HHS Public Access

Author manuscript

Birth Defects Res. Author manuscript; available in PMC 2019 March 01.

Published in final edited form as:

Birth Defects Res. 2018 March 01; 110(4): 342–351. doi:10.1002/bdr2.1147.

Maternal report of fever from cold or flu during early pregnancy and the risk for noncardiac birth defects, National Birth Defects Prevention Study, 1997–2011

Dorothy Kim Waller[1], **Syed Shahrukh Hashmi**[2], **Adrienne T. Hoyt**[3], **Hao T. Duong**[4], **Sarah C. Tinker**[5], **Michael Shayne Gallaway**[6], **Richard S. Olney**[7], **Richard H. Finnell**[8], **Jacqueline Tauber Hecht**[2], **Mark A. Canfield**[3], and **the National Birth Defects Prevention Study**

[1]School of Public Health at UTHealth, Houston, Texas [2]McGovern Medical School at UTHealth, Houston, Texas [3]Texas Department of State Health Services, Birth Defects Epidemiology and Surveillance Branch, Austin, Texas [4]The Partnership for Health Advancement in Vietnam (HAIVN), HCMC, Vietnam [5]National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, Georgia [6]U.S. Army Public Health Command, Behavioral and Social Health Outcomes Program, Aberdeen Proving Ground, Maryland [7]Genetic Disease Screening Program, California Department of Public Health, Richmond, California [8]Department of Pediatrics, Dell Pediatric Research Institute, The University of Texas at Austin Dell Medical School, Austin, Texas

Abstract

Background—As maternal fever affects approximately 6–8% of early pregnancies, it is important to expand upon previous observations of an association between maternal fever and birth defects.

Methods—We analyzed data from the National Birth Defects Prevention Study, a multistate, case-control study of major structural birth defects. Telephone interviews were completed by mothers of cases (n = 17,162) and controls (n = 10,127). Using multivariable logistic regression, we assessed the association between maternal self-report of cold or flu *with fever* and cold or flu *without fever* during early pregnancy and 30 categories of non-cardiac birth defects.

Results—Maternal report of cold or flu *with fever* was significantly associated with 8 birth defects (anencephaly, spina bifida, encephalocele, cleft lip with or without cleft palate, colonic atresia/stenosis, bilateral renal agenesis/hypoplasia, limb reduction defects, and gastroschisis) with

Correspondence: Dorothy Kim Waller, UTHealth, School of Public Health, 1200 Pressler Street, E643 Houston, TX 77030. kim.waller@uth.tmc.edu.

CONFLICT OF INTEREST

The authors report no conflict of interest.

DISCLOSURE STATEMENT

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

ORCID

Dorothy Kim Waller http://orcid.org/0000-0003-2211-4773

elevated adjusted odds ratios ranging from 1.2 to 3.7. Maternal report of cold or flu *without fever* was not associated with any of the birth defects studied.

Conclusions—This study adds to the evidence that maternal fever during early pregnancy is associated with an increased risk for selected birth defects. Elevated associations were limited to mothers who reported a fever, suggesting that it is fever that contributes to the excess risk rather than illnesses associated with it. However, fever may also serve as a marker for more severe infections.

Keywords

cold; colonic atresia; fever; flu; gastroschisis; limb reduction defects; neural tube defects; oral clefts; renal agenesis

1 | INTRODUCTION

The possibility of a teratogenic effect of fever was first postulated by researchers conducting ecologic studies of influenza and birth defects (Janerich, 1971; MacMahon & Yen, 1971). Stronger evidence of an association between maternal exposure to hyperthermia and an increased occurrence of birth defects was subsequently provided by animal studies (Cawdell-Smith, Upfold, Edwards, & Smith, 1992; Edwards, Shiota, Smith, & Walsh, 1995; Finnell, Moon, Abbott, Golden, & Chernoff, 1986) and epidemiologic studies of fever and neural tube defects (NTDs) (Kurppa, Holmberg, Kuosma, Aro, & Saxen, 1991; Li et al., 2007; Lynberg, Khoury, Lu, & Cocian, 1994; Medveczky, Puho', & Czeizel, 2004; Milunsky et al., 1992; Moretti, Benjamin, Fried, & Koren, 2005; Shaw, Todoroff, Velie, & Lammer, 1998; Shaw et al., 2002; Suarez, Felkner, & Hendricks, 2004; Yin et al., 2011; Zhang and Cai, 1993). A recent systematic review by Dreier, Andersen, and Berg-Beckhoff (2014) noted that the literature supports an association between maternal fever and an increased risk of birth defects, with the strongest associations for NTDs, oral clefts and cardiac defects. However, the association with many other categories of birth defects has not been addressed and many of the existing studies do not distinguish between the effects of maternal fever and the illnesses that cause it.

Using data from the National Birth Defects Prevention Study (NBDPS), our objective was to determine whether maternal fever in response to a cold or flu during early pregnancy is a risk factor for any of 30 categories of noncardiac birth defects, independent of the underlying illness.

As maternal fever in early pregnancy affects approximately 6 to 8% of pregnant women in the United States (Dreier et al., 2014; Moretti et al., 2005), continued research in this area may generate findings that can be used to provide evidence-based advice to a large number of pregnant women and their health care providers. Also, clarification of the specific categories of birth defects associated with maternal fever may provide insight into differences in the mechanisms of teratogenicity across categories of birth defects.

2 | MATERIALS AND METHODS

The NBDPS is a population-based, multistate, case-control study of risk factors for selected major structural malformations. Detailed study methods have been published previously (Rasmussen et al., 2003; Reefhuis et al., 2015). Cases and controls had estimated dates of delivery between October 1, 1997 and December 31, 2011. Cases were ascertained by surveillance systems at ten sites (Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, and Utah). Controls were live born infants without birth defects, selected from birth certificates or birth hospital logs to be representative of the population from which the cases arose. This study was approved by the Institutional Review Boards of each study site and the Centers for Disease Control and Prevention.

Cases included live births, fetal deaths and pregnancy terminations. All cases were diagnosed by physical examination, imaging, autopsy, or pathology reports from surgical procedures. Case infants were aggregated across study sites and reviewed by clinical geneticists affiliated with the NBDPS according to established guidelines and classified as having isolated, multiple, or complex birth defects (Rasmussen et al., 2003). Cases with isolated birth defects were defined as having either 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. Cases with multiple birth defects had two or more major unrelated defects in different organ systems. Birth defects that were known or strongly suspected to have been caused by single-gene disorders or chromosomal abnormalities were excluded from the NBDPS. Utah was unable to contribute cases of orofacial clefts in 2003, and cases of congenital cataracts were only contributed study-wide beginning January 1, 2000. For calculations involving these birth defects, we excluded information from controls for those locations and study periods during which cases were not available. Controls for analyses of hypospadias were restricted to male infants because all cases of hypospadias were male.

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

3 | EXPOSURE ASSESSMENT

A sequence of interview questions were used to obtain maternal histories of cold or flu before and during pregnancy. Mothers were asked whether they had “a cold or flu” during this time period. If they answered yes, they were asked to give the dates that the illness began and ended and whether they had a fever in response to it. If they could not provide exact dates they were allowed to report the month immediately before conception or during gestation that the cold or flu occurred. For each fever they were asked “what was the highest temperature recorded during your fever?” Mothers were also asked about fevers not related to cold or flu. However, in this analysis we focused exclusively on the effect of fevers in response to a cold or flu, which comprised 83 percent of all fevers reported.

We assessed illnesses due to cold and flu during the 3 month time period beginning 1 month (30 days) prior to conception and ending 2 months (60 days) after conception. We classified maternal exposures that occurred during this time period into one of three categories; (1) maternal report of cold or flu *with fever*, (2) maternal report of cold or flu *without fever*, (3) no maternal report of cold or flu (referent). Mothers who reported a cold or flu outside of the defined time period were considered unexposed and included in the referent group. We also assessed whether our results for exposure to cold or flu with fever during the critical period changed when we stratified maternal reports of fever into three groups according to the mother's report of the maximum reported temperature and compared the effect of these three exposure subgroups with the referent group of no fever.

4 | STATISTICAL ANALYSIS

We excluded mothers who were missing information on whether or not they had a cold or flu during the exposure window of interest or missing information on one or more of the covariates described below.

Using logistic regression, we calculated crude and adjusted ORs (cOR and aOR, respectively) for the association between maternal report of cold or flu *with fever* and maternal report of cold or flu *without fever* and 30 categories of NBDPS noncardiac birth defects, compared with the referent group which was comprised of mothers who gave no report of a cold or flu during the defined time period. As Botto et al. (2014) published results for the association between maternal fever and different categories of cardiac birth defects using the NBDPS database, we limited the current study to non-cardiac birth defects. We included only those categories of noncardiac birth defects for which there were at least three cases exposed to cold or flu with fever.

We controlled for the potential of confounding by maternal age (<18 years, 19–24 years, 25–29 years, 30–34 years, 35–39 years, 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 [<9 years of completed education], some high school [9–11 years], high school graduate [12 years], some college [13–15 years], and college graduate [≥16 years]), any maternal smoking between 1 month before conception and 3 months after conception (yes, no), maternal prepregnancy body mass index (BMI; <18.5 kg/m^2, 18.5–24.9 kg/m^2, 25.0–29.9 kg/m^2, and ≥30.0 kg/m^2), first live birth (yes, no), timing and frequency of maternal use of supplements containing folic acid (optimal intake daily from 1 month before conception to 1 month after conception), suboptimal intake (any intake during the same period), poor intake (intake beginning later than 1 month after conception or no intake), and study site (Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, and Utah).

We also undertook five sensitivity analyses to determine whether specific changes in the analysis would affect our results. For each of these, we implemented a single change and recalculated all aORs: (a) To confirm that the effects of fever did not extend to exposures that occurred later than 60 days of gestation, we calculated aORs for maternal reports of cold or flu *with fever* during the 3rd or 4th month of pregnancy (61–120 days after

conception); (b) We calculated aORs excluding 17.5% of case mothers with infants with multiple or complex birth defects; (c) We calculated aORs excluding 7.0% of case and control mothers who reported a fever from an illness other than a cold or flu during the critical period from 1 month prior to conception to 2 months after conception (As we did not have information on the timing of fevers associated with urinary tract infection, in this step we excluded all fevers that were associated with a UTI, irrespective of their timing); (d) We calculated aORs excluding 2.0% of case and control mothers with pre-existing Type I or Type II diabetes mellitus; (e) As use of aspirin or ibuprofen during early pregnancy is associated with some categories of birth defects (Hernandez et al., 2012) we calculated aORs excluding 28.4% of case and control mothers who took these medications during the critical period from 1 month before conception to 2 months after conception. As a previous NBDPS analysis found no association between use of acetaminophen during early pregnancy and the birth defects that we studied, we did not run analyses excluding mothers who took acetaminophen during the critical period (Feldkamp, Meyer, Krikov, & Botto, 2010).

5 | RESULTS

After excluding 9.4% of study participants that were missing information on whether or not they had a cold or flu during the exposure window of interest and 6.6% who were missing information on one or more of the covariates, 17,162 cases mothers and 10,127 control mothers remained in our analysis.

Case and control mothers were similar with respect to use of supplements containing folic acid (Table 1). Case mothers were slightly more likely to be younger than 25 or older than 40 years of age, smokers, obese, having their first live birth or having attained less than a high school education. Case mothers were slightly less likely to be college graduates or of non-Hispanic Black race/ethnicity (Table 1).

We assessed the percentage of mothers that reported a cold or flu during the exposure period, separately by the 30 cases groups and the control group (Table 2). Among the controls, 6.5% (662/10,127) of mothers reported exposure to cold or flu *with fever*, and 12.7% (1282/10,127) reported exposure to cold or flu *without fever* (Table 2). Among cases, the percent of mothers who reported exposure to cold or flu *with fever* ranged from 3.4% (3/89) for sacral agenesis to 18.0% (9/50) for colonic atresia/stenosis and the percent of mothers who reported exposure to cold or flu *without fever* ranged from 6.4% for bladder extrophy (4/62) to 16.1% for choanal atresia (23/143) (Table 2).

After adjustment for covariates, maternal cold or flu *with fever* during the exposure period was associated with statistically significant elevated odds ratios ranging from 1.23 to 3.68 for 8 of the 30 birth defects that we studied (anencephaly, spina bifida, encephalocele, cleft lip with or without cleft palate, colonic atresia/stenosis, bilateral renal agenesis/hypoplasia, limb reduction defects, and gastroschisis) (Table 3). There were no statistically significant reduced risk aORs for maternal exposure to cold or flu *with fever* (Table 3). For mothers who reported a cold or flu *without fever* during the exposure period, none of the aORs indicated an elevated or reduced risk that was statistically significant (Table 3).

Among women who reported a cold or flu with fever during the critical period, 40% reported that the maximum temperature of fever was ≥101 degrees Fahrenheit (F), 21% reported it was <101 degrees F and 39% did not answer the question. The aORs associated with maternal reports of cold or flu with fever ≥101 were not substantially different from the aORs associated with maternal report of cold or flu with fever < 101 (not shown).

For the first sensitivity analysis, we observed no statistically significant elevated aORs between maternal reports of cold or flu *with fever* during the 3rd or 4th month of pregnancy (61–120 days) and major noncardiac birth defects (Table 4). However, the aOR for duodenal atresia showed a statistically significant reduced risk (aOR = 0.35, 95% CI = 0.13, 0.94). (Table 4)

The sensitivity analysis restricted to isolated birth defects (i.e., excluding the case mothers who had infants with multiple birth defects or complex birth defects) resulted in findings consistent with those observed in the main analyses in Table 3 (not shown), with the exception of glaucoma/anterior chamber defects, for which a statistically significant association was observed for maternal report of a cold or flu *without fever* (aOR = 1.78, 95% CI 1.12, 2.85).

The three additional sensitivity analyses resulted in findings very similar to those observed in Table 3 (not shown). In each of these three analyses, maternal report of cold or flu *with fever* during the critical gestational period was associated with statistically significant elevated aORs for the 8 birth defects described above with no additional significant findings.

6 | DISCUSSION

This study used data from the NBDPS to assess associations between (1) maternal exposure to a cold or flu with fever and (2) maternal exposure to cold or flu without fever and non-cardiac birth defects. The large size of this population based database allowed us to study the association between these exposures and 30 noncardiac birth defects, including 20 birth defects for which this relationship had not yet been studied.

6.1 | Positive associations between cold or flu with fever and eight birth defects

We observed statistically significant associations between maternal report of cold or flu with fever during early pregnancy and offspring with gastroschisis and colonic atresia/stenosis that, to the best of our knowledge, have not been reported previously.

We also observed statistically significant associations between exposure to a cold or flu with fever during early pregnancy and six birth defects (anencephaly, spina bifida, encephalocele, cleft lip with or without cleft palate, limb reduction defects, and bilateral renal agenesis or renal hypoplasia), that have been reported in previous studies (Dreier et al., 2014; Moretti et al., 2005; Shaw et al., 2002). In addition, a study by Acs, Ba'nhidy, Puho', and Czeizel (2005) reported associations for maternal fever and limb deficiencies and renal anomalies that were based on small numbers of exposed cases and did not achieve statistical significance.

6.2 | No association between cold or flu with fever and 22 birth defects

Twenty-two of the 30 birth defects that we studied were not associated with exposure to maternal fever from a cold or flu in this study, that is, the aORs were not significantly above or significantly below 1.0. Previous studies addressed the possibility of an association between maternal fever and only 4 of these 22 birth defects (hydrocephaly, anorectal atresia, ear defects, and congenital cataracts) as described below.

Consistent with our results, two studies reported no statistically significant association between maternal fever during early pregnancy and hydrocephaly (Acs et al., 2005; Stoll, Alembik, Dott, & Roth, 1992).

In contrast with our results, two studies observed strong and significant associations between maternal fever and anorectal atresia (van Rooij et al., 2010; Wijers et al., 2010) with odds ratios based on only three and five exposed cases, respectively. In comparison, our study had 56 exposed cases of anorectal atresia and we observed no statistically significant association between maternal fever from a cold or flu and this birth defect.

Only two previous studies, based on the Hungarian Case Control Surveillance of Congenital Anomalies, reported results that were both inconsistent with our findings and had adequate statistical power. These studies observed strong and statistically significant associations between maternal reports of influenza, cold or other respiratory illnesses during early pregnancy and isolated congenital anomalies of the ear, described as “mainly anotia or microtia” (Paput, Czeizel, & Ba’nhidy, 2011) and isolated congenital cataracts (Vogt, Puho’, & Czeizel, 2005). They did not include separate analyses for illnesses associated with or without a fever. Both of these studies and our own study included a large number of exposed cases and therefore low statistical power cannot explain the difference between our findings of no association between maternal cold or flu with fever and these two birth defects and the strong associations observed in these Hungarian studies.

6.3 | No associations between cold or flu without fever and 30 birth defects

The detailed questionnaire used by the NBDPS allowed us to make separate assessments of the effects of cold or flu with fever and cold or flu without fever. We observed no significant associations between cold or flu without fever and any of the 30 birth defects in this study. A similar distinction has been made by four of the previous studies (Abe, Honein, & Moore, 2003; Botto et al., 2014; Hashmi, Gallaway, Waller, Langlois, & Hecht, 2010; Lynberg et al., 1994). Studies of NTDs (Lynberg et al., 1994), renal anomalies (Abe et al., 2003) and previous NBDPS analyses of cardiac defects (Botto et al., 2014) and previous NBDPS analyses of oral clefts (Hashmi et al., 2010), observed no associations between cold or flu without illness and the birth defects they studied. This suggests that among mothers exposed to illnesses with fever, it may be fever that contributes to the excess risk of birth defect. However, it is possible that fever serves as a marker for infections that are more severe or due to specific microorganisms.

6.4 | Recall bias

Similar to most of the previous case control studies, we measured the occurrence of *fever due to cold or flu* during pregnancy by maternal interviews conducted after delivery, introducing the possibility that, compared to control mothers, mothers of infants with birth defects may be more likely to recall a "cold or flu" or fever. However, in this analysis, significant associations were present only among mothers who were exposed to fever during the most relevant developmental period of early pregnancy and not for those who were exposed to fevers later during the 3rd or 4th month or pregnancy. Also, there were no statistically significant associations among mothers who were exposed to a *cold or flu without a fever* during early pregnancy.

In order for this pattern of results to be explained by differential recall bias, it would be necessary for the mothers in our study to have known that: (1) The first 8 weeks of gestation is the developmental period when most birth defects occur (Sadler, 2012) and (2) We postulated that a *cold or flu with fever* would be more likely to be associated with birth defects than a *cold or flu without fever*. We believe it is unlikely that the mothers in this study had this knowledge and therefore we think our findings are unlikely to be explained by differential recall bias. Additional evidence against the presence of differential recall of maternal fever is provided by a meta-analysis of the association between maternal fever during early pregnancy and offspring affected by NTDs in which the summary odds ratio for 9 case control studies (OR = 1.93), was observed to be similar to the summary odds ratio for six cohort studies (OR = 1.95) (Moretti et al., 2005). As differential recall is not possible in cohort studies, the similarity of these results argues against it.

6.5 | Multiple statistical tests

We conducted many statistical tests and thus some of the statistically significant associations that we observed may be due to chance. As there is no biologically plausible reason for fever during the 3rd or 4th month of pregnancy to be associated with a reduced risk for duodenal atresia, it is likely that this result is due to chance. Assuming the null hypothesis, that maternal cold or flu with fever during early pregnancy is not associated with any of the 30 birth defects that we studied, by chance alone we would most likely observe approximately one birth defect with a statistically significantly elevated aOR (30*0.05*0.5 = 0.75). However, 8 of the 30 birth defects that we studied had an aOR that was significantly elevated and for 6 of these birth defects (anencephaly, spina bifida, encephalocele, cleft lip with or without cleft palate, limb reduction defects, and bilateral renal agenesis) elevated odds ratios have been reported by previous studies. To the best of our knowledge, the elevated odds ratios that we observed for gastroschisis and colonic atresia have not been reported previously and therefore our findings for these two birth defects should be interpreted more cautiously until they are confirmed by future studies.

6.6 | Summary

We observed that report of a cold or flu accompanied by fever during early pregnancy was associated with 8 of the 30 categories of birth defects that we studied. Six of these birth defects have been found to be associated with maternal fever in previous studies and two of them have not been previously studied for this risk factor. We also addressed a gap present in

most of the previous studies regarding whether or not illness without fever is associated with birth defects, observing that cold or flu without fever was not associated with any of the 30 categories of birth defects that we studied. This suggests that it may be fever that contributes to the excess risk of birth defect among mothers who have illnesses with fever. However, it is possible that fever serves as a marker for more severe infections.

Future research is needed to determine the role of fever, and whether use of antipyretic medication attenuates the associations we have observed. Women who are planning to become pregnant or have recently become pregnant should take measures to prevent themselves from developing an infection, particularly infections that may lead to a fever.

Acknowledgments

Funding information

Supported in part by a cooperative agreement (U01DD000494) between the Centers for Disease Control and Prevention and the Texas Department of State Health Services (DSHS).

References

Abe K, Honein MA, Moore CA. Maternal febrile illnesses, medication use, and the risk of congenital renal anomalies. Birth Defects Research Part A: Clinical and Molecular Teratology. 2003; 67:911–918. [PubMed: 14745928]

Acs N, Ba'nhidy F, Puho' E, Czeizel AE. Maternal influenza during pregnancy and risk of congenital anomalies in offspring. Birth Defects Research Part A: Clinical and Molecular Teratology. 2005; 73:989–996. [PubMed: 16323157]

Botto LD, Panichello JD, Browne ML, Krikov S, Feldkamp ML, Lammer E, the National Birth Defects Prevention Study. Congenital heart defects after maternal fever. American Journal of Obstetrics and Gynecology. 2014; 210(4):359.e1–e11. [PubMed: 24184180]

Cawdell-Smith J, Upfold J, Edwards M, Smith M. Neural tube and other developmental anomalies in the guinea pig following maternal hyperthermia during early neural tube development. Teratogenesis Carcinogenesis Mutagenesis. 1992; 12(1):1–9.

Dreier JW, Andersen AMN, Berg-Beckhoff G. Systematic review and meta-analyses: Fever in pregnancy and health impacts in the offspring. Pediatrics. 2014; 133(3):e674–e688. [PubMed: 24567014]

Edwards MJ, Shiota K, Smith MSR, Walsh DA. Hyperthermia and birth defects. Reproductive Toxicology. 1995; 9(5):411–425. [PubMed: 8563185]

Feldkamp ML, Meyer RE, Krikov S, Botto LD. Acetaminophen use in pregnancy and risk of birth defects. Obstetrics and Gynecology. 2010; 115:109–115. [PubMed: 20027042]

Finnell RH, Moon SP, Abbott LC, Golden LA, Chernoff GF. Strain differences in heat-induced neural tube defects in mice. Teratology. 1986; 33(2):247–252. [PubMed: 3738820]

Hashmi SS, Gallaway MS, Waller DK, Langlois PH, Hecht JT. Maternal fever during early pregnancy and the risk of oral clefts. Birth Defects Research Part A: Clinical and Molecular Teratology. 2010; 88(3):186–194. [PubMed: 20099315]

Hernandez RK, Werler MM, Romitti P, Sun L, Anderka M, the National Birth Defects Prevention Study. Non-steroidal anti-inflammatory drug use among women and the risk of birth defects. American Journal of Obstetrics and Gynecology. 2012; 206(3):228.e1–228. [PubMed: 22196851]

Janerich DT. Influenza and neural-tube defects. The Lancet. 1971; 2(7723):551–552.

Kurppa K, Holmberg KC, Kuosma E, Aro T, Saxen L. Anencephaly and maternal common cold. Teratology. 1991; 44(1):51–55. [PubMed: 1957263]

Li Z, Ren A, Liu J, Pei L, Zhang L, Guo Z, Li Z. Maternal flu or fever, medication use, and neural tube defects: A population based case-control study in Northern China. Birth Defects Research Part A: Clinical and Molecular Teratology. 2007; 79(4):295–300. [PubMed: 17216625]

Lynberg MC, Khoury MJ, Lu X, Cocian T. Maternal flu, fever, and the risk of neural tube defects: A population-based case-control study. American Journal of Epidemiology. 1994; 140(3):244–255. [PubMed: 8030627]

MacMahon B, Yen S. Influenza and neural-tube defects. The Lancet. 1971; 2(7718):260–261.

Medveczky E, Puho' E, Czeizel AE. An evaluation of maternal illness in the origin of neural-tube defects. Archives of Gynecology and Obstetrics. 2004; 270(4):244–251. [PubMed: 15024576]

Milunsky A, Ulcickas M, Rothman KJ, Willett W, Jick SS, Jick H. Maternal heat exposure and neural tube defects. JAMA. 1992; 268(7):882–885. [PubMed: 1640616]

Moretti ME, Benjamin BO, Fried S, Koren G. Maternal hyperthermia and the risk for neural tube defects in offspring: Systematic review and meta-analysis. Epidemiology. 2005; 16(2):216–219. [PubMed: 15703536]

Paput L, Czeizel AE, Ba'nhidy F. Maternal diseases and risk of isolated ear abnormalities in their children. Central European Journal of Public Health. 2011; 19(3):170–176. [PubMed: 22026295]

Rasmussen SA, Olney RS, Holmes LB, Lin AE, Keppler-Noreuil KM, Moore CA. Guidelines for case classification for the National Birth Defects Prevention Study. Birth Defects Research Part A: Clinical and Molecular Teratology. 2003; 67(3):193–201. [PubMed: 12797461]

Reefhuis J, Gilboa SM, Anderka M, Browne ML, Feldkamp ML, Hobbs CA, the National Birth Defects Prevention Study. The National Birth Defects Prevention Study: A review of the methods. Birth. Defects Research Part A: Clinical and Molecular Teratology. 2015; 103(8):656–669.

Sadler, TW. Langman's medical embryology. 12th. Philadelphia: Lippincott Williams & Wilkins; 2012.

Shaw GM, Nelsen V, Carmichael SL, Lammer EJ, Finnell RH, Rosenquist TH. Maternal periconceptional vitamins: interactions with selected factors and congenital anomalies. Epidemiology. 2002; 13(6):625–630. [PubMed: 12410002]

Shaw GM, Todoroff K, Velie EM, Lammer EJ. Maternal illness, including fever and medication use as risk factors for neural tube defects. Teratology. 1998; 57(1):1–7. [PubMed: 9516745]

Stoll C, Alembik Y, Dott B, Roth MP. An epidemiologic study of environmental and genetic factors in congenital hydrocephalus. European Journal of Epidemiology. 1992; 8(6):797–803. [PubMed: 1294384]

Suarez L, Felkner M, Hendricks K. The effect of fever, febrile illnesses, and heat exposures on the risk of neural tube defects in a Texas-Mexico border population. Birth Defects Research Part A: Clinical and Molecular Teratology. 2004; 70(10):815–819. [PubMed: 15468073]

van Rooij IALM, Wijers CHW, Rieu PNMA, Hendriks HS, Brouwers MM, Knoers NV, Roeleveld N. Maternal and paternal risk factors for anorectal malformations: a Dutch case control study. Birth Defects Research Part A: Clinical and Molecular Teratology. 2010; 88(3):152–158. [PubMed: 20073076]

Vogt G, Puho' E, Czeizel AE. Population-based case control study of congenital cataract. Birth Defects Research Part A: Clinical and Molecular Teratology. 2005; 73(12):997–1005. [PubMed: 16323161]

Wijers CH, de Blaauw I, Marcelis CL, Wijnen RM, Brunner H, Midrio P, Reutter H. Research perspectives in the etiology of congenital anorectal malformations using data of the International Consortium on Anorectal Malformations: Evidence for risk factors across different populations. Pediatric Surgery International. 2010; 26(11):1093–1099. [PubMed: 20730541]

Yin Z, Xu W, Xu C, Zhang S, Zheng Y, Wang W, Zhou B. A population-based case-control study of risk factors for neural tube defects in Shenyang, China. Child's Nervous System. 2011; 27(1):149–154.

Zhang J, Cai WW. Association of the common cold in the first trimester of pregnancy with birth defects. Pediatrics. 1993; 92(4):559–563. [PubMed: 8414827]

TABLE 1

Characteristics of noncardiac cases of birth defects and controls, National Birth Defects Prevention Study, 1997–2011

	Cases		Controls	
	Number	**Percent**	**Number**	**Percent**
Total	17162	100.0	10127	100.00
Mother's age (yrs)				
<18	623	3.6	327	3.2
19–24	5415	31.6	2948	29.1
25–29	4556	26.6	2815	27.8
30–34	4041	23.6	2604	25.7
35–39	2062	12.0	1192	11.7
> 40	465	2.7	241	2.4
Mother's race/ethnicity				
Non-Hispanic White	10324	60.2	6043	59.7
Non-Hispanic Black	1665	9.7	1179	11.6
Hispanic	3950	23.0	2222	21.9
All others	1223	7.1	683	6.7
Mother's educational level				
<High school	651	3.8	330	3.3
Some high school	2078	12.1	1165	11.5
Completed high school	4558	26.6	2417	23.9
Some college	4796	28.0	2813	27.8
≥College graduate	5079	29.6	3402	33.6
Mother's smoking status[a]				
Yes	3665	21.4	1895	18.7
No	13497	78.6	8232	81.3
First live birth				
Yes	7894	46.0	4112	40.6
No	9268	54.0	6015	59.4
Mother's BMI[b](kg/m^3)				
< 18.5	945	5.5	541	5.3
18.5–24.9	8833	51.5	5406	53.4
25.0–29.9	3903	22.7	2297	22.7
≥30.0	3481	20.3	1883	18.6
Mother's use of supplements containing folic acid[c]				
Optimal	7967	46.4	4651	45.9
Less than optimal	4603	26.8	2664	26.3

	Cases		Controls	
	Number	**Percent**	**Number**	**Percent**
Inadequate	4592	26.8	2812	27.8

[a] Maternal smoking between 1 month before conception and 3 months after conception.

[b] BMI; body mass index.

[c] 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).

TABLE 2

Percent of mothers reporting cold or flu with fever or cold or flu without fever during the periconceptional period[a], National Birth Defects Prevention Study, 1997–2011

	Mother reported cold or flu with fever		Mother reported cold or flu with fever	
	Percentage	**Exposed/total**	**Percentage**	**Exposed/total**
Controls[b]	6.5%	662/10127	12.7%	1282/10127
Anencephaly	9.0%	50/553	15.0%	83/553
Spina bifida	8.8%	93/1053	13.8%	145/1053
Encephalocele	9.5%	18/190	13.2%	25/190
Dandy-Walker	6.3%	10/159	15.1%	24/159
Holoprosencephaly	8.1%	12/148	10.8%	16/148
Hydrocephaly	5.9%	26/440	14.1%	62/440
Anophthalmos/microphthalmos	7.0%	14/201	9.0%	18/201
Glaucoma/anterior chamber defects	7.7%	12/155	15.4%	24/155
Congenital cataract	7.3%	25/341	13.4%	46/341
Anotia/microtia	5.9%	33/555	11.9%	66/555
Choanal atresia	7.7%	11/143	16.1%	23/143
Cleft palate alone	6.6%	92/1386	13.6%	189/1386
Cleft lip with or without cleft palate	8.0%	215/2700	12.1%	327/2700
Oesophageal atresia/stenosis	6.4%	42/657	12.3%	81/657
Intestinal atresia/stenosis	8.1%	33/409	12.4%	51/409
Duodenal atresia/stenosis	7.4%	15/202	10.9%	22/202
Colonic atresia/stenosis	18.0%	9/50	10.0%	5/50
Anorectal atresia/stenosis	6.1%	56/922	12.9%	119/922
Biliary atresia/stenosis	4.1%	7/170	11.8%	20/170
Hypospadias	6.1%	134/2211	12.3%	271/2211
Bilateral renal agenesis/hypoplasia	12.3%	19/154	13.6%	21/154
Bladder extrophy	8.1%	5/62	6.4%	4/62
Cloacal extrophy	8.5%	7/82	14.6%	12/82
Limb reduction defects	8.0%	86/1078	13.4%	144/1078
Craniosynostosis	6.5%	88/1349	13.0%	175/1349
Diaphragmatic hernia	6.8%	50/737	11.8%	87/737
Omphalocele	6.8%	26/380	15.0%	57/380
Gastroschisis	8.1%	100/1239	12.3%	153/1239
Amniotic band syndrome	7.9%	23/292	11.3%	33/292
Sacral agenesis	3.4%	3/89	11.2%	10/89

[a]Period from 30 days prior to conception to 60 days after conception.

[b]For some defects the number of controls is less than the number shown here because of adjustments for differences in ascertainment of those birth defects. Percentages calculated after all exclusions.

TABLE 3

Adjusted associations[a] between maternal reports of cold or flu with fever and cold or flu without fever during the periconceptional period[b] and major birth defects, the National Birth Defects Prevention Study, 1997–2011

	Report of cold or flu with fever		Report of cold or flu without fever	
	aOR[c]	95% CI[d]	aOR[c]	95% CI[d]
Anencephaly	**1.52**	**(1.11, 2.07)**	1.25	(0.98, 1.60)
Spina bifida	**1.39**	**(1.11, 1.76)**	1.13	(0.93, 1.36)
Encephalocele	**1.66**	**(1.01, 2.74)**	1.17	(0.76, 1.80)
Dandy-Walker	1.11	(0.58, 2.13)	1.31	(0.84, 2.04)
Holoprosencephaly	1.32	(0.72, 2.42)	0.94	(0.55, 1.59)
Hydrocephaly	0.94	(0.63, 1.42)	1.14	(0.86, 1.50)
Anophthalmos/microphthalmos	1.04	(0.60, 1.81)	0.70	(0.43, 1.15)
Glaucoma/anterior chamber defects	1.37	(0.75, 2.50)	1.39	(0.89, 2.17)
Congenital cataract	1.23	(0.81, 1.88)	1.12	(0.81, 1.54)
Anotia/microtia	0.96	(0.66, 1.38)	1.01	(0.77, 1.32)
Choanal atresia	1.17	(0.62, 2.20)	1.34	(0.84, 2.11)
Cleft palate alone	1.00	(0.80, 1.26)	1.09	(0.93, 1.29)
Cleft lip w/wo cleft palate	**1.23**	**(1.05, 1.45)**	0.97	(0.85, 1.10)
Oesophageal atresia/stenosis	0.98	(0.71, 1.37)	0.99	(0.78, 1.26)
Intestinal atresia/stenosis	1.33	(0.92, 1.82)	1.05	(0.77, 1.42)
Duodenal atresia/stenosis	1.27	(0.74, 2.17)	0.89	(0.56, 1.39)
Colonic atresia/stenosis	**3.68**	**(1.72, 7.85)**	0.96	(0.37, 2.48)
Anorectal atresia/stenosis	0.95	(0.72, 1.27)	1.07	(0.87, 1.31)
Biliary atresia/stenosis	0.64	(0.30, 1.39)	0.93	(0.58, 1.49)
Hypospadias	1.01	(0.81, 1.25)	0.99	(0.84, 1.16)
Bilateral renal agenesis/hypoplasia	**2.10**	**(1.28, 3.46)**	1.21	(0.76, 1.95)
Bladder extrophy	1.11	(0.44, 2.82)	0.48	(0.17, 1.33)
Cloacal extrophy	1.40	(0.64, 3.09)	1.25	(0.67, 2.32)
Limb reduction defects	**1.29**	**(1.01, 1.63)**	1.11	(0.92, 1.34)
Craniosynostosis	0.91	(0.72, 1.16)	0.97	(0.82, 1.15)
Diaphragmatic hernia	1.04	(0.77, 1.41)	0.94	(0.74, 1.18)
Omphalocele	1.21	(0.80, 1.82)	1.32	(0.99, 1.77)
Gastroschisis	**1.42**	**(1.11, 1.81)**	1.06	(0.87, 1.29)
Amniotic band syndrome	1.37	(0.88, 2.14)	0.92	(0.63, 1.34)
Sacral agenesis	0.48	(0.15, 1.53)	0.86	(0.44, 1.66)

[a] Adjusted for maternal age, race, educational level, first birth, body mass index, study site and smoking and folic acid intake during the periconceptional period.

[b] Period from 30 days prior to conception to 60 days after conception.

[c] aOR: Adjusted odds ratio.

[d] 95% CI: 95% confidence interval.

TABLE 4

Adjusted[a] associations between maternal report of cold or flu with fever in the 3rd or 4th month of pregnancy and major birth defects, National Birth Defects Prevention Study, 1997–2011

	aOR[b]	95% CI[c]
Anencephaly	0.72	(0.47, 1.10)
Spina bifida	1.01	(0.77, 1.32)
Encephalocele	1.16	(0.64, 2.10)
Dandy-Walker	0.83	(0.38, 1.78)
Holoprosencephaly	0.69	(0.30, 1.58)
Hydrocephaly	0.69	(0.43, 1.12)
Anophthalmos/microphthalmos	0.96	(0.51, 1.78)
Glaucoma/anterior chamber defects	0.73	(0.32, 1.67)
Congenital cataract	1.26	(0.81, 1.96)
Anotia/microtia	1.15	(0.81, 1.64)
Choanal atresia	0.81	(0.37, 1.75)
Cleft palate alone	1.05	(0.83, 1.33)
Cleft lip w/wo cleft palate	0.86	(0.71, 1.04)
Oesophageal atresia/stenosis	0.95	(0.67, 1.33)
Intestinal atresia/stenosis	1.19	(0.80, 1.78)
Duodenal atresia/stenosis	**0.35**	**(0.13, 0.94)**
Colonic atresia/stenosis	1.00	(0.30, 3.27)
Anorectal atresia/stenosis	0.94	(0.70, 1.27)
Biliary atresia/stenosis	0.59	(0.26, 1.34)
Hypospadias	0.96	(0.76, 1.20)
Bilateral renal agenesis/hypoplasia	1.02	(0.53, 1.96)
Bladder extrophy	0.95	(0.34, 2.66)
Cloacal extrophy	0.59	(0.19, 1.89)
Limb reduction defects	1.09	(0.84, 1.42)
Craniosynostosis	0.95	(0.75, 1.21)
Diaphragmatic hernia	0.84	(0.59, 1.18)
Omphalocele	1.04	(0.67, 1.62)
Gastroschisis	0.98	(0.74, 1.29)
Amniotic Band Syndrome	1.47	(0.94, 2.29)
Sacral agenesis	0.93	(0.37, 2.31)

[a] Adjusted for maternal age, race, educational level, first birth, body mass index, study site and smoking and folic acid intake during the periconceptional period.

[b] aOR: Adjusted odds ratio.

[c] 95% CI: 95% confidence interval.