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Maternal Diarrhea During the Periconceptional Period and the Risk of Birth Defects, National Birth Defects Prevention Study, 2006–2011

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Abstract

Background: The primary objective of this study was to assess associations between maternal reports of diarrhea during early pregnancy and a range of different birth defects, most of which have not been assessed in previous studies. The secondary objective was to determine whether associations were modified by maternal use of multivitamins.

Methods: We analyzed data on 16,675 mothers who participated in the National Birth Defects Prevention Study (NBDPS) and delivered between 2006 and 2011. Logistic regression was used to evaluate associations between maternal report of diarrhea during the periconceptional period and 32 categories of birth defects. Odds ratios were adjusted for nine covariates.

Results: Eleven percent of women reported having diarrhea during the periconceptional period. We observed elevated associations ($p < 0.10$) between maternal report of diarrhea lasting 1–5 days and 9 of 32 independent categories of birth defects (hypoplastic left heart, muscular ventricular septal defect, single ventricle complex, secundum atrial septal defect, esophageal atresia, diaphragmatic hernia, omphalocele, gastroschisis, and amniotic band syndrome). The elevated adjusted odds ratios (aORs) ranged from 1.45 to 2.62. There were no decreased associations between maternal report of diarrhea lasting 1–5 days and any of the 32 birth defects. There was no evidence for a significant linear trend of stronger associations between maternal diarrhea and birth defects among mothers who had inadequate or suboptimal use of multivitamins.

Conclusion: Our results are consistent with modest associations between shorter, but not longer, bouts of maternal diarrhea and specific categories of birth defects. These results add to existing evidence, suggesting maternal diarrhea and gastrointestinal infections during early pregnancy are associated with a higher frequency of some birth defects.

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Conflicts of Interest

The authors declare no conflicts of interest. 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.

Keywords

amniotic band syndrome; atrial septal defect secundum; diaphragmatic hernia; esophageal atresia; gastroschisis; hypoplastic left heart; muscular ventricular septal defect; omphalocele; single ventricle complex

1 | Introduction

Insufficient maternal intake of vitamins has been linked to higher rates of neural tube defects and other categories of birth defects (Werler et al. 1999; Botto, Olney, and Erickson 2004; Canfield et al. 2005). Further, diarrhea in pregnant women may lead to malabsorption of nutrients, alterations in the intestinal microbiome, and altered food or vitamin intake (Thomas, Andrew, and Gerald 1972; Rosenberg, Solomons, and Schneider 1977; Camilo et al. 1996; The and Le 2022). As diarrhea is a common complaint (Singh et al. 2018), it is important to determine whether it is an independent risk factor for birth defects.

A previous study observed an association between maternal reports of diarrhea during early pregnancy and increased odds of neural tube defects among their offspring (Felkner et al. 2003). Two additional studies observed associations between diagnoses of gastrointestinal infections during early pregnancy and an increased odds of selected birth defects (Acs et al. 2010) and all birth defects in aggregate (Rumbo et al. 2021). However, many types of birth defects were not assessed by these studies. And, most of the previous studies were limited by small sample sizes.

Our primary goal was to use data from the National Birth Defects Prevention Study (NBDPS) to conduct a comprehensive study of the association of maternal diarrhea and 32 well defined categories of birth defects, most of which have not been assessed in previous studies. Our secondary goal was to determine whether associations between maternal diarrhea and birth defects were modified by maternal use of multivitamins during the periconceptional period.

2 | Methods

The NBDPS was a population-based, case–control study that collected data on pregnant women with estimated dates of delivery between 1997 and 2011. Because the study questionnaire did not include a question on diarrhea until 2006, the current analysis includes only NBDPS data for births with estimated dates of delivery from 2006 to 2011. Cases were identified from birth defect surveillance programs at nine sites (Arkansas, California, Georgia, Iowa, Massachusetts, 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 same populations from which the cases were sampled.

Cases were diagnosed by physical examination, imaging, autopsy, or pathology reports from surgical procedures and include live births, fetal deaths, and pregnancy terminations. Cases were aggregated across study sites and reviewed by clinical geneticists affiliated with the NBDPS, according to established guidelines (Rasmussen et al. 2003; Reefhuis et al. 2015).

“Geneticists classified cases as having isolated defects if there was 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 were classified as having multiple birth defects if there were two or more major unrelated defects in different organ systems.” (Rasmussen et al. 2003; Reefhuis et al. 2015). Birth defects that were strongly suspected or known to have been caused by single-gene disorders or chromosomal abnormalities were excluded from the NBDPS. Maternal interviews were conducted using a standardized computer-assisted telephone interview, in either English or Spanish, between 6 weeks and 24 months from the date of delivery. The frequency of participation was 63.0% for controls and 59.4% for cases. Interviews were completed within an average of 1 year from the estimated date of delivery for case mothers and 9 months for control mothers.

Mothers were asked whether they had “three or more unusually loose stools in one day” any time between 90 days before conception to 90 days after conception. If they answered yes, they were asked, “On about how many days did you have diarrhea?”. Mothers who responded that they did not have diarrhea during this period were coded as unexposed. Hereafter, the period between 90 days before and 90 days after the estimated date of conception is referred to as the “periconceptional period” for maternal exposure to diarrhea.

3 | Statistical Analysis

We included all NBDPS birth defects among subjects that were born or delivered during 2006 to 2011 and had 125 cases or more in the NBDPS database during this period. Mothers with missing information for the initial question on diarrhea or missing information for one or more of the final covariates (described below) were excluded. For analyses of hypospadias, controls were restricted to pregnancies that had male infants.

Using logistic regression, we estimated adjusted odds ratios (aORs) and 95% confidence intervals (CI) for associations between maternal report of diarrhea and 32 categories of birth defects (18 non-cardiac and 14 cardiac). Because previous studies suggested that acute infectious diarrhea was associated with birth defects (Acs et al. 2010; Rumbo et al. 2021) and the average duration of infectious diarrhea is two to four days (Bellido-Blasco and Arnedo-Pena 2011), we conducted separate analyses for diarrhea reported as lasting one to five days and diarrhea reported as lasting six days or more. The referent group for both categories of maternal diarrhea was comprised of mothers who stated they had no diarrhea during the periconceptional period. Adjusted odds ratios were only calculated for birth defects if there were three or more exposed cases.

We adjusted our analyses for nine potential confounders: maternal age (< 18 years, 18–24 years, 25–29 years, 30–34 years and ≥ 35 years), maternal race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, and other race/ethnicity), maternal level of educational attainment (less than high school [≤ 11 years], completed high school [12 years], some college [13–15 years] and college graduate [≥ 16 years]), first live birth (yes, no), pre-pregnancy diabetes (yes, no), pre-pregnancy high blood pressure (yes, no), any maternal smoking between one month before conception and three months after conception (yes, no), and three levels of maternal use of multivitamins during the periconceptional

period (optimal use [daily intake between 1 month before and 1 month after conception], suboptimal use [less than daily intake], inadequate use [no intake or intake beginning later than one month after conception]), and language of interview (English, or other language).

We described aORs for specific birth defects as elevated (or decreased) if they were statistically significant or borderline in significance ($p < 0.10$) in either the main analysis or one of the sensitivity analyses. When the analysis was restricted to isolated birth defects, any birth defect for which the aOR had been elevated in the main analysis but was subsequently both decreased by 10% or more and no longer elevated ($p < 0.10$), was deleted from the list of birth defects with elevated aORs.

We did not determine a minimally sufficient number of covariates because it would have entailed publishing separate sets of covariates for each of the 32 birth defects. Also, statistical power for this common exposure (maternal diarrhea) was more than adequate. Instead, we adjusted each birth defect for the same covariates that were included in previous NBDPS papers that assessed a range of different birth defects and then dropped two covariates whose inclusion in the models had a negligible effect on the results (see below). We also considered DAGS (directed acyclic graphs) to ensure that none of the covariates were colliders.

Variables for maternal pre-pregnancy body mass index (BMI) and study site were also initially included as covariates. High maternal BMI is a modest risk factor for many NBDPS birth defects (Waller et al. 2007). However, compared to the other covariates, it has a relatively large percentage of missing values (4.4%) and dropping it from our logistic regression models had a negligible effect on the aORs. Including study site in the model, decreased the precision of our models and when it was dropped it also had a negligible effect on the aORs. Therefore, both maternal BMI and study site were dropped from the final models.

Because maternal fever or antibiotic use may either precede or follow diarrhea, neither of these conditions met the definition of a confounder. Therefore, we did not adjust for them in our primary analyses. However, we addressed the question of whether our results were independent of these conditions in the sensitivity analyses described below.

Three sensitivity analyses were conducted. (1) To determine if associations between diarrhea and specific birth defects were independent of the presence of other birth defects, we repeated the main analysis restricted to isolated birth defects. To determine if our results were independent of cases of diarrhea associated with fever or use of antibiotics: (2) We repeated the main analysis restricted to mothers who did not report a fever during the periconceptional period and (3) We repeated the main analysis restricted to mothers who did not report use of antibiotics during the periconceptional period.

For those birth defects that had an elevated aOR in either the main analysis or one of the sensitivity analyses, we calculated the change in the aOR associated with each sensitivity analysis (aOR for the sensitivity analysis minus the aOR for the main results/aOR for the main results). If an aOR in a sensitivity analysis decreased by 10% or more (compared with the main analysis), it was considered to be an “important” change.

Finally, results were generated, stratified by the three categories of maternal use of multivitamins, described above. For each of the birth defects in the study, we employed weighted linear regression to evaluate whether there was a linear trend in the magnitude of the aORs across the three categories (Brownstein and Cai 2019). Weights were assigned based on the sample size used to calculate each aOR. Results were considered meaningful if the p value for the test for trend was < 0.10 .

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

4 | Results

A total of 18,072 participating mothers and their infants were delivered within the study period (2006–2011). We excluded 670 (3.7%) of study participants who were missing information on the initial question regarding diarrhea. After this exclusion, there remained 17,402 participants. An additional 727 (4.2%) of the participants were excluded due to missing information on one or more of the covariates in the final model, leaving 16,675 participants in the analysis. Of these, 12,023 were case mothers and 4652 were control mothers.

A total of 1790 (10.7%) women reported having diarrhea. Of these, 908 mothers (50.7%) reported diarrhea lasting one to 5 days and 768 mothers (42.9%) reported diarrhea lasting 6 days or more during the periconceptional period. The median number of days reported for duration of diarrhea in these two groups was 2 days and 22 days respectively. There were 114 mothers (6.4%) who indicated that they had diarrhea during this period, but did not provide the number of days that it occurred.

In Table 1, we computed crude odds ratios (cORs) and 95% confidence intervals for associations between 11 maternal characteristics and maternal report of diarrhea (of any duration) during the periconceptional period. This analysis was restricted to mothers of controls. Mothers who were 25 to 29 years of age, had high pre-pregnancy blood pressure, were smokers, reported fever or reported use of antibiotics were more likely to report diarrhea (cORs of 1.29, 1.47, 1.61, 1.87 and 1.59, respectively) Mothers who were Hispanic, reported inadequate use of multivitamins, or did not interview in English were less likely to report diarrhea (cORs of 0.56, 0.78 and 0.65, respectively) (Table 1).

4.1 | Adjusted Odds Ratios for Maternal Diarrhea Lasting 1–5 Days

Most of the elevated associations that we observed between periconceptional maternal diarrhea and specific birth defects were confined to maternal reports of diarrhea lasting 1–5 days. For 11 of the 32 birth defects (hypoplastic left heart syndrome, secundum atrial septal defects, muscular ventricular septal defect (not simple), single ventricle complex, esophageal atresia, anorectal atresia/stenosis, longitudinal limb deficiency, diaphragmatic hernia, omphalocele, gastroschisis and amniotic band syndrome), maternal diarrhea lasting 1–5 days was associated with an elevated aOR (in either the primary analyses (Table 2), the

sensitivity analyses (Table S1) or both). In the main analysis, elevated aORs for these 11 birth defects ranged in magnitude from 1.45 to 2.62 (Table 2).

4.2 | Adjusted Odds Ratios for Maternal Diarrhea Lasting Six or More Days

In the primary analysis, we calculated aORs for maternal report of diarrhea lasting six or more days for 30 birth defects. This exposure was not associated with any elevated aORs in the primary analysis (Table 2). However, in two of the sensitivity analyses (described below), it was associated with elevated aORs for hypoplastic left heart syndrome (Table 3).

4.3 | Sensitivity Analyses

Table 3 summarizes important findings from the sensitivity analyses. Specifically, it shows aORs from the three sensitivity analyses for 11 birth defects that had an elevated aOR in either the primary analysis in Table 2 or in one or more of the sensitivity analyses in Tables S1 and S2. Ten of these aORs were elevated only for exposure to diarrhea lasting 1 to 5 days and one of them (for hypoplastic left heart syndrome) was elevated both for diarrhea lasting 1 to 5 days and for diarrhea lasting 6 days or more. Table 3 also shows the percentage change in the aORs when each of the sensitivity analyses were implemented for these 11 birth defects.

For the first sensitivity analysis (restricted to cases with isolated birth defects), the aORs for diarrhea lasting 1–5 days were no longer elevated for anorectal atresia and longitudinal limb deficiency, decreasing by 29.5% and 34.2%, respectively (Table 3). Additionally, for two birth defects, (muscular ventricular septal defect (not simple) and single ventricle complex) the aOR for diarrhea lasting 1–5 days, only became elevated after this restriction was implemented. And, for diarrhea lasting 6 or more days, the aOR for hypoplastic left heart syndrome became elevated when this restriction was implemented.

For the second sensitivity analysis, we repeated the primary analyses, excluding 9.2% of mothers who reported a fever associated with a cold, flu, UTI, or other illness, during the periconceptional period. For diarrhea lasting 1–5 days, the aORs for single ventricle complex, and gastroschisis were no longer elevated, decreasing by 21.5%, and 12.2%, respectively (Table 3). Although, the aOR for amniotic band syndrome decreased by 25.2%, it remained elevated with a p value < 0.10 . For diarrhea lasting 1–5 days, the aOR for hypoplastic left heart syndrome became elevated with this restriction, OR = 1.71, 95% CI 1.03, 2.83. For diarrhea lasting 6 or more days, there were no elevated aORs when this restriction was implemented.

For the third sensitivity analysis, we excluded 11.4% of mothers who reported use of any antibiotic during the periconceptional period. For maternal diarrhea lasting 1–5 days, all of the 11 birth defects retained elevated aORs except for muscular ventricular septal defect (not simple), for which the aOR decreased by 16.6% and was no longer elevated (Table 3). Although, the aOR for diaphragmatic hernia decreased by 14.1%, it remained elevated with a p value < 0.10 . Compared to the main analysis, the aOR for hypoplastic left heart syndrome and single ventricle complex were increased by 10.1% and 15.2%, respectively, and the aOR for hypoplastic left heart syndrome became elevated. Also, when this restriction

was implemented, for diarrhea lasting 6 or more days, the aOR for hypoplastic left heart syndrome also became elevated.

4.4 | Lack of Protective Associations

Regardless of the duration of maternal diarrhea, we did not observe any protective associations (aOR < 1.0) that were significant or borderline significant (p value < 0.10) in either the primary analysis or the sensitivity analyses.

4.5 | Trends Across Categories of Maternal Use of Multivitamins

We assessed trends in associations between maternal diarrhea and birth defects across three categories of maternal use of multivitamins. The categories were optimal, suboptimal, and inadequate, comprising 29.5%, 26.2%, and 44.3% of the study population, respectively (Table 1).

When aORs for exposure to diarrhea lasting 1–5 days were stratified by these three levels of multivitamin use, eight birth defects had too few exposed cases to generate aORs in all three strata. Among the 24 birth defects with aORs in all three strata, there were no positive trends for increasing aORs (effect of maternal diarrhea) with decreasing use of multivitamins that were significant (p < 0.10) (Table S3). However, two of these birth defects had results that were opposite to the study hypothesis, that is, d-transposition of the great arteries and cleft lip had negative trends with p values < 0.10.

When aORs for exposure to diarrhea lasting six or more days were stratified by the three levels of multivitamin use, 13 birth defects had too few exposed cases to generate aORs in all three strata. Among the 17 birth defects with aORs across all three strata, there were no positive trends that were significant (p < 0.10) (Table S4). However, one of these birth defects had a result that was opposite to the study hypothesis, that is, that is, craniosynostosis had a negative trend with a p value < 0.10.

5 | Discussion

This is the first analysis of the association between maternal report of diarrhea and birth defects to include a wide range of different categories of cardiac and non-cardiac birth defects. We utilized data from the CDC sponsored NBDPS, one of the largest population-based studies of birth defects ever conducted. The large sample size of this dataset allowed us to make separate assessments for each birth defect, including the effect of excluding mothers who reported a fever or used antibiotics during the periconceptional period.

We also had sufficient statistical power to assess results for many (but not all) of the birth defects stratified by three levels of maternal use of multivitamins.

Among infants whose mothers were exposed to 1–5 days of diarrhea, after restricting to isolated birth defects, the results for two of the eleven birth defects (anorectal atresia/stenosis, longitudinal limb deficiency) that had elevated aORs in the main analysis, were decreased by more than 10% and were no longer associated with a p value < 0.10. Because the main results for these two birth defects (Table 2) may have been driven by

the inclusion of other birth defects, we did not include them among the birth defects that we interpreted to be associated with maternal diarrhea. Of the 32 birth defects studied, there remain a total of nine birth defects that have elevated aORs for associations with maternal diarrhea lasting 1–5 days (hypoplastic left heart syndrome, secundum atrial septal defect, muscular ventricular septal defect (not simple), single ventricle complex, esophageal atresia, diaphragmatic hernia, omphalocele, gastroschisis and amniotic band syndrome).

Sensitivity analyses that excluded mothers who reported fever during the periconceptional period revealed that, for maternal diarrhea lasting 1–5 days, the elevated aORs for five birth defects; single ventricle complex, esophageal atresia, longitudinal limb, gastroschisis and amniotic band syndrome decreased by 21.5%, 9.6%, 7.8%, 12.2% and 25.2%, respectively. Similar results were not observed for mothers who reported diarrhea lasting 6 days or more. As acute gastrointestinal infections are usually of short duration and often accompanied by fever (Bellido-Blasco and Arnedo-Pena 2011), these results support the possibility that the large difference in our results for diarrhea lasting 1–5 days compared with diarrhea lasting six or more days, are due to a higher proportion of acute gastrointestinal infections (often with fever) in the group with a shorter duration of diarrhea. This explanation is also supported by previous studies that observed that maternal fever during early pregnancy is associated with a number of different types of cardiac and non-cardiac structural birth defects (Dreier, Andersen, and Berg-Beckhoff 2014; Botto et al. 2014; Waller et al. 2018; Mohan Dass et al. 2022).

For maternal diarrhea lasting 1–5 days, sensitivity analyses restricted to mothers who did not report using antibiotics during the periconceptional period revealed that the elevated aORs for two other birth defects; muscular ventricular septal defects (not simple) and diaphragmatic hernia, were decreased by 16.6% and 14.1%, respectively. These modest decreases in the effect of maternal diarrhea for two birth defects, suggest that maternal use of antibiotics is less likely to explain our results compared with maternal fever.

Three previous studies reported associations between maternal diarrhea (Felkner et al. 2003) or maternal acute gastrointestinal infections (Rumbo et al. 2021; Acs et al. 2010) and birth defects.

Felkner et al. (2003) conducted a case control study and observed that 9.9% of mothers reported one or more episodes of periconceptional diarrhea and these mothers had an increased risk of pregnancies affected by neural tube defects (anencephaly, spina bifida and encephalocele), aOR = 3.7, 95% CI = 1.8, 7.6. Using the same definition of maternal diarrhea as Felkner et al. (2003), we observed no association between maternal diarrhea and either of the two neural tube defects that we studied (anencephaly and spina bifida). This may be explained by a difference in the frequency of severe gastrointestinal infections between our study population and that of Felkner et al., which was restricted to Mexican American mothers living in border counties in Texas.

Rumbo et al. conducted a case control study of diagnoses of gastrointestinal infections and birth defects in Columbia (Rumbo et al. 2021). A diagnosis of a gastrointestinal infection during early pregnancy was associated with an increased risk for all birth defects

in aggregate (crude OR = 2.06, 95% CI = 1.18, 3.59), but individual birth defects were not assessed (Rumbo et al. 2021).

Acs et al. (2010) reported results of a Hungarian case-control study of infants of pregnant women diagnosed with infectious diarrhea. Exposed mothers had significantly increased risks of congenital heart defects (in aggregate) (aOR = 2.4; 95% CI = 1.0, 6.3), and limb deficiencies (in aggregate) (aOR = 14.1; 95% CI = 4.8, 41.4), which may be consistent with the associations we observed for narrower categories of congenital heart and limb defects. Acs et al. also observed that exposed mothers had increased risks of cleft lip with or without cleft palate (aOR = 12.3; 95% CI = 5.4, 28.0), a finding we did not observe. We suspect that their focus on diagnoses of infectious diarrhea may have represented a more severe condition than the exposure in our study (maternal report of diarrhea of any cause).

There are several ways by which diarrhea might cause lower maternal plasma levels of vitamins, which can then lead to deleterious effects in the developing embryo: (1) Diarrhea may disrupt bacterial species in the maternal microbiome that make important contributions to plasma vitamin levels (Camilo et al. 1996); (2) The increase in intestinal transit associated with diarrhea may allow insufficient time for absorption of vitamins from food; (3) And, mothers who are experiencing diarrhea may limit or change their food intake.

We did not find evidence to support our hypothesis that maternal use of multi-vitamins might modify associations between maternal diarrhea and birth defects. This may be explained if maternal diarrhea interferes not only with the absorption of vitamins from food but also with the absorption of multivitamins. And, for many birth defects, the statistical power to detect an effect of multivitamin use was limited, resulting in aORs that were imprecise or could not be calculated.

Differential recall bias, in which mothers of cases are more likely to recall exposures that could be deleterious to the embryo, is a potential concern when exposures are based on maternal interviews conducted after delivery. However, there has been limited research in this area and when Case et al. studied responses to the NBDPS interview question (What do you think causes birth defects?) (Case et al. 2014), no respondents mentioned diarrhea or gastrointestinal illnesses. Therefore, it is doubtful that mothers are aware that maternal diarrhea is a risk factor for birth defects. Thus, case mothers are probably not more likely to report diarrhea than control mothers.

To address the multiple statistical tests made in this study, we calculated the number of elevated aORs that we expected to observe under the null hypothesis that maternal report of diarrhea is not associated with any of the categories of birth defects in this study. And, because associations were assessed between diarrhea lasting 1–5 days and 32 birth defects and between diarrhea lasting 6 days or more and 30 birth defects, we made separate calculations for each of these independent exposures. These numbers were calculated based on a *p* value of 0.10 and the assumption that under the null hypothesis that 0.5 of all aORs would be elevated ($32 \times 0.10 \times 0.50 = 1.60$ and $30 \times 0.10 \times 0.50 = 1.50$, respectively). By chance alone, for diarrhea, lasting 1–5 days, we would expect to observe approximately 1.6 birth defects with elevated aORs and for diarrhea lasting 6 days or more, we would expect to

observe approximately 1.5 birth defects with elevated aORs. Thus, multiple statistical tests may explain the single elevated aOR that we observed for diarrhea lasting 6 days or more. However, multiple statistical tests are very unlikely to explain all nine of the birth defects with elevated aORs that we observed for diarrhea lasting 1–5 days.

Some misclassification of exposure (diarrhea) is likely to have occurred due to the wide periconceptional period (3 months before to 3 months after conception) that was used in the NBDPS question on diarrhea. Therefore, the question on diarrhea may have misclassified some mothers as exposed to diarrhea, who were exposed prior to conception; which is a time period when this exposure is unlikely to increase the risk of a birth defect. Also, the question on diarrhea asked about “unusually loose stools”, which may have been interpreted differently from one participant to the next. Thus, in this study, misclassification of diarrhea is likely to be non-differential, that is, occurring among cases and controls with a similar frequency. It follows that estimates from this study are most likely to have underestimated the magnitude of the increase in risk of birth defects associated with maternal diarrhea.

Another limitation of our study is that because information on the timing of maternal fever is also based on maternal recall, it is possible that some of the study participants did not accurately recall the time period in pregnancy during which a fever occurred.

This study provides evidence that short bouts of maternal diarrhea are associated with an increase in the frequency of approximately 28% (9 of 32) of the structural birth defects we examined. In addition, previous studies have observed that maternal gastrointestinal infections, which generally resolve in a few days (Bellido-Blasco and Arnedo-Pena 2011), have also been linked to an increased frequency of birth defects. Therefore, women who are planning to become pregnant or have recently become pregnant may benefit from measures to avoid infections, including those of gastrointestinal origin.

To date, only a few studies have addressed the possibility that maternal diarrhea or gastrointestinal infections are associated with birth defects. Additional research should be undertaken to confirm the associations we observed and to identify additional exposures that may modify them.

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 the NBDPS data sharing committee. Interested parties may submit requests to use the data to the NBDPS data sharing committee.

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TABLE 1 |

Frequency of reports of diarrhea during the periconceptional period (from 3 months before conception to 3 months after conception) among control mothers stratified by maternal characteristics, National Birth Defects Prevention Study, 2006–2011.

	Any diarrhea				cOR	95% CI
	n	%	Total			
Total	469	10.1	4652			
Maternal age at delivery (years)						
< 18	8	6.5	124	0.69	0.33, 1.45	
18–24	117	9.1	1291	1.00	Referent	
25–29	156	11.4	1368	1.29	1.00, 1.66	
30–34	122	10.1	1210	1.13	0.86, 1.47	
35 and above	66	10.0	659	1.12	0.81, 1.53	
Mother's race/ethnicity						
Non-Hispanic White	303	11.6	2610	1.00	Referent	
Non-Hispanic Black	41	8.6	475	0.72	0.51, 1.01	
Hispanic	84	6.8	1228	0.56	0.44, 0.72	
Other	41	12.1	339	1.05	0.74, 1.48	
Mothers education (years)						
Less than high school (≤ 11)	58	7.8	745	0.80	0.57, 1.12	
Completed high school (12)	100	9.5	1048	1.00	Referent	
Some college (13–15)	143	11.6	1237	1.24	0.95, 1.62	
Completed college degree (≥ 16)	168	10.4	1622	1.10	0.84, 1.42	
First birth						
Yes	167	9.2	1825	0.84	0.69, 1.03	
No	302	10.7	2827	1.00	Referent	
Pre-pregnancy diabetes						
Yes	4	12.9	31	1.33	0.46, 3.80	
No	465	10.1	4621	1.00	Referent	
High blood pressure ^a						
Yes	86	13.4	642	1.47	1.14, 1.88	
No	383	9.6	4010	1.00	Referent	

	Any diarrhea			cOR	95% CI
	n	%	Total		
Total	469	10.1	4652		
Peri-conceptual smoking ^b					
Yes	111	14.1	787	1.61	1.28, 2.02
No	358	9.3	3865	1.00	Referent
Supplements containing multivitamins ^c					
Optimal	156	11.0	1424	1.00	Referent
Suboptimal	134	11.3	1188	1.03	0.81, 1.32
Inadequate	179	8.8	2040	0.78	0.62, 0.98
Language of interview					
English	427	10.5	4059	1.00	Referent
Other ^d	42	7.1	593	0.65	0.47, 0.90
Maternal fever ^e					
Yes	66	16.4	403	1.87	1.41, 2.48
No	403	9.5	4249	1.00	Referent
Maternal use of antibiotics ^e					
Yes	69	14.4	478	1.59	1.21, 2.09
No	400	9.6	4174	1.00	Referent

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

^aPre-pregnancy high blood pressure.

^bFrom 1 month before conception to 2 months after conception.

^cOptimal, suboptimal or inadequate use of multivitamins, explained under methods.

^dInterviews conducted in Spanish and other languages.

^eFrom 1 month before conception to 3 months after conception.

TABLE 2 |

Adjusted associations (adjusted for maternal age, race/ethnicity, education, smoking, first birth, use of supplements containing folic acid during the periconceptional period, language of interview, diabetes and hypertension) between report of maternal diarrhea (from 3 months before conception to 3 months after conception; A bolded aOR and 95% CI corresponds to a $p < 0.10$) and selected birth defects, National Birth Defects Prevention Study, 2006–2011.

	1—5 days of diarrhea				≥6 days of diarrhea					
	Cases		aOR	95% CI	Cases		aOR	95% CI		
	E	uE			E	uE				
Heterotaxia with CHD	7	111	1.14	0.53	2.65	4	111	0.77	0.28	2.14
Tetralogy of Fallot	27	404	1.27	0.84	1.93	23	404	1.05	0.67	1.65
Dextro-Transposition GA	15	251	1.14	0.66	1.96	11	251	0.76	0.41	1.41
AVSD	5	143	0.65	0.26	1.59	11	141	1.39	0.74	2.64
TAPVR	4	113	0.64	0.22	1.68			NC		
Hypoplastic left heart	19	232	1.49	0.91	2.44	18	232	1.41	0.85	2.33
Coarctation aorta	24	429	0.99	0.64	1.54	26	429	1.07	0.70	1.63
Aortic stenosis	12	200	1.05	0.58	1.93	12	200	1.02	0.56	1.87
Pulmonary valve stenosis	32	559	1.01	0.69	1.48	31	559	0.94	0.64	1.39
VSD perimembranous	11	185	1.06	0.56	1.99	9	185	0.85	0.43	1.71
VSD muscular NS	16	192	1.51	0.88	2.58	6	192	0.61	0.27	1.41
ASD secundum	59	725	1.45	1.07	1.96	28	725	0.71	0.47	1.06
ASD NOS	5	74	1.20	0.48	3.04			NC		
Single ventricle complex	8	97	1.58	0.74	3.39	3	97	0.67	0.21	2.16
Anencephaly	13	249	0.97	0.54	1.72	12	249	1.10	0.60	2.01
Spina bifida	26	444	1.07	0.70	1.63	26	444	1.18	0.78	1.81
Hydrocephaly	12	179	1.23	0.67	2.27	6	179	0.61	0.27	1.41
Cataracts	11	157	1.29	0.68	2.42	5	157	0.55	0.22	1.35
Anotia/microtia	15	236	1.25	0.72	2.15	11	236	1.07	0.57	2.03
Cleft palate w/o cleft lip	27	537	0.96	0.63	1.44	34	537	1.11	0.76	1.62
Cleft lip w/w/o cleft palate	73	1089	1.23	0.94	1.63	59	1089	1.01	0.75	1.37
Esophageal atresia	20	259	1.56	0.96	2.52	16	259	1.05	0.62	1.80
Intestinal atresia	11	179	1.10	0.58	2.06	4	179	0.45	0.16	1.23
Anorectal atresia/stenosis	32	353	1.73	1.17	2.56	15	353	0.87	0.51	1.50

	1—5 days of diarrhea					≥6 days of diarrhea				
	Cases		aOR	95% CI	E	Cases		aOR	95% CI	E
	E	uE				E	uE			
Hypospadias	44	1050	0.79	0.55	1.15	51	1050	0.84	0.59	1.19
Longitudinal limb	16	155	1.93	1.12	3.32	8	155	0.95	0.46	2.00
Transverse limb	15	255	1.15	0.67	1.97	10	255	0.76	0.39	1.45
Craniosynostosis	42	660	1.15	0.82	1.62	32	660	0.81	0.55	1.19
Diaphragmatic hernia	29	288	1.91	1.27	2.87	14	288	0.92	0.52	1.60
Omphalocele	12	133	1.79	0.97	3.31	9	133	1.29	0.64	2.60
Gastroschisis	36	561	1.48	1.00	2.21	27	561	0.94	0.60	1.47
Amniotic band sequence	13	98	2.62	1.42	4.83	5	98	0.94	0.37	2.38
Controls	227	4183		Referent		219	4183		Referent	

Abbreviations: E, exposed cases; uE, unexposed cases; aOR, adjusted odds ratio; CI, 95% confidence interval; NC, not calculated due to <3 exposed cases; CHD, congenital heart disease; GA, great arteries; AVSD, Atrioventricular septal defects; TAPVR, Total anomalous pulmonary venous return; VSD, ventricular septal defect; ASD, atrial septal defect; NS, not simple; wo, without; NOS, not otherwise specified; w/wo, with or without.

TABLE 3 |

Elevated adjusted (maternal age, race/ethnicity, education, smoking, first birth, use of supplements with folic acid during the periconceptional period, language of interview, diabetes and hypertension) associations between maternal diarrhea (report of diarrhea during the period 3 months before conception to 3 months after conception) and eleven selected birth defects(birth defects in this table have an elevated aOR in the main results or in one of the sensitivity analyses): comparing percent change(percent change was calculated as (aOR for sensitivity analysis – aOR for main analysis)/aOR for main analysis) between main results and three sensitivity analyses, National Birth Defects Prevention Study, 2006–2011.

Main result	Sensitivity analyses					
	Restricted to isolated cases			Restricted to mothers without fever ^a		
	aOR	aOR	% Change	aOR	% Change	% Change
Maternal diarrhea lasting 1–5 days						
Hypoplastic left heart	1.49	1.49	0.0	1.71	14.7	10.1
VSD muscular, not simple	1.51	1.76	16.6	1.51	0.0	-16.6
ASD secundum ^b	1.45	1.35	-6.9	1.38	-5.0	-0.7
Single ventricle complex	1.58	1.93	22.2	1.24	-21.5	15.2
Esophageal atresia	1.56	1.75	12.2	1.41	-9.6	7.7
Anorectal atresia/stenosis	1.73	1.22	-29.5	1.83	5.8	-1.7
Longitudinal limb	1.93	1.27	-34.2	1.78	-7.8	7.8
Diaphragmatic hernia	1.91	1.82	-4.7	1.97	3.1	-14.1
Omphalocele	1.79	1.95	8.9	1.89	5.6	8.4
Gastroschisis	1.48	1.43	-3.4	1.30	-12.2	4.1
Amniotic band sequence	2.62	2.70	3.1	1.96	-25.2	3.4
Maternal diarrhea lasting 6 or more days						
Hypoplastic left heart	1.41	1.58	12.1	1.28	-9.2	17.7

Abbreviations: aOR = adjusted odds ratio; VSD = ventricular septal defect; ASD = atrial septal defect. Bold for “aOR” corresponds to a change in the % change of ≥ 10.0%.

^aNo report of maternal fever during the periconceptional period.

^bNo report of maternal use of antibiotics during the periconceptional period.