maternal level of educational attainment (less than high school [≤11 years], completed high school [12 years], some college [13–15 years], and completed college degree [≥16 years]), maternal prepregnancy body mass index (BMI; <18.5, 18.5–24.9, 25.0–29.9, and ≥30.0 kg/m^2), any maternal cigarette smoking between 1 month before conception and 2 months after conception (yes, no), first live birth (yes, no), timing and frequency of maternal use of supplements containing folic acid (optimal use: intake daily from 1 month before conception to 1 month after conception; less than optimal use: any intake less than daily during the same period; inadequate use: intake beginning later than 1 month after conception or no intake), language of interview (English or Spanish/other), and study site (Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, or Utah).

Maternal prepregnancy BMI had a large number of missing values (4.6%) compared to the other covariates in our models. Although it is known to be a modest risk factor for many NBDPS birth defects (Waller et al., 2007), dropping it from our regression models had a negligible effect on the aOR estimates. Therefore, it was removed from our final models.

We undertook two sensitivity analyses in which we implemented a single change and recalculated all aORs. For the first sensitivity analysis, our sample was restricted to isolated cases (0–93.0% of cases, depending on the birth defect). By excluding cases in which more than one type of birth defect was present we were able to assess whether associations between fever and specific birth defects were independent of the presence of other birth defects. In the second sensitivity analysis, we restricted the exposure group to mothers who reported a fever with duration of 24 hr or more during the critical period (85.7% of all exposed case and control mothers). This was done to evaluate whether fever with a duration

of 24 hr or more might result in a stronger association with birth defects compared with fever of any duration.

This study was approved by the Institutional Review Boards of each study site and the Centers for Disease Control and Prevention. All analyses were completed in SAS 9.4 (SAS Institute, Inc.).

3 | RESULTS

A total of 44,029 mothers and their infants participated in NBDPS. Initially, 3,599 cases were excluded because they belonged to categories of birth defects that included fewer than three infants whose mothers were exposed to a miscellaneous fever during the critical period, leaving 40,430 mother-infant dyads. Subsequently, we excluded 4,348 dyads because they had fever from colds or influenza, UTIs or PID during the critical period (9.2%) or they had prepregnancy diabetes (1.5%), leaving 36,082 study participants. Finally, we excluded an additional 1,220 (3.4%) participants who had missing values; 1.1% were missing information on the question regarding fever from miscellaneous causes and 2.3% were missing information on one or more of the covariates in the final models. This left 34,862 mother and infant dyads in our final analysis (24,512 case mothers and 10,350 control mothers).

A total of 448 case and control mothers (1.3%) responded yes to the question on fever due to miscellaneous causes. They reported the following causes of miscellaneous fevers during the critical period: pneumonia, bronchitis or pleurisy (19.2%), strep throat (10.0%), sinus infection (7.9%), noninfectious causes (5.6%), stomach infection (4.0%), viral infection not otherwise specified (2.9%), ear infection (2.7%), other specified infections (18.5%), and “fevers of unknown origin” or unknown cause (29.2%).

Case and control mothers were similar with respect to the frequency of their use of supplements containing folic acid and the language of the interview (Table 1). Compared to control mothers, case mothers were slightly more likely to be 40 years of age or more, smokers, or having their first live birth. Case mothers were slightly less likely to be non-Hispanic Black women, college graduates, or from Iowa, New York, North Carolina or Texas (Table 1).

For noncardiac defects, we observed that 4 of 21 defects had significantly elevated odds for mothers reporting miscellaneous fever: spina bifida (aOR = 1.93, 95% CI = 1.18, 3.15), intestinal atresia/stenosis (aOR = 2.19, 95% CI = 1.05, 4.57), intercalary limb deficiency (aOR = 10.60, 95% CI = 3.96, 28.39), and transverse limb deficiency (aOR = 2.15, 95% CI = 1.17, 3.96; Table 2). All the other noncardiac birth defects had non-significant aORs, and all but one (longitudinal limb deficiency) had aORs that were greater than 1.0 (Table 2).

For cardiac birth defects, we observed that 4 out of 15 defects had significantly elevated ORs: congenital heart defect with heterotaxy (aOR = 3.54, 95% CI = 1.68, 7.46), tetralogy of Fallot (aOR = 2.04, 95% CI = 1.25, 3.32), pulmonary atresia (aOR 3.06, 95% CI = 1.32, 7.09), and atrial septal defect NOS (aOR = 2.44, 95% CI = 1.32, 4.54; Table 3). All other

cardiac birth defects examined had elevated aORs with 95% CI that included 1.0 (with the exception of simple muscular ventricular septal defect).

For each of the 36 birth defects in this study, we ran two sensitivity analyses resulting in 72 comparisons (Tables S1-S4). aORs were not calculated for eight of these comparisons because the number of exposed cases was less than three, leaving a total of 64 ORs in the sensitivity analyses.

The eight birth defects that were significantly associated with fever in the main analysis also had similarly elevated aORs when we conducted sensitivity analyses restricting the analyses to: (a) isolated birth defects and (b) fever with duration of 24 hr or more (Tables S1-S4). Some of the birth defects that were not significantly associated with fever in the main analysis became newly elevated and significant in one or both of the sensitivity analyses (see Tables S1-S4 for details).

4 | DISCUSSION

This study used data from the NBDPS, one of the largest population-based studies of birth defects, to assess associations between fever due to miscellaneous causes and 36 categories of birth defects. In contrast to this study, previous studies focused on maternal fever in general, or on maternal fevers due to specific causes, such as influenza, colds, or UTI (Botto et al., 2001; Botto et al., 2014; Cleves et al., 2008; Dreier et al., 2014; Hashmi et al., 2010; Moretti et al., 2005; Shi et al., 2014; Waller et al., 2018). Among the previous studies, Botto et al. (2014) analyzed NBDPS data from 1997 to 2005 for febrile illness due to any cause of fever (i.e., respiratory illnesses, PID, UTI, and other causes combined). However, Botto et al. did not conduct analyses restricted to miscellaneous or other fevers.

In our analyses, we restricted our exposure to mothers' reports of fever due to causes other than respiratory illness (cold or influenza), UTI or PID. The elevated aORs that we observed for eight birth defects suggest that the well-established association of maternal fever and birth defects is not restricted to fevers associated with colds, influenza, or UTI.

Studies in a variety of animal species have demonstrated that experimental hyperthermia during pregnancy can induce neural tube defects (NTDs), microcephaly, arthrogryposis, talipes, microphthalmia, abdominal wall defects, and limb deficiencies (Cawdell-Smith et al., 1992; Graham, 2005; Finnell et al., 1986). We observed associations between maternal fever and two birth defects (NTDs and limb reduction defects), which were associated with hyperthermia in animal studies. And, we observed no association between maternal fever and three birth defects that were associated with hyperthermia in animal studies; anophthalmos/microphthalmos and two types of abdominal wall defects (gastroschisis and omphalocele). As experimental studies expose pregnant animals to precise levels of hyperthermia, it is not surprising that they would detect stronger effects for some birth defects, compared to epidemiologic studies in which exposure to hyperthermia is based on maternal recall of fevers.

In experimental studies, exposure of mammalian embryos to hyperthermia has been shown to interrupt normal protein synthesis and generate heat shock proteins (Walsh et al., 1999).

Similar mechanisms may explain the associations that we have observed in the current study. It is also possible that all or part of the associations we have observed may be explained by physiologic changes other than fever that occur in many infections and may be harmful to the embryo, for example, elevated levels of interferons and cytokines (Yockey & Iwasaki, 2018).

The results of the current study are broadly consistent with previously reported associations between maternal report of fever during early pregnancy and offspring with noncardiac birth defects, primarily NTDs, and limb reduction defects (Abe, Honein, & Moore, 2003; Dreier et al., 2014; Moretti et al., 2005; Shaw et al., 2002; Waller et al., 2018). However, whereas previous studies assessed all limb reduction defects combined, we assessed three separate categories of limb defects, and observed elevated odds of intercalary limb deficiency and transverse limb deficiency and no association with longitudinal limb deficiency.

A previous NBDPS analysis of maternal fevers due to colds or influenza and noncardiac birth defects (Waller et al., 2018) reported significantly elevated aORs ranging from 1.23 to 1.52, for five relatively common noncardiac birth defects (anencephaly, spina bifida, cleft lip with or without cleft palate, all limb reduction defects, and gastroschisis). In the current study, we observed similar results for four of these five birth defects, that is, we found significantly elevated aORs for spina bifida and two types of limb defects and aORs for anencephaly and gastroschisis that are similar in magnitude to those reported by Waller et al., but not statistically significant.

We observed a significant association between maternal fever and intestinal atresia which Waller et al. did not observe (Waller et al., 2018). As this association has not been reported previously, it should be interpreted cautiously. Also, Waller et al. reported a significant association between maternal fever and cleft lip with or without cleft palate that we did not observe and they reported elevated aORs for three birth defects (encephalocele, colonic atresia/stenosis, and bilateral renal agenesis/hypoplasia) that were not included in the current study due to insufficient power (Waller et al., 2018).

Because the classification of cardiac defects has evolved over time, categories of cardiac defects are not always comparable across studies. Previous studies reported significantly elevated ORs (ranging from 1.71 to 7.54) for the association between any maternal fever and seven categories of cardiac defects that are similar to the categories included in this study: heterotaxy (Botto et al., 2014), hypoplastic left heart syndrome (Tikkanen & Heinonen, 1991), aortic stenosis (Botto et al., 2001; Botto et al., 2014), aortic coarctation (Botto et al., 2001), tricuspid atresia (Oster, Riehle-Colarusso, Alverson, & Correa, 2011), atrial septal defect (Tikkanen & Heinonen, 1991), and ventricular septal defect (Botto et al., 2001). In comparison, we observed elevated aORs that were significant or borderline significant for four of the seven cardiac birth defects that were associated with fever in the previous studies: congenital heart defect with heterotaxy, hypoplastic left heart syndrome, perimembranous ventricular septal defect (the largest NBDPS category for ventricular septal defect) and atrial septal defect, not otherwise specified. We also observed elevated aORs that were greater than 1.80, but not statistically significant, for two of the seven cardiac births that were linked to fever in previous studies, aortic stenosis and tricuspid atresia. And, we observed

significantly elevated aORs for two categories of cardiac defects that were not reported by previous studies, tetralogy of Fallot and pulmonary atresia.

In a prospective study of the associations between maternal fever and birth defects, no significant association between maternal fever and congenital heart defects was observed (Sass et al., 2017). However, because they only assessed a single category for all congenital heart defects, they may have failed to detect elevated aORs for specific phenotypes of congenital heart defects that were associated with maternal fever in the case control studies.

The magnitude of a fever varies by the time of day and the site of measurement (forehead, mouth, ear, axilla, or rectum; Mackowiak, Chervenak, & Grünebaum, 2021). A study by Hiller et al. reported that among 195 parents (165 mothers and 30 fathers), 72.2% reported using a number below 100.4 °F as the cutoff to determine if their child had a fever and 25.8% reported that the cutoff they used was a number below 100.0 °F (Hiller, Caffery, & Begue, 2019). Also, although, the NBDPS questionnaire asked mothers who had a fever to give their maximum temperature, we did not use this question because 38.4% of mothers did not answer it. Due to the issues described above, misclassification of maternal fever is likely to have occurred in this study and previous studies that assessed fever based on maternal interviews.

Because exposures in the NBDPS and other case control studies were based on maternal report after delivery, recall bias is a possibility, that is, mothers of infants with birth defects may be more likely to recall having had a fever compared with mothers of controls. However, in order for this to account for the results in this study, mothers of cases must be aware that maternal fever is a risk factor for birth defects. In an analysis of NBDPS mothers, Case et al. (2014) studied responses to a final question on the interview (What do you think causes birth defects?). The most common responses given by study participants were: illicit drugs (15% of all responses), alcohol (14%), smoking/tobacco (9%) and genetics/heredity (6%; Case et al., 2014). Only 2% of the study participants mentioned fever as a possible cause. Additional evidence against the presence of differential recall of maternal fever is provided by a meta-analysis that examined the association between maternal fever during early pregnancy and offspring affected by NTDs. This study observed summary ORs for nine case–control studies (OR = 1.93) to be similar to the summary ORs for six prospective cohort studies (OR = 1.95; Moretti et al., 2005). As differential recall of exposures is not possible in prospective cohort studies, the similarity of these results argues against differential recall of maternal fever. Thus, we believe it is likely that the misclassification of fever in this study was similar in cases and controls, that is, nondifferential. If so, then in the current study, misclassification of fever would most likely have biased the aORs toward the null and the true associations between fever and certain birth defects may be greater than those observed in this study.

Besides the potential for misclassification of fever, this analysis has several other possible limitations. Similar to other modern case control studies, NBDPS interview participation rates were low. However, a comparison of participating NBDPS controls and the birth certificates for the geographic areas from which the controls were sampled, concluded that control mothers who opted to participate in the NBDPS are generally representative of their

base populations (Cogswell et al., 2009). Another potential limitation to our study were small sample sizes which limit the precision of our results for some birth defects and limits our ability to compare our results for specific birth defects with results for the same birth defect in other studies.

Use of antipyretics or antibacterial medications may act in a confounding or moderating role in the associations we observed. However, due to limited sample size and imprecision in timing of medication use, exploration of these factors was beyond the scope of the current analysis.

We also conducted multiple statistical tests. Assuming the null hypothesis, that maternal report of miscellaneous fever during early pregnancy is not associated with any of the 36 birth defects that we studied, by chance alone, we would expect to observe approximately 1 birth defect with a significantly elevated OR ($36 \times 0.05 \times 0.5 = 0.90$). In contrast, 8 of the 36 birth defects that we studied had aORs that were significantly elevated, suggesting that all of the significant aORs observed in this study are unlikely to be due to chance. However, it remains possible that one or more of the elevated aORs that we observed may be due to chance.

In conclusion, we addressed a gap in the previous research on the association between maternal fevers due to miscellaneous causes and birth defects. The associations that we observed may be due to direct effects of fever or other physiologic changes that occur in most infections. Pregnant women and women planning to become pregnant can employ hand washing, social distancing, and recommended vaccinations, to protect themselves from developing infections and resulting fevers. Women who are pregnant or planning to become pregnant may want to consider speaking with their healthcare provider about the best ways to avoid infections that may cause fever and for guidance on how to treat fevers during pregnancy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from CDC. Restrictions apply to the availability of these data, which were used under license for this study. Data are available from CDC provided the NBDPS data sharing committee has approved a proposal for their use.

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TABLE 1

Characteristics of study participants, National Birth Defects Prevention Study (NBDPS), 1997–2011

	Cases (*N* = 24,512)		Controls (*N* = 10,350)			
	Number	**Percent**	**Number**	**Percent**	**OR**	**95% CI**
Maternal age at birth (years)						
≤18	815	3.3	334	3.2	0.99	0.86, 1.13
19–24	7,460	30.4	3,020	29.2	1.00	referent
25–34	12,517	51.2	5,537	53.5	0.92	0.87, 0.97
35–39	2,994	12.2	1,213	11.7	1.00	0.92, 1.08
≥40	726	2.9	246	2.4	**1.20**	**1.03, 1.39**
Mother's race/ethnicity						
Non-Hispanic White	14,626	59.7	5,997	57.9	1.00	referent
Non-Hispanic Black	2,396	9.8	1,161	11.3	**0.85**	**0.78, 0.91**
Hispanic	5,839	23.8	2,516	24.3	0.95	0.90, 1.01
Other	1,651	6.7	676	6.5	1.00	0.91, 1.10
Mothers education (years)						
Less than high school (≤11)	4,252	17.4	1,727	16.7	0.97	0.90, 1.04
Completed high school (12)	6,270	25.6	2,461	23.8	1.00	referent
Some college (13–15)	6,653	27.1	2,752	26.6	0.95	0.89, 1.01
Completed college degree (≥16)	7,337	29.9	3,410	32.9	**0.85**	**0.79, 0.90**
Maternal smoking[a]						
Yes	4,869	19.8	1,834	17.7	**1.15**	**1.08, 1.22**
No	19,643	80.2	8,516	82.3	1.00	referent
First birth						
Yes	10,648	43.4	4,170	40.3	**1.14**	**1.07, 1.19**
No	13,864	56.6	6,180	59.7	1.00	referent
Mother's use of multivitamins[b]						
Optimal use	6,469	26.4	2,806	27.2	1.00	referent
Suboptimal use	6,457	26.3	2,642	25.5	1.06	0.99, 1.13
Inadequate use	11,586	47.3	4,902	47.3	1.03	0.97, 1.08
Study site						

	Cases (*N* = 24,512)		Controls (*N* = 10,350)			
	Number	**Percent**	**Number**	**Percent**	**OR**	**95% CI**
Arkansas	3,307	13.5	1,304	12.6	1.03	0.94, 1.13
California	2,968	12.3	1,117	10.8	1.08	0.98, 1.19
Iowa	2,287	9.4	1,148	11.1	**0.81**	**0.73, 0.89**
Massachusetts	3,183	12.9	1,249	12.1	1.04	0.94, 1.14
New Jersey	1,303	5.3	517	5.0	1.03	0.91, 1.16
New York	1,649	6.7	869	8.4	**0.77**	**0.69, 0.86**
Texas	2,548	10.4	1,173	**11.3**	**0.88**	**0.80, 0.97**
Georgia	2,738	10.8	1,113	10.8	1.00	referent
North Carolina	1,885	7.7	882	8.5	**0.87**	**0.78, 0.97**
Utah	2,644	11.0	978	9.4	1.10	0.99, 1.22
Language of interview						
English	22,345	91.2	9,372	90.6	0.93	0.86, 1.01
Spanish/other language[c]	2,167	8.8	978	9.4	1.00	referent

Note: Bold values are statistically significant, $p < 0.05$.

Abbreviations: OR, crude odds ratio; CI, confidence interval.

[a]Smoking between 1 month before conception and 2 months after conception.

[b]Use of supplements containing folic acid; optimal (daily intake between 1 month before conception and 1 month after conception), less than optimal (any intake between 1 month before conception and 1 month after conception), and inadequate (intake of folic acid beginning later than 1 month after conception or never).

[c]Interviews conducted in Spanish and other languages.

TABLE 2

Adjusted[a] associations between maternal reports of periconceptional[b] fever from miscellaneous causes[c] and selected noncardiac birth defects, National Birth Defects Prevention Study, 1997–2011

	Unexposed	Exposed	aOR	95% CI
Anencephaly	551	9	1.65	0.82, 3.32
Spina bifida	1,072	20	**1.93**	**1.18, 3.15**
Hydrocephaly	437	6	1.31	0.57, 3.01
Anophthalmos/microphthalmos	204	3	1.62	0.50, 5.18
Anotia/microtia	600	6	1.30	0.56, 3.01
Choanal atresia	138	3	2.02	0.63, 6.53
Cleft palate alone[d]	1,377	22	1.59	0.99, 2.53
Cleft lip with or without cleft palate[d]	2,678	30	1.16	0.77, 1.75
Esophageal atresia/stenosis	663	8	1.20	0.58, 2.49
Intestinal atresia/stenosis	406	8	**2.19**	**1.05, 4.57**
Anorectal atresia/stenosis	922	14	1.57	0.89, 2.77
Biliary atresia/stenosis	171	4	2.57	0.93, 7.15
Hypospadias[e]	2,263	27	1.21	0.74, 2.00
Intercalary limb deficiency	43	5	**10.60**	**3.96, 28.39**
Longitudinal limb deficiency	393	3	0.80	0.25, 2.55
Transverse limb deficiency	610	12	**2.15**	**1.17, 3.96**
Craniosynostosis	1,421	16	1.12	0.66, 1.93
Diaphragmatic hernia	757	8	1.12	0.54, 2.32
Omphalocele	386	5	1.31	0.53, 3.28
Gastroschisis	1,196	16	1.44	0.81, 2.57
Amniotic band syndrome	287	5	1.91	0.76, 4.80
Controls	10, 249	101	referent	

Note: Bold values are statistically significant, $p < 0.05$.

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval.

[a]Odds ratio adjusted for maternal age, race, educational level, first birth, study site, smoking, language of interview, and folic acid intake.

[b]Period from 1 month before conception to 3 months after conception.

[c] Fever from miscellaneous cause was any fever that was reported to be due to causes other than colds, influenza, urinary tract infections or pelvic inflammatory disease.

[d] Utah only contributed to cases of orofacial clefts on or after July 1, 2004, so Utah controls for this analysis were restricted to those ascertained on or after July 1, 2004.

[e] Because all cases of hypospadias were male, for this analysis controls were restricted to male infants.

TABLE 3

Adjusted[a] associations between maternal reports of periconceptional[b] fever from miscellaneous causes[c] and selected cardiac birth defects, National Birth Defects Prevention Study, 1997–2011

	Unexposed	Exposed	aOR	95% CI
Congenital heart defect with heterotaxy	267	8	**3.54**	**1.68, 7.46**
Tetralogy of Fallot	1,041	20	**2.04**	**1.25, 3.32**
d-Transposition of the great arteries	669	10	1.49	0.77, 2.87
Ventricular septal defect, conoventricular	120	3	2.82	0.87, 9.15
Hypoplastic left heart syndrome	555	10	1.87	0.97, 3.63
Coarctation of the aorta	1,013	13	1.39	0.77, 2.50
Aortic stenosis	428	8	1.84	0.88, 3.84
Pulmonary atresia	228	6	**3.06**	**1.32, 7.09**
Pulmonary valve stenosis[d]	1,343	17	1.28	0.75, 2.17
Tricuspid atresia	146	3	2.77	0.86, 8.94
Ventricular septal defect, perimembranous	1,431	21	1.53	0.95, 2.48
Ventricular septal defect, muscular—simple[e]	141	3	0.88	0.23, 3.37
Ventricular septal defect, muscular—not simple	535	8	1.67	0.80, 3.49
Atrial septal defect, secundum	2057	24	1.21	0.76, 1.91
Atrial septal defect, not otherwise specified	536	13	**2.44**	**1.32, 4.54**
Controls	10,249	101	referent	

Note: Bold values are statistically significant, $p < 0.05$.

Abbreviations: aOR, adjusted odds ratio; CI, confidence interval.

[a] Odds ratio adjusted for maternal age, race, educational level, first birth, study site, smoking, language of interview, and folic acid intake.

[b] Period from 1 month before conception to 3 months after conception.

[c] Fever from miscellaneous cause was any fever that was reported to be due to causes other than colds, influenza, urinary tract infections, or pelvic inflammatory disease.

[d] As California did not contribute any cases of pulmonary valve stenosis before 2002, for this analysis controls from California were restricted to those ascertained ≥2002.

[e] As the NBPDS only ascertained cases of ventricular septal defect muscular, simple during 1997 and 1998, for this analysis controls were only included if they were ascertained in 1997–1998.