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Associations between maternal water consumption and birth defects in the National Birth Defects Prevention Study (2000-2005)

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Abstract

Background: Water and water-based beverages constitute a major part of daily fluid intake for pregnant women, yet few epidemiologic studies have investigated the role of water consumption on birth outcomes.

Methods: We used data from the National Birth Defects Prevention Study to conduct a case-control study investigating associations between maternal water consumption during pregnancy and birth defects (BD). We used interview data on water consumption during the first trimester of pregnancy in 14,454 cases (major BDs $n \geq 50$) and 5,063 controls. Total water consumption was analyzed as a continuous variable and in quartiles. We evaluated the role of dietary quality and sugar sweetened beverage consumption. Logistic regression models were used to assess effects of water consumption on risk of BDs with adjustment for relevant covariates.

Results: Mean daily maternal water consumption among controls was 4.4 8-ounce glasses. We observed decreases in estimated risk associated with increases in water consumption for several BDs, including neural tube defects (spina bifida), oral clefts (cleft lip), musculoskeletal defects (gastroschisis, limb deficiencies), and congenital heart defects (hypoplastic left heart syndrome, right-sided obstructions, pulmonary valve stenosis). Our results were generally unchanged when an indicator for overall dietary quality was included, however there was evidence of effect measure modification by heavy consumption of sugar-sweetened beverages for some defects, but not all.

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Conclusion: These analyses suggest the importance of sufficient water consumption during early pregnancy, above and beyond it being a marker of higher diet quality. Additional analyses are warranted to understand the biological mechanism for this association.

Keywords

maternal water consumption; birth defects; pregnancy; nutrition; National birth defects prevention study

Introduction:

Cold tap water and tap-water based beverages constitute a major part of daily fluid intake for pregnant women, the majority of which occurs at home for both unemployed and employed women (Smith et al., 2009). In one study, 65% of study subjects reported having water ingestion habits during pregnancy that were different from their non-pregnant status (Villanueva et al., 2007). Maternal self-reporting of tap water consumption during pregnancy collected via questionnaire and prospective water diaries has been reported to range from 1.8 liters/day to 3.4 liters/day (Barbone et al., 2002; Kaur et al., 2004; Shimokura et al., 1998; Smith et al., 2009; Zender et al., 2001), with some differences for water consumption according to age, employment status, income and ethnicity. Forssen et al. (2007) reported that healthier behaviors (e.g., vitamin intake, lack of drug, alcohol and cigarette use) were associated with increased tap water ingestion, though demographic variables (e.g. socioeconomic status, race/ethnicity) were more strongly predictive than the health and behavioral variables. Several of these studies have concluded that a larger part of the variability in daily water consumption is found between subjects (likely due to employment status (Shimokura et al., 1998)) rather than within subjects (based on comparison of pre- and post-delivery questionnaire responses concerning the intake of water (Barbone et al., 2002)).

While adequate fluid intake during pregnancy is essential for fetal circulation, maintaining appropriate amniotic fluid levels, and increasing blood volume (Montgomery, 2002), few epidemiologic studies have investigated the role of water consumption on adverse reproductive outcomes. The majority of studies that examine water consumption and reproductive outcomes tend to focus on the effects of specific contaminants such as disinfection by-products (DBPs). However, despite increasing potential exposure to DBPs and other impurities, higher water consumption during pregnancy may be protective for adverse birth outcomes. The few studies to examine this relationship between maternal water consumption levels and birth outcomes have provided mixed results. Savitz et al. (1995) reported that an increasing amount of ingested water was associated with decreased risks of miscarriage, preterm delivery (PTD), and low birth weight. Compared to those reporting no water intake, odds ratios (ORs) were 0.5 and 0.6 for mothers who reported more than 4 glasses/day for small-for-gestational age (SGA) infancy and PTD, respectively. However, relative to low intake (1–7 glasses/week), Aggazzotti et al. (2004) showed little evidence of an association between high intake of tap water (>35 glasses/week) and risk of SGA or PTD. Other studies have shown a decreased risk of spontaneous abortion (Swan et al., 1998).

Using data from the National Birth Defects Prevention Study (NBDPS), a population-based case-control study, we examined a spectrum of birth defects in relation to total water consumption (including both tap and bottled water). Logistic regression analysis was used to test the hypothesis that water consumption during pregnancy is associated with a reduced risk of birth defects. We purposely adjusted for diet quality and examined the possible effect measure modification by sugar-sweetened beverage (SSB) consumption to examine the independent association of water with these outcomes.

Methods:

Study Population:

We utilized data from the NBDPS, including all eligible, interviewed cases and all control births with delivery dates from January 1, 2000 through December 31, 2005. The 2000 birth year represents the first full birth year for mothers to be administered the water module in the NBDPS interview. During this time period, the participation rate was 69% among all cases and 65% for controls. The methods of the NBDPS have been described previously (Yoon et al., 2001). Briefly, cases are livebirths, stillbirths greater than 20 weeks gestation or at least 500 grams, and elective terminations where available, that are identified by the birth defects monitoring programs in ten sites within the United States (US) (Arkansas, metropolitan Atlanta, California, Iowa, Massachusetts, New York, North Carolina, Texas, Utah). We included as cases in this spectrum analysis all major birth defects (with $n \geq 50$) of the following systems: cardiovascular, musculoskeletal, digestive, genitourinary, neural tube, eyes and ear, cleft, and respiratory defects. Case records were submitted to in-depth clinical review by clinical geneticists affiliated with the NBDPS. Controls are livebirths without major defects, identified through vital records or hospital records, depending upon site-specific protocols. Case and control mothers were invited to participate in a computer-assisted telephone interview which included questions about pregnancy and medical history, diet, lifestyle, occupational exposures, medication use, and residential history. The interview was conducted with women whose infants are between 6 weeks and 2 years of age.

Exposure:

Maternal water consumption (i.e., total water consumption from bottled and tap water) was estimated using exposure variables constructed from the NBDPS water module of the computer-assisted telephone interview. This included consumption of hot beverages (e.g., coffee, tea) or other beverages (e.g., juices and other beverages prepared from a powdered mix or from concentrate) prepared with tap or bottled water. We assessed mother's water consumption for the period beginning 1 month prior to the estimated date of conception through the third month of gestation, using questions from the NBDPS interview that retrospectively inquired about typical daily water consumption habits during each of the four months included in the exposure window. Specifically, mothers were asked about the source of their tap water, the number of 8-ounce glasses of filtered or unfiltered tap or bottled water consumed on an average day during the period starting one month before conception through the first trimester, and whether their drinking habits changed during pregnancy. This allowed us to account for changes in water consumption behaviors that might occur during early pregnancy, due to changes in water consumption behaviors related to the pregnancy or

to changes in season. Mothers estimated the average number of glasses of water consumed per day for each of the four months that made up the exposure window. Water consumption was defined as the estimated glasses per day, averaged across each of the four months of the exposure window.

Outcome:

We examined the relationship between maternal water consumption and each of the 76 birth defect phenotypes included in the NBDPS. Conducting this type of spectrum analysis facilitated an efficient and consistent exposure assessment process, since all cases and controls were assessed at the same time using the same methods (i.e., the same statistical model). Each defect was examined individually.

Statistical Analysis:

The relationship between birth defects and water consumption was analyzed for total water consumption as a linear variable and also by quartile (based on distribution among the controls), to account for possible non-linear relationships. Analyses were used to assess effects of water consumption on risk of birth defects with adjustment for relevant covariates, which were assessed for their potential confounding effects on the risk estimates using a backwards selection methods. Potential confounders that were statistically significant at the $p < 0.10$ level or that changed the odds ratio of the water consumption covariate by 10% or more were retained in the model. Unadjusted and adjusted odds ratios and 95% confidence intervals (CI) were calculated using logistic regression. All statistical analyses were performed using SAS version 9.4 (Cary, NC).

Due to the wide array of birth defects analyzed, and the exploratory nature of this analysis, three distinct regression models were applied to all birth defect outcomes. In addition to an unadjusted model, the other two models were intended to account for varying levels of potential confounders identified from univariate analyses of a set of a priori covariates. Potential confounders assessed in the univariate analyses include birth outcome (liveborn, stillborn, induced abortion), plurality (singleton birth, non-singleton birth), maternal race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other), maternal age (19 years, 20–34 years, 35 years), education (less than high school, high school graduate, post-secondary education), periconceptional multivitamin use (none, daily use, less than daily use), cigarette smoking (yes/no), alcohol consumption (yes/no), maternal pre-pregnancy BMI, dietary folic acid consumption, maternal fever (yes/no), job outside the home (including students) and center (AR, CA, GA, IA, MA, NJ, NC, NY, TX, UT). Maternal race/ethnicity, maternal age, maternal education level, and periconceptional multivitamin use were retained in the adjusted model.

To account for the possibility that maternal water consumption could serve as a surrogate for maternal diet quality, we evaluated a second adjusted model that included each of the potential confounders listed above, as well as an indicator of dietary quality. Diet quality was measured using the diet quality index for pregnancy by Bodnar and Siega-Riz (2002) and the score modified by Carmichael et al. (2012). The index captures overall diet quality using guidelines from the Dietary Guidelines for Americans. Estimates from the food

frequency questionnaire administered as part of the NBDPS survey (Willet shortened version) were used to score each component of the diet, and are described in Carmichael et al. (2012). Briefly, the food frequency questionnaire captures usual maternal intake the year prior to conception. Overall servings of food per day were calculated, and each food-based component was ranked by quartile based on its distribution in controls in the study population. The quartiles were then summed to create a final value to be used in an adjusted model. When examined, there was no strong correlation between DQI quartile and water consumption (Spearman $R = 0.21$).

We also examined potential effect measure modification by SSB consumption by stratifying at the 75th percentile. Dietary intake of SSB was assessed by the food frequency questionnaire and a set of detailed questions concerning soda consumption (described in Browne et al. (2011)). Similar to DQI, there was no strong correlation observed between SSB and water consumption (Spearman $R = -0.18$).

Analyses differed slightly for heart defects compared to non-heart defects. Non-heart defects did not include complex or syndromic cases, while heart defects did, due to the large reduction in number of cases for certain phenotypes (e.g., Tetralogy of fallot) if complex or syndromic cases were removed. It should be noted that this research constitutes a broad spectrum evaluation of many different birth defect phenotypes, and, if any associations are observed for heart defects they would need to be confirmed in a more thorough evaluation that is restricted to only isolated cases.

Sensitivity analysis:

Within our study population, 1,087 women, representing 6.4% of the total number of women participating, reported drinking no water during pregnancy. These women may differ in other ways from the women who reported drinking one or more glasses of water, thus potentially biasing the estimates. To assess potential bias caused by the inclusion of these women in the original analyses, a sensitivity analysis was conducted, which excluded women who did not report drinking any water.

Results:

Cases and controls were similar demographically, and the majority were white, non-hispanic, had a post-secondary education, a job, and were between 20 and 34 years old (Table 1). Study participants reported consuming similar amounts of water by source, with the exception of sources that didn't fit into any of the predefined groups (i.e., "other"), and the mean number of glasses of water (8 ounces) consumed per day was 4.4 (Table 2).

Overall, we looked at seventy-six clinically relevant subgroups of different birth defects, representing nine different common phenotypes of defects. Out of those subgroups, eleven showed a pattern of increasing or decreasing odds of birth defect with reported water consumption (Figures 1 & 2). No defect in the amniotic band syndrome (ABS) and limb body wall, gastrointestinal, genitourinary, or associated heart birth defects phenotypes had any clinically relevant subgroup that showed a relationship with water consumption during pregnancy (See Supplemental Table S1 for quantitative results). Of those birth defects that

did show a pattern, neural tube defects (spina bifida), oral clefts (cleft lip with or without cleft palate), musculoskeletal defects (gastroschisis, limb deficiencies) and congenital heart defects (hypoplastic left heart syndrome, right-sided obstructions, pulmonary valve stenosis) all showed decreasing odds of the birth defect with increasing water consumption. Only anotia/ microtia showed the opposite pattern of increasing odds of the birth defect, and point estimates were consistently elevated from the referent group (Figure 2). Crude estimates were similar to adjusted estimates, but overall were further away from the null. These effects were not consistent across biological systems, for instance, not every musculoskeletal defect examined showed an association.

Results for the examination of effect measure modification by SSB on the association of water consumption (measured on a continuous scale) and birth defects are presented in Figure 3. Overall, several cardiac defects (i.e., anomalous pulmonary venous return, total anomalous pulmonary venous return, tricuspid atresia, and single ventricle complex), and several non-cardiac defects (i.e., anophthalmos / microphthalmus, esophageal atresia, hypospadias, bilateral renal agenesis or hypoplasia, and longitudinal limb deficiency) showed some evidence of possible effect measure modification by SSB consumption. However, modification by SSB consumption was not consistent across all birth defects (e.g. among mothers with higher SSB consumption, the association between water consumption and birth defects is elevated for eye, esophageal, and hypospadias defects when compared to mothers with lower SSB consumption, though the opposite was observed for renal and longitudinal limb defects compared to lower SSB). Results for the examination of effect measure modification by diet quality (Using DQI) on the association of water consumption (measured on a continuous scale) and birth defects are presented in Figure 4. Similar to the SSB analysis, higher DQI scores representing better diets modifies the relationship between water consumption and birth defects inconsistently.

For the sensitivity analysis, women who reported drinking no water during pregnancy (6.4% of all observations) were removed, and quartiles were recalculated. We saw changes in the estimates only for the second and third quartiles (Table 3). Overall patterns of decreasing or increasing odds remained the same with the exception of the subgroups under the heart defects phenotype and the oral cleft subgroup, suggesting that for the most part, women who reported drinking no water did not differ from women who reported drinking water in a way that would substantially impact the relationship between water consumption and risk of birth defects (Table 3). This suggests that women who reported drinking no water during pregnancy did not substantially bias our results. When the sensitivity analysis was conducted among the heart defects phenotype and the oral clefts subgroup, the pattern of decreasing OR with increasing water consumption disappeared, suggesting a plateau, rather than linear effect.

Discussion:

Overall, we observed small to moderate decreases in risk associated with increases in water consumption independent of diet quality, for several birth defects, including spina bifida, cleft lip with or without cleft palate, gastroschisis, limb deficiencies and several congenital heart defects (i.e., hypoplastic left heart syndrome, right-sided obstructions, pulmonary valve

stenosis). Only anotia/microtia showed the opposite pattern of increasing odds. There is some evidence to suggest that diet quality and SSB consumption may act as effect measure modifiers on the association between water consumption and some birth defects; however, results were inconsistent.

Our findings provide preliminary evidence that water consumption during early pregnancy may be associated with the risk of birth defects, but a lack of experimental studies examining the direct relationship between maternal water consumption and birth defects limits understanding and biological plausibility of the observed association. In animal toxicological studies using concurrent controls paired to test groups for water consumption, where drinking water was used as the vehicle of a test toxicant, decreased water consumption was reported to have contributed to developmental and/or reproductive toxicity in rodents (e.g., death, malformations, impaired fetal growth, impaired reproduction) (Campbell et al., 2009). However, the co-occurrence of a toxicant and reduced water intake limits our ability to understand the independent effects of reduced water consumption and extrapolate these findings to humans. Additional studies in which maternal dehydration was induced in the absence of a test toxin have not reported direct evidence of an association between maternal water restriction and birth defects, though these studies have shown associations between maternal water restriction during pregnancy and long-term alterations in osmoregulatory and cardiovascular adaptations in offspring (Desai et al., 2005; Ross et al., 2005). This evidence provides possible biological mechanisms by which inadequate water consumption during pregnancy could impact fetal development. Further experimental research is needed to explore the potential mode of action by which trends in maternal water consumption might impact the development of congenital anomalies.

Water intake may very well be a proxy for a healthier lifestyle. The common alternative to water intake, higher consumption of sugar-sweetened beverages, has been associated with obesity and other less desirable health outcomes (Popkin et al., 2006). Additionally, previous studies suggest that increased water consumption may be associated with healthier diets (Kant and Graubard, 2010; Popkin et al., 2006) and behaviors (Forssen et al., 2007). The potential association between water consumption and diet is particularly important given a recent study suggesting that healthier maternal diet is associated with reduced risks of NTDs and orofacial clefts (Carmichael et al., 2012). However, after including a model adjustment for the same diet quality measure used in Carmichael et al., our results remained consistent (see supplemental material). This suggests that diet quality is not fully responsible for driving the observed relationship between water consumption and birth defects. This is not surprising, considering that neither SSB, nor diet quality as measured by the DQI were strongly correlated with water consumption. It's possible that rather than acting as potential confounders, both DQI and SSB may act as effect measure modifiers on the association between water consumption and birth defects. Another possibility is that diet quality is poorly measured by the DQI for this purpose. Our study is novel in its use of indicators of dietary quality and sugar-sweetened beverage consumption, as other studies on maternal water consumption have been largely unable to take into account dietary considerations.

Overall, the women in our study reported drinking less water than what has previously been reported. The average reported daily water consumption in our study was about 1 liter/day,

2–3 times less than what has been reported by pregnant women in previous studies (Barbone et al., 2002; Kaur et al., 2004; Shimokura et al., 1998; Smith et al., 2009; Zender et al., 2001). It is unclear why water consumption might have been lower among these women compared to women that have participated in previous studies. It is possible that a narrow range in the exposure variable could make it difficult to observe associations with birth defects. Furthermore, we were not able to distinguish between reported water intake and hydration that may be obtained from food rather than directly from water.

We are aware of one other study that examined the association between maternal water consumption and risk of birth defects. A case-control study conducted in California examined the association between a mother's water consumption during pregnancy and cardiac birth defects (Shaw et al., 1990) following the detection of solvents in the groundwater. These analyses revealed elevated effect measures for a mother's reported consumption of cold tap water at home relative to having a child with cardiac anomalies unrelated to the known incident of water contamination. However, this association was imprecise and largely driven by births that occurred over the course of one year. With respect to bottled water consumption, a negative association was found between a mother's use of bottled water and cardiac birth defects among the infants (OR 0.51, 95% CI: 0.26–0.99 for sometimes or usual use of bottled water versus never use bottled water). The bottled water results are consistent with what we observed for congenital heart defects, and specifically for hypoplastic left heart syndrome, right-sided obstructions, and pulmonary valve stenosis. The contrast between tap and bottled water in the Shaw et al. (1990) study may have been the result of an unknown contaminant in the water.

While we generally observed negative associations between the risk of birth defects and increasing maternal water consumption during early pregnancy, these associations were not always consistent across birth defect phenotype groups. For example, we observed negative associations for some congenital heart defects (i.e., hypoplastic left heart syndrome, right-sided obstructions, and pulmonary valve stenosis), but not for others (e.g., conotruncal defects). Similarly, in categorical analyses of quartiles, we observed monotonic associations for some phenotypes, but not for others (See Figures 1 and 2). This lack of consistency could be due to different etiologies for the different birth defect phenotypes or different biological pathways by which the defect phenotypes are initiated.

This study has a number of strengths, including the large sample size and expansive geographic scale of the NBDPS that allows for the analysis of systematically classified birth defects in a nationally representative population-based cohort. The inclusion of live births, fetal deaths, and elective terminations provided for more complete case ascertainment. While the interview portion of the NBDPS presents a risk of recall bias, the scope of the interview has allowed us to gather information on both maternal water consumption, and food intake, which was used to create a DQI. This is one of the first studies of maternal water consumption and birth defects to take other portions of the diet, such as SSB consumption, into consideration.

These preliminary analyses suggest the importance of sufficient water consumption during early pregnancy independent of diet quality. Additional analyses are warranted to understand

the potential biological mechanism responsible for the association, as well as potential regional differences that may arise from different water contaminants

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1:

Odds ratios and 95% confidence intervals for associations between water consumption during the first four months of pregnancy and central nervous system and orofacial birth defects. Water consumption levels from left to right are: Ref (referent, 0–2 glasses), Q2 (quartile 2, 3–4 glasses), Q3 (quartile 3, 5–6 glasses), Q4 (quartile 4, 7+ glasses). Numerical ORs and 95% CIs are reported in Table 3.

Figure 2:

Odds ratios and 95% confidence intervals for associations between water consumption and musculoskeletal, heart, and eye and ear birth defects. Water consumption levels from left to right are: Ref (referent, 0–2 glasses), Q2 (quartile 2, 3–4 glasses), Q3 (quartile 3, 5–6 glasses), Q4 (quartile 4, 7+ glasses). Numerical ORs and 95% CIs are reported in Table 3.

Figure 3:

Odds ratios and 95% confidence intervals for associations between water consumption and select birth defects modified by sugar sweetened-beverage (SSB) consumption. Water consumption is measured on a continuous scale (per 1 glass of water increase). High SSB defined as greater than or equal to the 75th percentile measured among controls (black circles) Low SSB defined as below the 75th percentile measured among controls (white circles). APVR: anomalous pulmonary venous return; TAPVR: total anomalous pulmonary venous return; SV Complex: single ventricle complex; Renal: bilateral renal agenesis or hypoplasia; Tri Atresia: tricuspid atresia.

Figure 4.

Odds ratios and 95% confidence intervals for associations between water consumption and birth defects modified by dietary quality index (DQI). Water consumption is measured on a continuous scale (per 1 glass of water increase). High DQI, representing better dietary quality, defined as greater than or equal to the 75th percentile measured among controls (black circles) Low DQI defined as below the 75th percentile measured among controls (white circles).

Table 1.

Maternal characteristics of cases and controls enrolled in the National Birth Defects Prevention Study, 2001–2005

Variable	All Subjects: n (%)	Cases: n (%)	Controls: n (%)
n	16,973	12,043	4,930
Parity			
0	5,023 (29.7)	3,591 (29.9)	1,432 (29.1)
1	4,840 (28.6)	3,407 (28.4)	1,433 (29.1)
2	3,319 (19.4)	2,332 (19.5)	987 (20.1)
3	1,880 (11.1)	1,357 (11.3)	523 (10.6)
4	956 (5.7)	676 (5.6)	280 (5.7)
5	891 (5.3)	629 (5.3)	262 (5.3)
Missing	64 (0.4)	51 (0.4)	13 (0.3)
Birth Outcome			
Live Birth	16,547 (97.6)	11,621 (96.6)	4,926 (99.9)
Stillbirth/Abortion	415 (2.5)	415 (3.5)	0 (0.0)
Missing	11 (0.1)	7 (0.1)	4 (0.1)
Race			
White Non-Hispanic	9,922 (58.5)	7,062 (58.7)	2,860 (58.0)
Black Non-Hispanic	1,790 (10.6)	1,221 (10.1)	569 (11.5)
Hispanic	4,149 (24.5)	2,985 (24.8)	1,164 (23.6)
Other	1,105 (6.5)	769 (6.4)	336 (6.8)
Missing	7 (<0.1)	6 (0.1)	1 (<0.1)
Age at Delivery			
19 and Under	1,789 (10.5)	1,278 (10.6)	511 (10.4)
20–34	12,700 (74.8)	8,963 (74.4)	3,737 (75.8)
35+	2,484 (14.6)	1,802 (15.0)	682 (13.8)
Missing	0 (0.0)	0 (0.0)	0 (0.0)
Education			
<High School	3,071 (18.4)	2,215 (18.7)	856 (17.7)
High School	4,240 (25.4)	3,063 (25.9)	1,177 (24.3)
Post-Secondary	9,368 (56.2)	6,558 (55.4)	2,810 (58.0)
Missing	294 (1.7)	207 (1.7)	87 (1.8)
Multivitamin Use (B3-P1)			
Little/No Use (0–30 days)	11,337 (68.0)	8,091 (68.4)	3,246 (66.9)
Some Use (>30 days, but less than daily)	1,507 (9.0)	1,055 (8.9)	452 (9.3)
Daily	3,830 (23.0)	2,677 (22.6)	1,153 (23.8)
Missing	299 (1.8)	220 (1.8)	79 (1.6)
Smoking (B1-P3)			
Yes	3,352 (20.0)	2,460 (20.7)	892 (18.4)
No	13,372 (80.0)	9,404 (79.3)	3,968 (81.7)
Missing	249 (1.5)	179 (1.5)	70 (1.4)

Variable	All Subjects: n (%)	Cases: n (%)	Controls: n (%)
Alcohol Consumption (B1-P3)			
Yes	5,919 (35.6)	4,211 (35.6)	1,708 (35.3)
No	10,730 (64.5)	7,599 (64.3)	3,131 (64.7)
Missing	324 (1.9)	233 (1.9)	91 (1.9)
BMI			
Underweight (<18.5)	871 (5.4)	616 (5.4)	255 (5.4)
Normal Weight (18.5 ≤ BMI < 25)	8,495 (52.5)	5,923 (51.6)	2,572 (54.7)
Overweight (25 ≤ BMI < 30)	3,753 (23.2)	2,658 (23.2)	1,095 (23.3)
Obese (≥ 30)	3,061 (18.9)	2,280 (19.9)	781 (16.6)
Missing	793 (4.7)	566 (4.7)	227 (4.6)
Dietary Quality Index (DQI)^a			
Quartile 1	4,939 (30.3)	3,570 (30.9)	1,369 (28.8)
Quartile 2	4,130 (25.3)	2,988 (25.9)	1,142 (24.0)
Quartile 3	3,931 (24.1)	2,751 (23.8)	1,180 (24.8)
Quartile 4	3,308 (20.3)	2,246 (19.4)	1,062 (22.9)
Missing	665 (3.9)	488 (4.1)	177 (3.6)
Employment (B3-Delivery)			
Had Job/Student	12,443 (74.5)	8,826 (74.5)	3,617 (74.5)
No Job	4,263 (25.5)	3,025 (25.5)	1,238 (25.5)
Missing	267 (1.6)	192 (1.6)	75 (1.5)
NBDPS Center			
Arkansas	2,265 (13.3)	1,619 (13.4)	646 (13.1)
California	2,285 (13.5)	1,638 (13.6)	647 (13.1)
Iowa	1,687 (9.9)	1,167 (9.7)	520 (10.5)
Massachusetts	2,051 (12.1)	1,510 (12.5)	541 (11.0)
New Jersey	1,100 (6.5)	786 (6.5)	314 (6.4)
New York	1,198 (7.1)	787 (6.5)	411 (8.3)
Texas	2,081 (12.3)	1,506 (12.5)	575 (11.7)
CDC/Atlanta	1,986 (11.7)	1,464 (12.2)	522 (10.6)
North Carolina	1,025 (6.0)	628 (5.2)	397 (8.1)
Utah	1,295 (7.6)	938 (7.8)	357 (7.2)

^aDQI is a quartile-level categorical variable that serves as an indicator for maternal diet quality. Higher quartiles are indicative of a higher diet quality.

Table 2.

Summary of maternal water consumption during the first four months of pregnancy by source

	Mean (SD)	25 th percentile	75 th percentile	Range
Glasses of unfiltered tap	1.42 (2.82)	0.00	2.00	0–32
Glasses of filtered tap	1.17 (2.73)	0.00	1.00	0–32
Glasses of bottled	1.79 (2.92)	0.00	3.00	0–32
Glasses other	0.14 (0.91)	0.00	0.00	0–16
Glasses Total	4.40 (3.11)	2.00	6.00	0–32

Note: 1 glass is assumed to be 8 oz.

Conversion: 33.8 oz. = 1 liter

Table 3.

Adjusted associations between maternal water consumption quartiles and select birth defects, with sensitivity analysis

Birth defect subgroup	Including 0 glasses of water ^a			Sensitivity analysis excluding 0 glasses of water ^a		
	Cases	Controls	Adjusted ^b OR (95% CI)	Cases	Controls	Adjusted ^b OR (95% CI)
Central nervous system defects						
<i>Neural tube defects (NTD)</i>						
Q1 (0–2 total glasses) ^c	243	1,316	1 [†]	303	1,764	1 [†]
Q2 (3–4 total glasses) ^d	290	1,537	0.99 (0.81, 1.21)	155	798	1.12 (0.89, 1.40)
Q3 (5–6 total glasses)	149	971	0.78 (0.61, 0.99)	149	971	0.86 (0.68, 1.08)
Q4 (7+ total glasses)	148	1,105	0.69 (0.54, 0.88)	148	1,105	0.76 (0.60, 0.95)
<i>Spina bifida</i>						
Q1 (0–2 total glasses) ^c	138	1,316	1 [†]	184	1,764	1 [†]
Q2 (3–4 total glasses) ^d	174	1,537	1.04 (0.81, 1.34)	90	798	1.07 (0.81, 1.42)
Q3 (5–6 total glasses)	94	971	0.86 (0.63, 1.15)	94	971	0.88 (0.66, 1.17)
Q4 (7+ total glasses)	88	1,105	0.68 (0.50, 0.92)	88	1,105	0.70 (0.52, 0.93)
Eye and ear defects						
<i>Anotia / microtia</i>						
Q1 (0–2 total glasses) ^c	45	1,316	1 [†]	72	1,764	1 [†]
Q2 (3–4 total glasses) ^d	83	1,537	1.51 (1.00, 2.30)	45	798	1.46 (0.95, 2.23)
Q3 (5–6 total glasses)	40	971	1.20 (0.74, 1.95)	40	971	1.06 (0.68, 1.64)
Q4 (7+ total glasses)	48	1,105	1.40 (0.88, 2.22)	48	1,105	1.23 (0.81, 1.86)
Orofacial defects						
<i>Oral clefts</i>						
Q1 (0–2 total glasses) ^c	530	1,289	1 [†]	687	1,731	1 [†]
Q2 (3–4 total glasses) ^d	518	1,496	0.80 (0.69, 0.93)	244	772	0.80 (0.67, 0.95)
Q3 (5–6 total glasses)	281	937	0.74 (0.62, 0.88)	281	937	0.79 (0.67, 0.94)
Q4 (7+ total glasses)	319	1,075	0.73 (0.61, 0.86)	319	1,075	0.78 (0.66, 0.92)
<i>Cleft lip + cleft palate</i>						
Q1 (0–2 total glasses) ^c	237	1,289	1 [†]	294	1,731	1 [†]
Q2 (3–4 total glasses) ^d	223	1,496	0.78 (0.63, 0.96)	110	772	0.84 (0.66, 1.08)
Q3 (5–6 total glasses)	120	937	0.69 (0.54, 0.89)	120	937	0.77 (0.60, 0.98)
Q4 (7+ total glasses)	123	1,075	0.64 (0.49, 0.82)	123	1,075	0.71 (0.56, 0.90)
<i>Cleft lip with or without cleft palate</i>						
Q1 (0–2 total glasses) ^c	357	1,289	1 [†]	465	1,731	1 [†]
Q2 (3–4 total glasses) ^d	365	1,496	0.83 (0.69, 0.98)	174	772	0.85 (0.69, 1.04)
Q3 (5–6 total glasses)	189	937	0.72 (0.59, 0.89)	189	937	0.78 (0.64, 0.95)

Birth defect subgroup	Including 0 glasses of water ^a			Sensitivity analysis excluding 0 glasses of water ^a		
	Cases	Controls	Adjusted ^b OR (95% CI)	Cases	Controls	Adjusted ^b OR (95% CI)
Q4 (7+ total glasses)	208	1,075	0.69 (0.56, 0.85)	208	1,075	0.75 (0.62, 0.91)
Musculoskeletal defects						
<i>Limb deficiencies</i>						
Q1 (0–2 total glasses) ^c	111	1,316	1 [†]	146	1,764	1 [†]
Q2 (3–4 total glasses) ^d	118	1,537	0.84 (0.63, 1.13)	61	798	0.92 (0.66, 1.27)
Q3 (5–6 total glasses)	61	971	0.70 (0.50, 1.00)	61	971	0.75 (0.54, 1.05)
Q4 (7+ total glasses)	72	1,105	0.74 (0.53, 1.04)	72	1,105	0.80 (0.58, 1.09)
<i>Gastroschisis</i>						
Q1 (0–2 total glasses) ^c	169	1,316	1 [†]	213	1,764	1 [†]
Q2 (3–4 total glasses) ^d	156	1,537	0.88 (0.68, 1.14)	71	798	0.92 (0.68, 1.25)
Q3 (5–6 total glasses)	84	971	0.84 (0.62, 1.14)	84	971	0.88 (0.66, 1.18)
Q4 (7+ total glasses)	73	1,105	0.67 (0.49, 0.93)	73	1,105	0.71 (0.52, 0.96)
Heart Defects						
<i>Hypoplastic left heart syndrome</i>						
Q1 (0–2 total glasses) ^c	89	1,361	1 [†]	111	1,764	1 [†]
Q2 (3–4 total glasses) ^d	84	1,577	0.81 (0.58, 1.12)	34	798	0.60 (0.39, 0.92)
Q3 (5–6 total glasses)	53	994	0.77 (0.52, 1.13)	48	971	0.71 (0.48, 1.03)
Q4 (7+ total glasses)	55	1,152	0.74 (0.51, 1.07)	49	1,105	0.69 (0.48, 1.00)
<i>Right-sided obstructions (RVOTO)</i>						
Q1 (0–2 total glasses) ^c	300	1,361	1 [†]	351	1,764	1 [†]
Q2 (3–4 total glasses) ^d	286	1,577	0.80 (0.66, 0.96)	117	798	0.73 (0.57, 0.92)
Q3 (5–6 total glasses)	171	994	0.77 (0.62, 0.96)	149	971	0.79 (0.63, 0.98)
Q4 (7+ total glasses)	189	1,152	0.71 (0.57, 0.88)	157	1,105	0.73 (0.59, 0.90)
<i>Pulmonary valve stenosis (PVS)</i>						
Q1 (0–2 total glasses) ^c	228	1,290	1 [†]	266	1,686	1 [†]
Q2 (3–4 total glasses) ^d	217	1,508	0.81 (0.66, 1.01)	92	766	0.77 (0.59, 1.01)
Q3 (5–6 total glasses)	130	954	0.79 (0.61, 1.01)	114	932	0.81 (0.63, 1.04)
Q4 (7+ total glasses)	146	1,093	0.77 (0.60, 0.98)	118	1,046	0.77 (0.60, 0.98)

^aThe sensitivity analysis uses new quartiles of exposure that were calculated when mothers who report drinking 0 glasses of water were excluded. All other covariates remained the same.

^bAdjusted for maternal race, maternal age, maternal education, plurality, maternal BMI, and prenatal vitamin use and dietary index

^c1–3 in sensitivity analysis excluding 0 glasses

^d4 in sensitivity analysis excluding 0 glasses

[†]Referent Group