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Maternal Periconceptional Alcohol Consumption and Gastroschisis in the National Birth Defects Prevention Study, 1997-2011

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Abstract

Background: Gastroschisis is particularly prevalent among offspring of young women and has increased over recent decades. Although previous studies suggest that maternal alcohol consumption is associated with increased gastroschisis risk, none have explored whether maternal age modifies that association.

Objective: To evaluate associations between self-reported maternal periconceptional alcohol consumption (one month prior through the third month after conception) and risk of gastroschisis among offspring, by maternal age.

Methods: We used data from the National Birth Defects Prevention Study (NBDPS), a multi-site population-based case-control study. Our analysis included 1,450 gastroschisis cases and 11,829 unaffected liveborn controls delivered during 1997-2011 in ten US states. We estimated adjusted odds ratios (aORs) and 95% confidence intervals (CIs) for the individual and joint effects of alcohol consumption and young maternal age at delivery (<25 years vs. ≥25 years) on gastroschisis risk. We estimated the relative excess risk due to interaction (RERI) to quantify additive interaction.

Results: Periconceptional alcohol consumption was common regardless of maternal age (women <25 years: cases 38.8%, controls 29.3%; women ≥25: cases 43.5%, controls 39.5%). Compared

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to women ≥25 years who did not consume alcohol, we observed increased risk of gastroschisis among women <25 years, with higher estimates among those who consumed alcohol (women <25 years who did not consume alcohol: aOR 5.90, 95% CI 4.89, 7.11; women <25 years who did consume alcohol: aOR 8.21, 95% CI 6.69, 10.07). Alcohol consumption among women ≥25 years was not associated with gastroschisis (aOR 1.12, 95% CI 0.88, 1.42). This suggests super-additive interaction between alcohol consumption and maternal age (RERI=2.19, 95% CI 1.02, 3.36).

Conclusions: Periconceptional alcohol consumption may disproportionately increase risk of gastroschisis among young mothers. Our findings support public health recommendations to abstain from alcohol consumption during pregnancy.

Keywords

gastroschisis; pregnancy; alcohol; NBDPS; additive interaction

Background

Gastroschisis is a serious abdominal birth defect characterized by improper attachment of the umbilical cord to the umbilical ring, allowing the fetus' intestines to protrude.[1,2] The estimated prevalence of gastroschisis in the US is 3.8/10,000 live births. Although the prevalence had been increasing over the past several decades[3,4], recent evidence suggests the trend is now leveling off or even decreasing.[5,6] Gastroschisis is particularly prevalent among young mothers, ranging in the US from 1.7/10,000 live births among women 25 years and older, to 8.1/10,000 among women aged 20-24 years, to 16.1/10,000 among women younger than 20 years.[4] The causes of these trends are not well understood, but may be due in part to changing patterns over time in environmental and/or behavioral risk factors for gastroschisis, such as alcohol intake.[7] Alcohol is a known teratogen.[8] The existing literature generally—although not universally[9-11]—supports the hypothesis that periconceptional alcohol consumption is associated with increased risk of gastroschisis.[12-17] However, previous studies were limited in their ability to assess effects of different levels of alcohol intake (i.e., binge drinking) or joint effects with other factors strongly associated with gastroschisis, such as maternal age. Using data from the National Birth Defects Prevention Study (NBDPS), this study aimed to further investigate associations between maternal periconceptional alcohol consumption and gastroschisis and the potential role of maternal age in modifying those associations.

Methods

The NBDPS was a multi-site, population-based, case-control study designed to investigate risk factors for more than 30 major structural birth defects. A detailed description of recruitment, eligibility criteria, and data collection methods have been published elsewhere.[18] Briefly, data on pregnancy exposures were collected via computer-assisted telephone interview in English or Spanish between 6 weeks and 2 years after the estimated dates of delivery. Participants provided informed consent and each site and the Centers for Disease Control and Prevention obtained institutional review board approval.

Case and Control Selection

NBDPS was conducted in 10 US states (Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, and Utah) among recently-pregnant women with estimated delivery dates during October 1997 through December 2011. Liveborn, stillborn, or terminated pregnancies affected by gastroschisis ("cases") were ascertained from birth defect surveillance systems in each participating state. Liveborn infants without any major birth defects ("controls") were randomly selected from birth records or hospital discharge reports in the same geographic catchment areas as cases.

Outcome Assessment

Clinical geneticists reviewed abstracted medical records for each case to determine eligibility and further classify the diagnosed birth defects according to study criteria. Each case of gastroschisis was classified as either isolated (gastroschisis was the only major defect, or only occurred with another developmentally related defect, such as intestinal atresia) or multiple (gastroschisis occurred in addition to another unrelated major structural defect, in another organ system).[19] Cases with gastroschisis in conjunction with limb-body wall complex were classified as amniotic band sequence and not gastroschisis. Those with known chromosomal abnormalities or single gene disorders were excluded.

Exposure Assessment

Consistent with previously published NBDPS studies[12,20-22], we assessed self-reported maternal alcohol consumption in response to six interview questions about the timing, frequency, amount, and type of alcohol consumption during the three months before through the end of pregnancy (eFigure 1). Because the developing embryo is most susceptible to teratogens early in gestation, this study focused on alcohol exposure during the periconceptional period (defined as the month before conception through the third month of gestation). We calculated dichotomous exposure variables for any alcohol consumption and any binge drinking (defined as ≥4 drinks on one occasion). We created categorical variables indicating the average number of drinks consumed per periconceptional month and the number of days per periconceptional month in which alcohol was consumed (i.e., frequency). For analysis, we used the values assigned to the month with the highest number of drinks consumed ("maximum average number of alcoholic drinks per month") and the highest number of days in which alcohol was consumed ("maximum frequency of alcohol consumption per month"). We calculated duration of alcohol exposure as the number of gestational months during which alcohol was consumed.

Overall, 65% of eligible case mothers and 65% of control mothers participated in the NBDPS interview. Among the participants in this analysis, the median time from estimated delivery date to completed interview was approximately 9 months for case mothers (268 days) and 7.5 months for control mothers (226 days). Our final study population included 1,450 gastroschisis cases and 11,829 controls.

Statistical Analysis

Using unconditional logistic regression, we estimated odds ratios (OR) and 95% confidence intervals (CI) to assess the association between alcohol consumption and gastroschisis. We

selected model covariates *a priori* based on subject area expertise and a review of the literature: periconceptional cigarette smoking status (any vs. none), prepregnancy body mass index (BMI: weight in kg/height in m^2) (BMI<18.5 or "underweight", BMI 25.0-29.9 or "overweight", or BMI ≥30 or "obese" vs. BMI 18.5-24.9 or "normal"), self-reported race/ethnicity (Non-Hispanic Black, Hispanic, or Other vs. Non-Hispanic White), and study site. Because we were interested in effect measure modification by maternal age, we stratified by dichotomous maternal age (<25 years at delivery vs. ≥25 years). We chose this age cut point because this was the point in our data at which the association between gastroschisis and maternal age flipped from increased to decreased/null risk, and it is a cut point used by others.[23]

We compared the prevalence of select maternal characteristics and each measure of alcohol consumption (any drinking, any binge drinking, maximum average number of drinks per month, maximum number of days drinking per month, and drinking duration) by case/control status within maternal age strata. We assessed individual and joint effects of alcohol consumption (any vs. none; binge vs. none) and maternal age, calculating adjusted ORs and 95% CIs for each combination of alcohol intake and maternal age, using the "doubly unexposed" women (i.e., women ≥25 years at delivery who did not consume alcohol periconceptionally) as the reference group. To measure interaction on the additive scale, we calculated the relative excess risk due to interaction (RERI) with 95% CIs based on standard errors calculated using the delta method.[24] The RERI indicates presence and direction of interaction, where 0 constitutes the null value. A value other than 0 indicates a departure from additivity but does not necessarily represent the magnitude of interaction. We assessed interaction on the multiplicative scale by including a product term for maternal age and alcohol consumption in our adjusted models.

Missing Data

To account for missingness of self-reported exposure and model covariates, we conducted a sensitivity analysis using multiple imputation with fully conditional specification and 40 imputed datasets. In addition to our model covariates and outcome, our imputation model included interview language (Spanish or English), maternal education level, any maternal alcohol consumption during pregnancy, and household income as auxiliary variables. To preserve the interaction effects between age and alcohol consumption on gastroschisis risk, we imputed data separately within each strata of dichotomous maternal age.[25] We calculated ORs and the RERI for each imputed dataset and pooled results, using the mathematical average for point estimates and Rubin's rules to estimate the variance.[26]

Sensitivity Analyses

As a sensitivity analysis, we developed indicators of alcohol intake based on more specific measures of consumption frequency and quantity, as well as more specific timing of exposure. We evaluated additive interaction between maternal age and frequent consumption (maximum monthly consumption frequency of 16-30 days vs. none), heavy consumption (maximum monthly quantity of >30 drinks vs. none; maximum average monthly consumption ≥4 drinks per occasion vs. no periconceptional drinking), and consistent consumption (any and binge consumption in each periconceptional month vs. no

periconceptional intake). We assessed additive interaction between these alcohol exposures during the first two post-conception months compared to none, as this may more precisely capture the period of embryogenesis when gastroschisis occurs.[27] Finally, we evaluated interaction between periconceptional alcohol consumption (any vs. none and binge vs. none) and more specific young maternal age categories: <20 years at delivery, 20-24 years, 25-29 years, and ≥30 years.

All analyses were conducted in SAS (version 9.4; SAS Institute, Cary, NC).

Results

Overall, gastroschisis case mothers were disproportionately young compared to control mothers in our sample: 78.1% of cases were among women <25 years (1133/1450), compared to 32.5% of controls (3845/11,829). Regardless of age strata, case mothers more often than control mothers reported Hispanic race/ethnicity, normal or underweight BMI, nulliparity, family history of gastroschisis, unintended pregnancy, and periconceptional cigarette use, opioid use, and genitourinary infection (Table 1). Among women ≥25 years, case mothers also reported lower household income, less folic acid supplement use, and more periconceptional selective serotonin reuptake inhibitor (SSRI) use than control mothers.

Periconceptional alcohol consumption was more commonly reported among women ≥25 years (cases: 43.5%, controls: 39.5%) than among women <25 years (cases: 38.8%, controls: 29.3%) (Table 2). However, younger women more often reported binge drinking and to report drinking liquor or mixed drinks than older women, who reported drinking more beer and wine. Across both age groups and case/control status, the highest proportion of periconceptional drinkers reported alcohol consumption (any and binge) in the month before conception, with decreasing prevalence in every subsequent month.

We observed that women <25 years had markedly higher risk of gastroschisis than older women, regardless of alcohol consumption status (Tables 3a-b). Younger women who did not consume alcohol had six times higher risk of gastroschisis than older women who did not consume alcohol (OR 5.90, 95% CI 4.89, 7.11). Periconceptional alcohol consumption was not associated with increased risk of gastroschisis among older women (OR 1.12, 95% CI 0.88, 1.42), but it was among younger women (OR 8.21, 95% CI 6.69, 10.07). These estimates represent super-additive interaction between alcohol and young maternal age (RERI 2.19, 95% CI 1.02, 3.36); in other words, the OR associated with double exposure was greater than expected, given the ORs associated with each single exposure. Binge consumption modestly increased risk among older women (OR 1.77, 95% CI 1.31, 2.41), but again not to the same extent as among younger women (OR 8.49, 95% CI 6.68, 10.80). The joint effects of binge consumption and young maternal age had a similar pattern to any consumption, but the RERI estimate was less precise (RERI 1.70, 95% CI 0.10, 3.30). We did not find evidence of interaction on the multiplicative scale between either measure of alcohol consumption and maternal age.

Across the 5 covariates and 2 exposure variables in our analysis, data were missing for 0-6.1% of subjects within age strata (Tables 1 and 2). Our analysis using multiple imputation yielded estimates that were largely unchanged from analyses using observed data (eTable 1). Patterns observed in our primary analyses generally held across all sensitivity analyses conducted with different exposure measures based on quantity, frequency, and timing of alcohol consumption (eTables 2-3). In our analyses of finer maternal age categories, risk of gastroschisis was highest among women <20 years at delivery, and lowest among women ≥30 years. The super-additive effect of alcohol consumption on gastroschisis risk in women <20 years and 20-24 years remained when compared to women ≥30 years (eTable 4). Any alcohol consumption increased the risk of gastroschisis from 20.24 (95% CI 17.41, 37.24) to 25.47 (95% CI 17.41, 37.24) among women <20 years and from 8.11 (95% CI 5.88, 11.19) to 13.92 (95% CI 9.99, 19.42) among women aged 20-24 years; alcohol was not associated with increased risk of gastroschisis among women ≥30 years (OR 1.01, 95% CI 0.66, 1.54). These results largely support our dichotomous age analyses, demonstrating that the super-additive effective of young age and alcohol consumption on gastroschisis risk is present among even moderately young women (20-24 years) and not only women <20 years.

Comment

Principal findings

In our study, periconceptional alcohol consumption was common, particularly among women aged 25 years and older at delivery (39.5% among controls). We observed evidence of super-additive interaction between young maternal age and periconceptional alcohol consumption, such that their joint effect was associated with a disproportionate increase in the risk of having a pregnancy affected by gastroschisis.

Strengths

NBDPS cases were classified by clinical geneticists according to a standard protocol, ensuring a homogenous case group for analysis. Interviewers were highly trained to establish rapport and build trust with subjects, including probing to ensure complete and detailed responses to exposure questions. The NBDPS interview included questions on a wide range of other exposures, improving our ability to control for confounding. Finally, as one of the largest case-control studies of birth defects in the US, our sample size enabled us to analyze various combinations of alcohol- and age-exposure strata, exploring interaction in a level of detail that others have not.

Limitations

When interpreting our results, it is important to acknowledge that our alcohol exposure data are all self-reported. Alcohol is widely understood to be associated with adverse pregnancy outcomes, potentially leading to social stigma against women who choose to consume alcohol during pregnancy or before they become aware of their pregnancy. This perceived stigma could lead to underreporting. Prevalence of prenatal alcohol exposure has been shown to be lower when based on maternal self-report compared to estimates based on presence of fatty acid ethyl esters in meconium, a validated biomarker for fetal alcohol exposure during the second and third trimesters.[28] Given that NBDPS is a retrospective

case-control study, with exposures self-reported after the pregnancy outcome is known, data on alcohol may be particularly susceptible to social desirability bias. If cases were more likely to underreport their true alcohol consumption than controls, and younger women were more likely to underreport than older women, our estimates could be biased towards the null, underestimating the true risk. It is also possible, given that women were eligible for interview for two years after their estimated date of delivery, that there is some unintentional exposure misclassification due to poor recall. However, our prevalence estimates of periconceptional alcohol consumption among controls are generally higher than that reported based on Behavioral Risk Factor Surveillance System data[29], another self-reported data source including pregnant women aged 18-44 years.

Another limitation is potential bias due to uncontrolled confounding. NBDPS involved a detailed questionnaire about many potential risk factors, and we controlled for several in our adjusted models: cigarette smoking[11,17], BMI[30,31], race[32,33]. Nevertheless, there may be unmeasured confounders affecting the alcohol-gastroschisis relationship that we observed. For instance, recreational drugs may be consumed in combination with alcohol and have been shown to be associated with gastroschisis risk.[34] However, these data were inconsistently collected throughout NBDPS, making it difficult to control for other types of substance use.

Finally, missingness for key alcohol exposure measures was 5% for cases and 3% for controls, while smoking status and BMI were each missing for 3-5% of participants. Taken together, 8.3% of cases and 7.4% of controls were missing data on periconceptional alcohol consumption (any or binge) or at least one model covariate, which may have introduced selection bias. Based on the information we have on women missing data, we know that they were disproportionately young, Hispanic, less educated, and lower income. However, the results of our sensitivity analysis using multiple imputation were not meaningfully different than our observed data analysis results, suggesting that bias due to data missing not at random in our study was minimal.

Interpretation

Although both alcohol and young maternal age were associated with increased risk of gastroschisis in our study, young maternal age was a much stronger risk factor. The relationship between young maternal age and gastroschisis has been consistently demonstrated.[9,11,13-15] Studies of the association between alcohol consumption and gastroschisis have more mixed results. Two previous analyses of NBDPS data have found modestly positive associations between periconceptional alcohol and gastroschisis.[12,13] Neither assessed interaction between alcohol and maternal age; Richardson et al. controlled for maternal age at delivery, Bird et al. did not. Our study adds six years of additional data to the Richardson et al. analysis and eight to Bird et al. Not surprisingly, our estimates of the association between alcohol and gastroschisis within maternal age strata are similar to the common odds ratios previously reported from NDBPS data (AOR 1.4 in both studies), but these estimates mask the magnitude of the effect of young maternal age on gastroschisis risk, with or without alcohol consumption, that we observed.

Analyses of other data sets have yielded a wide range of effect estimates associated with alcohol consumption treating maternal age as a confounder rather than an effect modifier. Studies from California[9] and Canada[35] observed estimates similar to those from NBDPS (ORs 1.6-1.7), while others report protective effects (OR 0.8)[11] as well as ORs well above null (OR 15.1).[17] Many studies rely on administrative exposure data[9,17,35] and differences in alcohol consumption measurement makes it difficult to compare results. However one age-matched case-control study in Brazil used a modified version of the NBDPS questionnaire and reported a moderately strong association between periconceptional alcohol consumption and gastroschisis (OR 2.6).[16] That this estimate is higher than among NBDPS participants may reflect different consumption patterns between populations.

To our knowledge, ours is the first study to explicitly describe additive interaction between maternal age and alcohol consumption when estimating gastroschisis risk. At least one other exploratory study of gastroschisis risk factors stratified by maternal age (<20 years vs. ≥20 years), but did not find alcohol consumption to be independently associated with gastroschisis in either age group.[10] This does not necessarily conflict with our results, as we did not find strong evidence of interaction on the multiplicative scale between slightly different age categories and alcohol, and our stratified estimates were modest with lower CIs close to null. It is worth noting that interaction on the additive scale is often overlooked, likely because it can be more computationally onerous.[36] Others have observed additive interaction between BMI and age on gastroschisis risk[37], as well as between genitourinary infection and age.[23,38] Like ours, these studies also found super-additive effects on gastroschisis risk among the doubly-exposed (young age with low BMI or young age with any genitourinary infection).

Young women continue growing for several years post menarche, regardless of their fecundity.[39,40] Thus, pregnancy among women under age 25 does not necessarily imply biologic maturity. These physiological differences between younger and older mothers may affect the way alcohol consumption affects their developing embryos. There is evidence from animal models that at least some of the effects of alcohol consumption vary by age. Adolescent rats are less sensitive to short-term sedative, anxiolytic, and motor-impairing effects of acute alcohol consumption compared to adult rodents, but more sensitive to longer-term neurodevelopmental effects of chronic consumption.[41] Some have hypothesized that reduced susceptibility to the effects of acute alcohol may be due to age-specific differences in alcohol pharmacokinetics[42], but this finding has not been replicated in all animal models.[43]

Another possible explanation for our findings is that young women consume alcohol differently than older women in a way that our interview questions did not fully capture. Among study participants, younger women were less likely to report periconceptional alcohol consumption than their older counterparts, but younger women who did report drinking reported more drinks per occasion than older women. The RERI for the interaction between young age and binge alcohol consumption on the risk of gastroschisis was less precise than that for any alcohol consumption, with a confidence interval bordering the null value, suggesting that differences in the quantity of alcohol consumed may account for some of the variation by age. We did not ask women about frequency of binge episodes, making it

difficult to differentiate between women with true alcohol use disorder and women with only one binge episode. Younger women also more commonly reported drinking liquor or mixed drinks. Although our interviewers explicitly defined one drink as “one beer, one glass of wine, one mixed drink, or one shot of liquor”, customary serving sizes may not reflect these amounts, particularly for mixed drinks. Measurement error may be present if “one drink” reported by young women more often contained more alcohol than “one drink” among older women, who more often reported drinking wine or beer.

Finally, because alcohol is illegal in the US for women under age 21, consumption among this age group is an inherently riskier behavior than it is among older women. Sexual activity in the context of alcohol and substance use is one aspect of a spectrum of sexual risk-taking behaviors that also result in higher rates of sexually transmitted infections and unintended pregnancy among young women.[44] We cannot rule out the possibility that alcohol use in our study serves as a proxy for other behaviors that often co-occur with alcohol use among young women that are driving the observed increase risk of gastroschisis.

Conclusions

We observed evidence that maternal age modifies the measured effect of periconceptional alcohol consumption on the risk of gastroschisis. We demonstrated a super-additive relationship between young maternal age and alcohol. Although independent associations between young age and alcohol on gastroschisis have been demonstrated elsewhere, we presented their joint effects on the additive scale. Further investigation of underlying age-specific consumption patterns is necessary to better understand how these two factors are related to gastroschisis risk.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Sharing and Data Accessibility:

The study questionnaires and process for accessing the data used in this study is described at https://www.cdc.gov/ncbddd/birthdefects/nbdps-public-access-procedures.html. The code book may be made available upon request.

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Synopsis

- **Study question:** Is maternal alcohol consumption during early pregnancy associated with risk of gastroschisis among offspring? Is the effect of alcohol consumption on gastroschisis risk modified by maternal age?
- **What's already known:** Young maternal age is a strong risk factor for having a pregnancy affected by gastroschisis. Alcohol is a known teratogen, with consumption patterns associated with age, and with evidence of a modest effect on gastroschisis risk.
- **What this study adds:** The joint effects of young maternal age and maternal alcohol consumption—two common and modifiable exposures—on gastroschisis risk are not well understood. Our results suggest that alcohol consumption during early pregnancy may disproportionately increase risk of gastroschisis among young women.

Table 1.

Characteristics of study sample, by maternal age category and case/control status, NBDPS 1997-2011. Unless noted otherwise, values are n(%).

	Overall (n=13,279)		Women ≥25 years (n=8,301)		Women <25 years (n=4,978)	
Characteristic	**Controls**	**Cases**	**Controls**	**Cases**	**Controls**	**Cases**
Overall	11829	1450	7984	317	3845	1133
Maternal age at delivery						
<20 years	1177 (10.0)	520 (35.9)	-	-	1177 (30.6)	520 (45.9)
20-24 years	2668 (22.6)	613 (42.3)	-	-	2668 (69.4)	613 (54.1)
25-29 years	3271 (27.7)	223 (15.4)	3271 (41.0)	223 (70.4)	-	-
30-34 years	3049 (25.8)	75 (5.2)	3049 (38.2)	75 (23.7)	-	-
≥35 years	1664 (14.1)	19 (1.3)	1664 (20.8)	19 (6.0)	-	-
Missing	*0 (0)*	*0 (0)*	*0 (0)*	*0 (0)*	*0 (0)*	*0 (0)*
Maternal race/ethnicity						
Non-Hispanic white	6836 (57.8)	731 (50.4)	5110 (64.0)	189 (59.6)	1726 (44.9)	542 (47.8)
Non-Hispanic black	1308 (11.1)	128 (8.8)	708 (8.9)	27 (8.5)	600 (15.6)	101 (8.9)
Hispanic	2908 (24.6)	470 (32.4)	1618 (20.3)	78 (24.6)	1290 (33.6)	392 (34.6)
Other	770 (6.5)	121 (8.3)	544 (6.8)	23 (7.3)	226 (5.9)	98 (8.7)
Missing	*7 (0.1)*	*0 (0)*	*4 (0.1)*	*0 (0)*	*3 (0.1)*	*0 (0)*
Prepregnancy body mass index (BMI)						
Underweight (BMI<18.5)	599 (5.1)	126 (8.7)	294 (3.7)	10 (3.2)	305 (7.9)	116 (10.2)
Normal (BMI 18.5-24.9)	6045 (51.1)	942 (65.0)	4120 (51.6)	206 (65.0)	1925 (50.1)	736 (65.0)
Overweight (BMI 25-29.9)	2557 (21.6)	252 (17.4)	1794 (22.5)	72 (22.7)	763 (19.8)	180 (15.9)
Obese (BMI ≥30)	2074 (17.5)	78 (5.4)	1453 (18.2)	21 (6.6)	621 (16.2)	57 (5.0)
Missing	*554 (4.7)*	*52 (3.6)*	*323 (4.1)*	*8 (2.5)*	*231 (6.1)*	*44 (3.9)*
Diabetes status						
Preexisting type 1/type 2	83 (0.7)	5 (0.3)	61 (0.8)	3 (1.0)	22 (0.6)	2 (0.2)
Gestational diabetes	811 (6.9)	33 (2.3)	638 (8.0)	12 (3.8)	173 (4.5)	21 (1.9)
Missing	*95 (0.8)*	*8 (0.6)*	*57 (0.7)*	*3 (1.0)*	*38 (1.0)*	*5 (0.4)*
Parity[a] ≥1	7164 (60.6)	515 (35.5)	5529 (69.3)	192 (60.6)	1635 (42.5)	323 (28.5)
Missing	*51 (0.4)*	*5 (0.3)*	*26 (0.3)*	*1 (0.3)*	*25 (0.7)*	*4 (0.4)*
Plurality >1	351 (3.0)	33 (2.3)	286 (3.6)	8 (2.5)	65 (1.7)	25 (2.2)

	Overall (n=13,279)		Women ≥25 years (n=8,301)		Women <25 years (n=4,978)	
Characteristic	**Controls**	**Cases**	**Controls**	**Cases**	**Controls**	**Cases**
Missing	*1 (0.01)*	*0 (0)*	*1 (0.01)*	*0 (0)*	*0 (0)*	*0 (0)*
Infant sex (male)	6024 (50.9)	729 (50.3)	4064 (50.9)	153 (48.3)	1960 (51.0)	576 (50.8)
Missing	*12 (0.1)*	*3 (0.2)*	*9 (0.1)*	*1 (0.3)*	*3 (0.1)*	*2 (0.2)*
Family history of gastroschisis	8 (0.1)	16 (1.1)	6 (0.1)	7 (2.2)	2 (0.1)	9 (0.8)
Missing	*0 (0)*	*0 (0)*	*0 (0)*	*0 (0)*	*0 (0)*	*0 (0)*
Annual household income						
<$30,000	4819 (40.7)	893 (61.6)	2265 (28.4)	153 (48.3)	2554 (66.4)	740 (65.3)
$30,000-$49,999	1864 (15.8)	198 (16.7)	1403 (17.6)	59 (18.6)	461 (12.0)	139 (12.3)
≥$50,000	3889 (32.9)	149 (10.3)	3642 (45.6)	80 (25.2)	247 (6.4)	69 (6.1)
Missing	*1257 (10.6)*	*210 (14.5)*	*674 (8.4)*	*25 (7.9)*	*583 (15.2)*	*185 (16.3)*
Pregnancy intention						
Intended then	7100 (60.0)	582 (40.1)	5493 (68.8)	170 (53.6)	1607 (41.8)	412 (36.4)
Mistimed/unintended	3800 (32.1)	732 (50.5)	1875 (23.5)	118 (37.2)	1925 (50.1)	614 (54.2)
Ambivalent	843 (7.1)	125 (8.6)	566 (7.1)	27 (8.5)	277 (7.2)	98 (8.7)
Missing	*86 (0.7)*	*11 (0.8)*	*50 (0.6)*	*2 (0.6)*	*36 (0.9)*	*9 (0.8)*
Periconceptional[b] folic acid supplement use	7100 (60.0)	582 (40.1)	4808 (60.2)	160 (50.5)	1357 (35.3)	391 (34.5)
Missing	3800 (32.1)	732 (50.5)	*89 (1.1)*	*4 (1.3)*	*68 (1.8)*	*22 (1.9)*
Periconceptional cigarette smoking	2075 (17.5)	499 (34.4)	1063 (13.3)	108 (34.1)	1012 (26.3)	391 (34.5)
Missing	*300 (2.5)*	*59 (4.1)*	*163 (2.0)*	*9 (2.8)*	*137 (3.6)*	*50 (4.4)*
Periconceptional opioid use	246 (2.1)	51 (3.5)	178 (2.2)	16 (5.1)	68 (1.8)	35 (3.1)
Missing	*219 (1.9)*	*40 (2.8)*	*127 (1.6)*	*6 (1.9)*	*92 (2.4)*	*34 (3.0)*
Periconceptional SSRI use	378 (3.2)	56 (3.9)	292 (3.7)	22 (6.9)	86 (2.2)	34 (3.0)
Missing	*215 (1.8)*	*39 (2.7)*	*123 (1.5)*	*6 (1.9)*	*92 (2.4)*	*33 (2.9)*
Periconceptional genitourinary infection[c]	1023 (8.7)	230 (15.9)	533 (6.7)	42 (13.3)	490 (12.7)	188 (16.6)
Missing	*214 (1.8)*	*38 (2.6)*	*127 (1.6)*	*10 (3.2)*	*87 (2.3)*	*28 (2.5)*

[a] Refers to number of live births and stillbirths prior to the index pregnancy (elective abortions after 20 weeks are not captured in this measure)

[b] One month before and one month after conception

[c] Includes sexually transmitted infections, kidney/bladder/urinary tract infections, pelvic inflammatory disease

Table 2.

Periconceptional alcohol consumption during pregnancy, by maternal age category and case/control status, NBDPS 1997-2011.

	Overall		Maternal Age ≥25 years		Maternal Age <25 years	
	Controls (n=8301)	Cases (n=7978)	Controls (n=7984)	Cases (n=317)	Controls (n=3845)	Cases (n=1133)
Exposure	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
No periconceptional alcohol consumption	7210 (61.0)	807 (55.7)	4640 (58.1)	168 (53.0)	2570 (66.8)	639 (56.4)
Any periconceptional alcohol consumption	4280 (36.2)	578 (39.9)	3152 (39.5)	138 (43.5)	1128 (29.3)	440 (38.8)
1 month preconception	3692 (31.2)	501 (34.6)	2779 (34.8)	123 (38.8)	913 (23.8)	378 (33.4)
Gestational month 1	2214 (18.7)	339 (23.4)	1609 (20.2)	82 (25.9)	605 (15.7)	257 (22.7)
Gestational month 2	718 (6.1)	126 (8.7)	514 (6.4)	23 (7.3)	204 (5.3)	103 (9.1)
Gestational month 3	445 (3.8)	54 (3.7)	340 (4.3)	12 (3.8)	105 (2.7)	42 (3.7)
Missing	*339 (2.9)*	*65 (4.5)*	*192 (2.4)*	*11 (3.5)*	*147 (3.8)*	*54 (4.8)*
Any periconceptional binge drinking[a]	1431 (12.1)	305 (21.0)	875 (11.0)	66 (20.8)	556 (14.5)	239 (21.1)
1 month preconception	1202 (10.2)	264 (18.2)	742 (9.3)	57 (18.0)	460 (12.0)	207 (18.3)
Gestational month 1	722 (6.1)	166 (11.5)	444 (5.6)	38 (12.0)	278 (7.2)	128 (11.3)
Gestational month 2	195 (1.7)	48 (3.3)	102 (1.3)	9 (2.8)	93 (2.4)	39 (3.4)
Gestational month 3	70 (0.6)	17 (1.2)	38 (0.5)	2 (0.6)	32 (0.8)	15 (1.3)
Missing	*400 (3.4)*	*78 (5.4)*	*227 (2.8)*	*14 (4.4)*	*173 (4.5)*	*64 (5.7)*
Maximum average number of alcoholic drinks/month						
1-4 drinks/month	1986 (16.38)	219 (15.1)	1506 (18.9)	47 (14.8)	480 (12.5)	172 (15.2)
5-15 drinks/month	1301 (11.0)	176 (12.1)	983 (12.3)	50 (15.8)	318 (8.3)	126 (11.1)
16-30 drinks/month	607 (5.1)	73 (5.0)	442 (5.5)	21 (6.6)	165 (4.3)	52 (4.6)
>30 drinks/month	344 (2.9)	99 (6.8)	204 (2.6)	18 (5.7)	140 (3.6)	81 (7.2)
Missing	*381 (3.2)*	*76 (5.2)*	*209 (2.6)*	*13 (4.1)*	*172 (4.5)*	*63 (5.6)*
Maximum frequency of periconceptional alcohol consumption/month						
1-4 days/month	3035 (25.7)	398 (27.5)	2194 (27.5)	98 (30.9)	841 (21.9)	300 (26.5)
5-15 days/month	967 (8.2)	132 (9.1)	753 (9.4)	30 (9.5)	214 (5.6)	102 (9.0)
16-30 days/month	255 (2.2)	42 (2.9)	194 (2.4)	9 (2.8)	61 (1.6)	33 (2.9)
Missing	*362 (3.1)*	*71 (4.9)*	*203 (2.5)*	*12 (3.8)*	*159 (4.1)*	*59 (5.2)*
Periconceptional drinking duration (months)						

	Overall		Maternal Age ≥25 years		Maternal Age <25 years	
	Controls (n=8301)	Cases (n=7978)	Controls (n=7984)	Cases (n=317)	Controls (n=3845)	Cases (n=1133)
Exposure	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
1	2397 (20.3)	276 (19.0)	1752 (21.9)	65 (20.5)	645 (16.8)	211 (18.6)
2	1278 (20.3)	203 (14.0)	948 (11.9)	55 (17.4)	330 (8.6)	148 (13.1)
3	270 (2.3)	54 (3.7)	183 (2.3)	7 (2.2)	87 (2.3)	47 (4.2)
4	323 (2.7)	44 (3.0)	258 (3.2)	11 (3.5)	65 (1.7)	33 (2.9)
Missing	*351 (3.0)*	*66 (4.6)*	*203 (2.5)*	*11 (3.5)*	*148 (3.9)*	*55 (4.9)*
Type of alcohol consumed (not mutually exclusive)						
Beer	2263 (19.1)	372 (25.7)	1611 (20.2)	93 (29.3)	652 (17.0)	279 (24.6)
Wine	2750 (23.3)	232 (16.0)	2301 (28.8)	75 (23.7)	449 (11.7)	157 (13.9)
Mixed drink/liquor	2047 (17.3)	389 (26.8)	1290 (16.2)	76 (24.0)	757 (19.7)	313 (27.6)
Other	158 (1.3)	25 (1.7)	86 (1.1)	1 (0.3)	72 (1.9)	24 (2.1)
Missing	*347 (2.9)*	*67 (4.6)*	*198 (2.5)*	*11 (3.5)*	*149 (3.9)*	*56 (4.9)*

[a]Binge drinking defined as ≥ 4 drinks per occasion; these subjects are also counted under "any periconceptional alcohol consumption"

Table 3a.

Modification of the effect of any periconceptional alcohol consumption on gastroschisis by maternal age, NBDPS 1997-2011. Odds ratios (ORs) are adjusted for any periconceptional cigarette smoking, prepregnancy BMI, maternal race/ethnicity, and study site.

	No alcohol		Any alcohol		OR (95% CI) for any vs. no alcohol exposure, within age strata
Exposure	**cases/controls**	**OR (95% CI)**	**cases/controls**	**OR (95% CI)**	
Age ≥25	168/4640	1.00 (Reference)	138/3152	1.12 (0.88, 1.42)	1.12 (0.88, 1.42)
Age <25	639/2570	5.90 (4.89, 7.11)	440/1128	8.21 (6.69, 10.07)	1.4 (1.19, 1.62)

Measure of additive effect modification: RERI=2.19 (1.02, 3.36)

Measure of multiplicative effect modification: Product term OR=1.24 (0.94, 1.64)

Table 3b.

Modification of the effect of periconceptional binge alcohol consumption on gastroschisis by maternal age, NBDPS 1997-2011.

	No alcohol		Binge alcohol		OR (95% CI) for binge vs. no alcohol exposure, within age strata
Exposure	**cases/controls**	**OR (95% CI)**	**cases/controls**	**OR (95% CI)**	
Age ≥25	168/4640	1.00 (Reference)	66/875	1.77 (1.31, 2.41)	1.77 (1.31, 2.41)
Age <25	639/2570	6.02 (4.99, 7.27)	239/556	8.49 (6.68, 10.80)	1.41 (1.16, 1.71)

Measure of additive effect modification: RERI=1.70 (0.10, 3.30)

Measure of multiplicative effect modification: Product term OR=0.80 (0.56, 1.13)