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Association between maternal periconceptional alcohol consumption and neural tube defects: Findings from the National Birth Defects Prevention Study, 1997–2011

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Abstract

Background—Neural tube defects (NTD)s are common birth defects with a multifactorial etiology. Findings from human studies examining environmental (non-inherited) exposures tend to be inconclusive. In particular, although animal studies of alcohol exposure and NTDs support its teratogenic potential, human studies are equivocal. Using data from the National Birth Defects Prevention Study (NBDPS), associations between maternal periconceptional (one month before through one month after conception) alcohol consumption and NTDs in offspring were examined.

Methods—NTD cases and unaffected live born singleton controls with expected dates of delivery from October 1997–December 2011 were enrolled in the NBDPS. Interview reports of alcohol consumption (quantity, frequency, variability, type) from 1,922 case and 11,251 control mothers were analyzed. Crude and adjusted odds ratios (aOR)s and 95% confidence intervals (CI)s for alcohol consumption and all NTDs combined and selected subtypes (spina bifida, anencephaly, encephalocele) were estimated using unconditional logistic regression analysis.

Results—Among mothers in the NBDPS, 28% of NTD case and 35% of control mothers reported any periconceptional alcohol consumption. For each measure of alcohol consumption, inverse associations were observed for all NTDs combined (aORs=0.6–1.0). Results for NTD

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subtypes tended to be similar, but CIs for spina bifida and encephalocele were more likely to include the null.

Conclusions—These findings suggest a lack of positive associations between maternal periconceptional alcohol consumption and NTDs. Future studies should continue to evaluate the association between maternal alcohol consumption and NTDs in offspring accounting for methodological limitations such as potential misclassification from self-reported alcohol consumption.

Keywords

alcohol; anencephaly; neural tube defects; pregnancy; spina bifida

1 | INTRODUCTION

Neural tube defects (NTDs) are major birth defects of the central nervous system characterized by incomplete closure of the neural tube (reviewed in Botto, Moore, Khoury, & Erickson, 1999). In the United States (US), approximately 2,800 pregnancies are affected by NTDs annually, with an estimated birth prevalence of approximately 7 per 10,000 live births (Williams et al., 2015). The two most common NTD subtypes are anencephaly and spina bifida, which affect the brain and spinal cord, respectively (Greene & Copp, 2014). Due to its severity, pregnancies affected by anencephaly often result in stillbirth or elective termination (Blencowe, Kancherla, Moorthie, Darlison, & Modell, 2018); survival of live born infants ranges from a few hours to days (Baird & Sadovnick, 1984). Pregnancies affected by spina bifida also may result in stillbirth or elective termination (Blencowe et al., 2018), and live born infants with spina bifida may have many health complications and life-long disability that includes varying degrees of paralysis (Sawin et al., 2015). The average lifetime cost of care per child with spina bifida, including caregiving costs, is estimated to be approximately US$ 790,000 (Grosse, Berry, Tilford, Kucik, & Waitzman, 2016).

NTDs are considered to have a multifactorial etiology, with previous studies reporting associations with genetic variants and environmental (non-inherited) exposures (reviewed in Greene & Copp, 2014). Aside from genetic factors, early studies identified maternal folic acid supplementation as a significant protective factor in NTD occurrence (reviewed in Viswanathan et al., 2017). Several other environmental exposures have been associated with an increased risk of NTDs, such as maternal diabetes (Correa et al., 2008), pre-pregnancy obesity (Huang, Chen, & Feng, 2017), and use of certain medications during early pregnancy (Brender et al., 2011; Jentink et al., 2010; Mitchell, 2005; Yazdy, Mitchell, Tinker, Parker, & Werler, 2013).

Maternal alcohol consumption during pregnancy is among the environmental exposures that may potentially increase the risk of NTDs. Animal studies have reported NTDs following administration of alcohol to pregnant animals (reviewed in Aronne, Evrard, Mirochnic, & Brusco, 2008; Becker, Diaz-Granados, & Randall, 1996). However, human studies examining early pregnancy alcohol consumption (defined as the number of alcoholic drinks consumed per day, week, or month) have mostly reported null or modestly positive associations with all NTDs combined (Grewal, Carmichael, Ma, Lammer, & Shaw, 2008;

McDonald, Armstrong, & Sloan, 1992; Shaw, Velie, & Morland, 1996; Suarez, Felkner, Brender, Canfield, & Hendricks, 2007) and some NTD subtypes (Benedum, Yazdy, Mitchell, & Werler, 2013; De Marco et al., 2011; Grewal et al., 2008). Also, associations generally near or below unity have been reported for associations between early pregnancy binge drinking and all NTDs combined (Grewal et al., 2008; Shaw et al., 1996; Suarez et al., 2007) and NTD subtypes (Benedum et al., 2013; Grewal et al., 2008). Most of these previous studies, however, were limited by the inability to examine NTD subtypes, which is important due to developmental and etiologic heterogeneity in NTD development (reviewed in Mitchell, 2005) and the lack of specificity in alcohol exposure measures (e.g. inability to examine type of alcohol consumed).

To address the limitations of these studies, an analysis using National Birth Defects Prevention Study (NBDPS) data from 1997–2005 examined associations between maternal alcohol exposure during the period from one month before conception (B1) through the second month of pregnancy and all NTDs combined and NTD subtypes; associations reported were mostly near unity (Makelarski et al., 2013). Since these analyses, an additional six years of data (2006–2011) were collected. The current study used the full NBDPS dataset (1997–2011) to examine associations between maternal alcohol exposure and all NTDs combined and selected NTD subtypes. These expanded data represent a substantially larger sample of NTD cases than previous studies and examined a more restricted period of periconceptional exposure (B1 through the month following conception [P1]), which more closely corresponds with the critical period of neural tube development.

2 | METHODS

2.1 | The National Birth Defects Prevention Study

The NBDPS, a population-based, multisite case-control study conducted in the US, was designed to study genetic and environmental (broadly defined) factors for major structural birth defects. Methods for the NBDPS are detailed elsewhere (Reefhuis et al., 2015). Briefly, the NBDPS included cases and controls with estimated dates of deliveries (EDD)s from October 1, 1997-December 31, 2011 identified by 10 birth defect surveillance programs (Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, Utah) (Reefhuis et al., 2015). Eligible cases were live births (all sites), fetal deaths at 20 weeks or greater gestation (six sites), and elective terminations (five sites); eligible controls were non-malformed, singleton live births. Case or control children were excluded from the NBDPS if their mother had participated in the study with a previous pregnancy, could not complete the interview in English or Spanish, or was incarcerated or otherwise did not have legal custody of their child at the time of the interview (Reefhuis et al., 2015). Maternal interviews were conducted between six weeks and 24 months following their EDD and collected data on maternal exposures, including infectious, chemical, physical, nutritional, and behavioral exposures (Reefhuis et al., 2015).

2.2 | Case enumeration and classification

NTD cases (modified British Paediatric Association diagnostic code) included in the NBDPS were anencephaly (including craniorachischisis; 740.020, 740.100), spina bifida

(741.000–741.990), and encephalocele (including cranial meningocele and encephalomyelocele; 742.000–742.090) (Rasmussen et al., 2003). Diagnosis of an NTD was confirmed using standardized criteria and clinical geneticist review of clinical data abstracted from medical records (Rasmussen et al., 2003). Clinical geneticists classified cases as isolated (no additional major defects or one or more additional major defects developmentally related to an NTD), multiple (one or more additional major defects in different organ systems), or complex (pattern of major defects embryologically related and likely to represent an early problem in morphogenesis). Cases with a known chromosomal defect or monogenetic disorder were excluded (Rasmussen et al., 2003).

2.3 | Control Selection

Control children – non-malformed live births delivered during the same time period and in the same geographic region as case children – were randomly selected from birth certificates or hospital records (Reefhuis et al., 2015).

2.4 | Exposure Assessment

Mothers were asked in the NBDPS interview if they drank alcohol any time during the three months before conception through the end of pregnancy. If mothers reported alcohol consumption, they were asked about the month(s) during which they drank (yes, no), average number of drinking days in a drinking month (frequency), average number of drinks per drinking day in each drinking month, greatest number of drinks on one occasion per drinking month (variability), and types of alcohol consumed (beer, wine, and/or distilled spirits). These data were used to assign maternal alcohol consumption during the periconceptional period (B1-P1) using an approach that was previously developed for the NBDPS (Romitti et al., 2007). Specifically, the average number of drinks per drinking month was calculated by multiplying the average number of drinking days by the average number of drinks per drinking day for the specified month. The average number of drinks in the periconceptional period was calculated using the average number of drinks per month (B1, P1, both) divided by the number of months a mother drank (B1, P1, both). The maximum average number of drinks per month also was calculated using the highest reported average number of drinks per month (B1 or P1) divided by the number of months a mother drank during the periconceptional period (B1, P1, both).

Four categories were used to classify reported periconceptional alcohol consumption using a 30-day month: monthly to weekly (1–4 drinks per month); weekly to every other day (5–15 drinks per month); every other day to daily (16–30 drinks per month); and daily with more than one drink per day (>30 drinks per month). Binge episodes were estimated using sex-specific norms for females of four or more drinks per day on average, on one occasion, or both (Wechsler, Dowdall, Davenport, & Rimm, 1995). To categorize binge episodes, case and control mothers were classified as those who reported: no consumption; consumption without any binge episodes; or one or more binge episodes. Additionally, mothers were classified by type of alcohol consumed as: beer only; wine only; distilled spirits only; or any combination of two or more types of alcohol.

2.5 | Covariates

Child covariates examined were sex (male, female), first-degree family history of NTDs (yes, no), and NBDPS site (Arkansas, California, Georgia, Iowa, Massachusetts, New Jersey, New York, North Carolina, Texas, Utah). Maternal covariates examined were race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other), age at delivery (<20, 20–34, ≥35 years), education at delivery (less than high school, high school graduate, some college or higher), pre-pregnancy body mass index (BMI) (underweight [<18.5], normal [18.5–24.9], overweight [25–29.9], obese [≥30] kg/m^2), gravidity (0, 1–2, ≥3), pregnancy intention (intended, mistimed, ambivalent, unwanted), pre-pregnancy hypertension (yes, no), pre-pregnancy daily caffeine intake (0–9, 10–99, 100–199, 200–299, ≥300 mg/day), and periconceptional cigarette smoke exposure (no active or passive smoking, active only, passive only, active and passive).

Periconceptional use of folic acid-containing supplements (yes, no) also was examined as a covariate. Vitamin and supplement use three months before conception through end of pregnancy was collected in the NBDPS interview. For each vitamin or supplement reported, mothers were asked to provide start and stop dates (or duration of use if dates were unknown) and frequency of use. Each reported supplement was assessed to determine whether it contained folic acid. Additionally, pre-pregnancy dietary folate intake (<600, ≥600 μg/day) was examined using responses from the dietary module of the NBDPS interview. The Willet Food Frequency questionnaire (Willett, Reynolds, Cottrell-Hoehner, Sampson, & Browne, 1987; Willett et al., 1985) was adapted for the NBDPS interview and measured food intake during the year before conception, along with reports of breakfast cereals consumed during P1. Reported food frequencies, standardized serving size, and US Department of Agriculture National Standard Reference 16–1 (United States Department of Agriculture, 2004) were used to estimate dietary folate equivalents (DFEs).

2.6 | Exclusions

Case and control mothers with an unknown or missing response to the question regarding alcohol consumption any time during the three months before through the end of pregnancy and those with a monthly average consumption estimate of 120 drinks or more were excluded from analyses. Also excluded were children classified as a complex case, mothers who had reported pre-pregnancy diabetes, and those with unknown or reported use of folate antagonist medications (aminopterin sodium, carbamazepine, cholestyramine resin, methotrexate, oxcarbazepine, pyrimethamine, sulfasalazine, triamterene, trimethoprim, phenytoin, primidone, phenobarbital, valproate sodium) during the periconceptional period.

2.7 | Statistical Analysis

Descriptive analyses used the chi-square test of independence to compare child and maternal covariates between cases and controls. Unconditional logistic regression analysis was used to estimate crude and adjusted odds ratios and their respective 95% confidence intervals (CI)s for associations between different categories of maternal alcohol consumption (any, binge episodes, average drinks per month, maximum drinks per month, type of alcohol) and all NTDs and NTD subtypes. Variables that differed statistically ($p<0.05$) between controls and all NTD cases combined in descriptive analyses were considered for adjusted models

(Table 1). Covariates in adjusted models were selected using a change-in-estimate approach. For each exposure-outcome pairing, individual covariates were entered into a model containing the alcohol exposure variable of interest. Covariates that altered the main effect by >10% were retained in the final model. Adjusted odds ratios and 95% CIs were estimated using models that contained all covariates for which the 10% change-in-estimate criteria was met for the respective exposure-outcome pair.

Several subanalyses were conducted, as data permitted. To evaluate the representativeness of the analytic sample following exclusions, we compared the distributions of covariates for NTD cases and controls in the analytic sample to those for all NBDPS NTD cases and controls prior to exclusions using the chi-square goodness-of-fit test. Subanalyses compared isolated NTD cases and controls, as there may be etiologic differences between isolated and multiple cases. Subanalyses also compared consumption patterns stratified by type of alcohol (beer only, wine only, distilled spirits only, any combination of alcohol) because some previous studies suggested beer consumption may increase red blood cell folate and plasma 5-methyltetrahydrofolic acid concentrations (Larroque et al., 1992; Stark et al., 2005). Additionally, interactions between alcohol exposure (any, binge episodes) and folate status were tested. A dichotomous variable was created by combining responses for use of folic acid supplements and dietary folate intake. Mothers who reported no use of folic acid-containing supplements and pre-pregnancy dietary folate intake <600μg/day were considered folate deficient, whereas those reporting either use of folic-acid containing supplements and/or pre-pregnancy dietary folate intake ≥600 μg/day were considered to have sufficient folate levels. The statistical significance of multiplicative interaction was determined using p-values, and the significance of additive interaction estimates (relative excess risk due to interaction) was determined using bootstrap 95% CIs (Knol, van der Tweel, Grobbee, Numans, & Geerlings, 2007). The relative excess risk due to interaction and bootstrap 95% CIs were estimated using a SAS program created by Sandra Richardson, RN, MS (personal communication, New York State Department of Health, 2011). To examine the potential for exposure misclassification, analyses were stratified by pregnancy intention and, also, by time between EDD and date of the NBDPS interview (0–6, 7–12, 13–18, >18 months). All analyses were conducted using the Statistical Analysis System (SAS) version 9.4 statistical software (SAS Institute Inc., 2013).

3 | RESULTS

Overall, 2,191 NTD cases and 11,829 controls were enrolled in the NBDPS. Among these mothers, 2,152 case and 11,626 control mothers completed the alcohol module of the NBDPS interview. Of the mothers who provided information on periconceptional alcohol consumption, 230 case and 375 control mothers were excluded due to: complex NTD cases (cases=3), maternal pre-pregnancy diabetes (cases=47; controls=82), reported or unknown maternal periconceptional exposure to folic acid antagonist medications (cases=39; controls=180), an unknown or missing response for alcohol consumption any time during the three months before through the end of pregnancy (cases=129, controls=69), or reported average monthly consumption estimate of ≥120 drinks (cases=12, controls=44). A total of 1,922 (88% of total) cases (anencephaly=541, spina bifida=1,173, encephalocele=208) and 11,251 controls (95% of total) remained in the final analytic sample.

Among all NTD cases, 87.5% were isolated, with a lower proportion of encephalocele cases classified as isolated compared to anencephaly and spina bifida (Table 1). Statistical differences ($p<0.05$) were observed between all NTDs combined and controls for first-degree family history of NTDs, NBDPS site, and maternal race/ethnicity, education at delivery, pre-pregnancy BMI, gravidity, periconceptional use of folic acid-containing supplements, pre-pregnancy daily folate intake, pregnancy intention, pre-pregnancy hypertension, pre-pregnancy caffeine intake, and periconceptional cigarette smoke exposure (Table 1). Statistical differences were observed between NTD subtypes and controls for child sex (anencephaly), first-degree family history of NTDs (spina bifida, encephalocele), and NBDPS site (anencephaly, spina bifida), along with maternal race/ethnicity (anencephaly, spina bifida, encephalocele), education at delivery (anencephaly, spina bifida), pre-pregnancy BMI (spina bifida), gravidity (anencephaly, spina bifida), pregnancy intention (spina bifida), periconceptional use of folic acid-containing supplements (encephalocele), pre-pregnancy hypertension (anencephaly) and periconceptional cigarette smoke exposure (anencephaly, spina bifida, encephalocele) (Table 1).

Overall, 27.5% of NTD case mothers and 35.4% of control mothers reported any periconceptional alcohol consumption (Table 2). The proportion of mothers reporting alcohol consumption during B1 only or B1+P1 was greater for mothers of controls than all NTDs combined; a similar proportion of NTD case and control mothers reported consumption during P1 only. Overall, mothers of cases and controls most frequently reported consumption of any combination of alcohol types. Proportions of NTD case and control mothers that reported consuming beer or distilled spirits (either alone or in combination) tended to be similar; however, a greater proportion of control mothers reported consuming wine only compared to case mothers. Among NTD subtypes, patterns of maternal periconceptional alcohol consumption tended to be similar to those for mothers of all NTDs combined.

Inverse associations were observed for any periconceptional consumption, consumption with and without binge episodes, all levels of periconceptional average number of drinks per month, and most types of alcohol for all NTDs combined; most CIs for these associations excluded the null (Table 3). Similar results were observed when using maximum average number of drinks per month (data not shown). Associations for each NTD subtype tended to be similar to those estimated for all NTDs combined; however, the CIs for spina bifida and encephalocele were more likely to include the null.

Results of subanalyses comparing the distributions of covariates for all NTD cases and controls prior to study exclusions was not materially different from the distributions of covariates in the analytic sample following exclusions (data not shown). Results examining only isolated cases were generally similar to their respective main analyses (data not shown), as were results for consumption patterns stratified by type of alcohol consumed (data not shown). Also, results of association analyses stratified by pregnancy intention tended to be similar to the respective main analyses, except for associations for spina bifida among mothers with unwanted pregnancies, where most aORs were greater than 1.5 (aORs=0.8–3.4). Additionally, no statistically significant multiplicative or additive interaction for alcohol consumption (any or binge episodes) and folate status were observed (data not

shown). Lastly, although case mothers more frequently completed the NBDPS interview 12 months or later after the child's EDD than control mothers, results of association analyses stratified by time to interview were not materially different than the respective main analyses (data not shown).

4 | DISCUSSION

The current study used data from the NBDPS, which improved upon the methodology of previous studies by examining several measures of alcohol exposure during a more restricted period (B1-P1) of neural tube development. Additionally, the NBDPS included over 2,000 NTD cases and 11,000 controls, making it the largest study of maternal alcohol consumption during pregnancy and NTDs. Observed associations with any periconceptional alcohol consumption, binge episodes, average and maximum number of drinks per month, and type of alcohol consumed were near or below unity for all NTDs combined. The findings for NTD subtypes generally paralleled those for all NTDs combined, although CIs for spina bifida and encephalocele more frequently included the null. The lack of positive associations observed is comparable with findings of most previous studies that examined any maternal alcohol consumption (Benedum et al., 2013; Grewal et al., 2008; McDonald et al., 1992; Shaw et al., 1996; Suarez et al., 2007) or binge drinking (Benedum et al., 2013; Grewal et al., 2008; Shaw et al., 1996; Suarez et al., 2007) and NTDs. Additionally, the results were similar to those of the previous NBDPS study using data from 1997–2005 (Makelarski et al., 2013).

Although animal models suggest associations between administration of alcohol to pregnant animals and NTDs in offspring (reviewed in Aronne et al., 2008; Becker et al., 1996), and several biologically plausible mechanisms have been proposed (Bannigan & Burke, 1982; Kotch & Sulik, 1992; Liu, Balaraman, Wang, Nephew, & Zhou, 2009; McMartin, 1984; Muldoon & McMartin, 1994), these results have not translated to human studies. The disparity in positive results between animal studies and the current study could be due to methodological differences between animal and human studies and the limitations inherent to epidemiologic designs. In particular, the alcohol dose of exposure in animal studies are often designed to produce teratogenic effects (e.g. animal dosing generally exceeds the level of consumption in humans). In the current study, only a small proportion of mothers reported heavy drinking, which may contribute to the observed null findings. The timing of exposure in animal studies also is typically very precise. Conversely, human studies rely on maternal recall to assign alcohol dose and determine exposure timing; inaccurate recall could result in exposure misclassification, potentially biasing results. However, a previous study that examined the potential for misclassification of maternal alcohol consumption during pregnancy did not find statistical differences between prospective and retrospective recall of consumption suggesting minimal recall bias (Verkerk, Buitendijk, & Verloove-Vanhorick, 1994). Also, results of our subanalyses examining the influence of time to NBDPS interview on recall of alcohol consumption were not materially different than results from the main analyses. Another source of potential exposure misclassification in human studies may be under-reporting of alcohol consumption due to the stigma associated with alcohol consumption during pregnancy. In the current study, control mothers more frequently reported alcohol consumption than case mothers, suggesting underreporting

among case mothers. However, the percentages of case and control mothers who reported any alcohol consumption in this study exceeded national estimates suggesting minimal bias due to underreporting (Denny, Acero, Naimi, & Kim, 2019).

An alternative explanation for the lack of positive associations could be that there is no positive association between low to moderate alcohol consumption and NTDs in humans, as suggested by the general consistency of studies. More likely, pregnancy intention may influence risk, as subanalyses suggested that for mothers of children with unwanted pregnancies, alcohol consumption was associated with increased risk of delivering a child with spina bifida. Also, with the number of statistical comparisons generated, some of the inverse associations with CIs that excluded the null may have been due to chance. Another explanation is that maternal alcohol consumption has been associated with early pregnancy loss (Henriksen et al., 2004) and could lead to survival bias (Khoury, James, Flanders, & Erickson, 1992). Early pregnancy loss (prior to 20 weeks gestation) was not able to be ascertained comprehensively in the NBDPS. An additional explanation may be the impact of prenatal alcohol consumption on genes involved in neural development and folate metabolism, which were not explored in the current study. For example, Wnt signaling is involved in vertebrate neural development (Mulligan & Cheyette, 2012) and folate metabolism (Gray et al., 2010). In particular, ethanol has been shown to suppress Wnt signaling proteins, including those involved in differentiating human neural stem cells (Vangipuram & Lyman, 2012).

Despite the limitations in alcohol exposure assessment, the current study had several strengths. NBDPS data provided a large, multisite population-based sample, minimizing the potential for selection bias. A study comparing maternal characteristics of controls to all live births at each site reported that NBDPS controls are similar to all live births on several maternal characteristics (Cogswell et al., 2009). The NBDPS included live births, fetal deaths of ≥20 weeks gestation, and elective terminations, helping to reduce potential biases related to case ascertainment, and diagnoses were confirmed by clinical geneticists, minimizing outcome misclassification. Also, the current study was able to evaluate associations between maternal alcohol consumption and NTD subtypes, which is important due to the heterogeneity of NTDs. Additionally, mothers who reported risk factors that are known to be strongly associated with the development of NTDs in offspring, such as pre-pregnancy diabetes or use of folate-antagonist medication, were excluded from analyses. Lastly, the NBDPS collected detailed information on alcohol consumption during pregnancy, allowing for the examination of alcohol consumption in multiple ways, including by alcohol type, which has not been evaluated in non-NBDPS studies.

In conclusion, this study used a large, population-based sample to examine associations between maternal periconceptional alcohol exposure and NTDs in offspring. Results for any maternal consumption, binge episodes, average and maximum number of drinks, and type of alcohol consumed were largely near or below unity for all NTDs combined and NTD subtypes. Even with biologically plausible mechanisms proposed from animal models, few positive associations between maternal alcohol consumption in early pregnancy and NTDs have been observed to date. This discordance may be due to limitations in human studies. Future studies should attempt to improve upon our study by increasing sample size,

particularly for rarer NTD subtypes, refining exposure classifications, including stratification of alcohol types and more precise consumption estimates, improving ascertainment of pregnancies ending in early fetal loss, and explore genomic contributions of alcohol exposure to NTD development.

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REFERENCES

Aronne MP, Evrard SG, Mirochnic S, & Brusco A (2008). Prenatal Ethanol Exposure Reduces the Expression of the Transcriptional FactorPax6in the Developing Rat Brain. Annals of the New York Academy of Sciences, 1139(1), 478–498 [PubMed: 18991895]

Baird PA, & Sadovnick AD (1984). Survival in infants with anencephaly. Clin Pediatr (Phila), 23(5), 268–271 [PubMed: 6705433]

Bannigan J, & Burke P (1982). Ethanol teratogenicity in mice: A light microscopic study. Teratology, 26(3), 247–254 [PubMed: 7163973]

Becker HC, Diaz-Granados JL, & Randall CL (1996). Teratogenic actions of ethanol in the mouse: A minireview. Pharmacology Biochemistry and Behavior, 55(4), 501–513

Benedum C, Yazdy M, Mitchell A, & Werler M (2013). Risk of Spina Bifida and Maternal Cigarette, Alcohol, and Coffee Use during the First Month of Pregnancy. International Journal of Environmental Research and Public Health, 10(8), 3263–3281 [PubMed: 23917813]

Blencowe H, Kancherla V, Moorthie S, Darlison MW, & Modell B (2018). Estimates of global and regional prevalence of neural tube defects for 2015: a systematic analysis. Annals of the New York Academy of Sciences, 1414(1), 31–46 [PubMed: 29363759]

Botto LD, Moore CA, Khoury MJ, & Erickson JD (1999). Neural-Tube Defects. New England Journal of Medicine, 341(20), 1509–1519 [PubMed: 10559453]

Brender JD, Werler MM, Kelley KE, Vuong AM, Shinde MU, Zheng Q,… The National Birth Defects Prevention, S. (2011). Nitrosatable drug exposure during early pregnancy and neural tube defects in offspring: National Birth Defects Prevention Study. Am J Epidemiol, 174(11), 1286–1295 [PubMed: 22047825]

Cogswell ME, Bitsko RH, Anderka M, Caton AR, Feldkamp ML, Sherlock SMH,… Reefhuis J (2009). Control Selection and Participation in an Ongoing, Population-based, Case-Control Study of Birth Defects. American Journal of Epidemiology, 170(8), 975–985 [PubMed: 19736223]

Correa A, Gilboa SM, Besser LM, Botto LD, Moore CA, Hobbs CA,… Reece EA (2008). Diabetes mellitus and birth defects. Am J Obstet Gynecol, 199(3), 237 e231–239 [PubMed: 18674752]

De Marco P, Merello E, Calevo MG, Mascelli S, Pastorino D, Crocetti L,… Capra V (2011). Maternal periconceptional factors affect the risk of spina bifida-affected pregnancies: an Italian case–control study. Child's Nervous System, 27(7), 1073–1081

Denny CH, Acero CS, Naimi TS, & Kim SY (2019). Consumption of Alcohol Beverages and Binge Drinking Among Pregnant Women Aged 18–44 Years - United States, 2015–2017. MMWR Morb Mortal Wkly Rep, 68(16), 365–368 [PubMed: 31022164]

Gray JD, Nakouzi G, Slowinska-Castaldo B, Dazard JE, Rao JS, Nadeau JH, & Ross ME (2010). Functional interactions between the LRP6 WNT co-receptor and folate supplementation. Hum Mol Genet, 19(23), 4560–4572 [PubMed: 20843827]

Greene ND, & Copp AJ (2014). Neural tube defects. Annu Rev Neurosci, 37, 221–242 [PubMed: 25032496]

Grewal J, Carmichael SL, Ma C, Lammer EJ, & Shaw GM (2008). Maternal periconceptional smoking and alcohol consumption and risk for select congenital anomalies. Birth Defects Research Part A: Clinical and Molecular Teratology, 82(7), 519–526 [PubMed: 18481814]

Grosse SD, Berry RJ, Tilford MJ, Kucik JE, & Waitzman NJ (2016). Retrospective Assessment of Cost Savings From Prevention: Folic Acid Fortification and Spina Bifida in the U.S. American Journal of Preventive Medicine, 50(5), S74–S80 [PubMed: 26790341]

Henriksen TB, Hjollund NH, Jensen TK, Bonde JP, Andersson AM, Kolstad H,… Olsen J (2004). Alcohol consumption at the time of conception and spontaneous abortion. Am J Epidemiol, 160(7), 661–667 [PubMed: 15383410]

Huang HY, Chen HL, & Feng LP (2017). Maternal obesity and the risk of neural tube defects in offspring: A meta-analysis. Obes Res Clin Pract, 11(2), 188–197 [PubMed: 27155922]

Jentink J, Loane MA, Dolk H, Barisic I, Garne E, Morris JK,… Group EASW (2010). Valproic acid monotherapy in pregnancy and major congenital malformations. N Engl J Med, 362(23), 2185–2193 [PubMed: 20558369]

Khoury MJ, James LM, Flanders WD, & Erickson JD (1992). Interpretation of recurring weak associations obtained from epidemiologic studies of suspected human teratogens. Teratology, 46(1), 69–77 [PubMed: 1641813]

Knol MJ, van der Tweel I, Grobbee DE, Numans ME, & Geerlings MI (2007). Estimating interaction on an additive scale between continuous determinants in a logistic regression model. Int J Epidemiol, 36(5), 1111–1118 [PubMed: 17726040]

Kotch LE, & Sulik KK (1992). Experimental fetal alcohol syndrome: Proposed pathogenic basis for a variety of associated facial and brain anomalies. American Journal of Medical Genetics, 44(2), 168–176 [PubMed: 1456286]

Larroque B, Kaminski M, Lelong N, d'Herbomez M, Dehaene P, Querleu D, & Crepin G (1992). Folate status during pregnancy: relationship with alcohol consumption, other maternal risk factors and pregnancy outcome. Eur J Obstet Gynecol Reprod Biol, 43(1), 19–27 [PubMed: 1737604]

Liu Y, Balaraman Y, Wang G, Nephew KP, & Zhou FC (2009). Alcohol exposure alters DNA methylation profiles in mouse embryos at early neurulation. Epigenetics, 4(7), 500–511 [PubMed: 20009564]

Makelarski JA, Romitti PA, Sun L, Burns TL, Druschel CM, Suarez L,… Olney RS (2013). Periconceptional maternal alcohol consumption and neural tube defects. Birth Defects Research Part A: Clinical and Molecular Teratology, 97(3), 152–160 [PubMed: 23456758]

McDonald AD, Armstrong BG, & Sloan M (1992). Cigarette, alcohol, and coffee consumption and congenital defects. American Journal of Public Health, 82(1), 91–93 [PubMed: 1536342]

McMartin KE (1984). Increased Urinary Folate Excretion and Decreased Plasma Folate Levels in the Rat after Acute Ethanol Treatment. Alcoholism: Clinical and Experimental Research, 8(2), 172–178

Mitchell LE (2005). Epidemiology of neural tube defects. American Journal of Medical Genetics Part C: Seminars in Medical Genetics, 135C(1), 88–94

Muldoon RT, & McMartin KE (1994). Ethanol Acutely Impairs the Renal Conservation of 5-Methyltetrahydrofolate in the Isolated Perfused Rat Kidney. Alcoholism: Clinical and Experimental Research, 18(2), 333–339

Mulligan KA, & Cheyette BN (2012). Wnt signaling in vertebrate neural development and function. J Neuroimmune Pharmacol, 7(4), 774–787 [PubMed: 23015196]

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

Reefhuis J, Gilboa SM, Anderka M, Browne ML, Feldkamp ML, Hobbs CA,… Honein MA (2015). The national birth defects prevention study: A review of the methods. Birth Defects Research Part A: Clinical and Molecular Teratology, 103(8), 656–669 [PubMed: 26033852]

Romitti PA, Sun L, Honein MA, Reefhuis J, Correa A, & Rasmussen SA (2007). Maternal Periconceptional Alcohol Consumption and Risk of Orofacial Clefts. American Journal of Epidemiology, 166(7), 775–785 [PubMed: 17609516]

SAS Institute Inc. (2013). SAS 9.4 (Version 9.4). Cary, NC: SAS Institute Inc.

Sawin KJ, Liu T, Ward E, Thibadeau J, Schechter MS, Soe MM, & Walker W (2015). The National Spina Bifida Patient Registry: Profile of a Large Cohort of Participants from the First 10 Clinics. The Journal of Pediatrics, 166(2), 444–450.e441 [PubMed: 25444012]

Shaw GM, Velie EM, & Morland KB (1996). Parental Recreational Drug Use and Risk for Neural Tube Defects. American Journal of Epidemiology, 144(12), 1155–1160 [PubMed: 8956628]

Stark KD, Pawlosky RJ, Beblo S, Murthy M, Flanagan VP, Janisse J,… Salem N Jr. (2005). Status of plasma folate after folic acid fortification of the food supply in pregnant African American women and the influences of diet, smoking, and alcohol consumption. Am J Clin Nutr, 81(3), 669–677 [PubMed: 15755838]

Suarez L, Felkner M, Brender JD, Canfield M, & Hendricks K (2007). Maternal Exposures to Cigarette Smoke, Alcohol, and Street Drugs and Neural Tube Defect Occurrence in Offspring. Maternal and Child Health Journal, 12(3), 394–401 [PubMed: 17641961]

United States Department of Agriculture. (2004). USDA National Nutrient Database for Standard Reference, release 16. Beltsville, MD

Vangipuram SD, & Lyman WD (2012). Ethanol affects differentiation-related pathways and suppresses Wnt signaling protein expression in human neural stem cells. Alcohol Clin Exp Res, 36(5), 788–797 [PubMed: 22150777]

Verkerk PH, Buitendijk SE, & Verloove-Vanhorick SP (1994). Differential Misclassification of Alcohol and Cigarette Consumption by Pregnancy Outcome. International Journal of Epidemiology, 23(6), 1218–1225 [PubMed: 7721524]

Viswanathan M, Treiman KA, Kish-Doto J, Middleton JC, Coker-Schwimmer EJ, & Nicholson WK (2017). Folic Acid Supplementation for the Prevention of Neural Tube Defects: An Updated Evidence Report and Systematic Review for the US Preventive Services Task Force. JAMA, 317(2), 190–203 [PubMed: 28097361]

Wechsler H, Dowdall GW, Davenport A, & Rimm EB (1995). A gender-specific measure of binge drinking among college students. American Journal of Public Health, 85(7), 982–985 [PubMed: 7604925]

Willett WC, Reynolds RD, Cottrell-Hoehner S, Sampson L, & Browne ML (1987). Validation of a semi-quantitative food frequency questionnaire: comparison with a 1-year diet record. J Am Diet Assoc, 87(1), 43–47 [PubMed: 3794132]

Willett WC, Sampson L, Stampfer MJ, Rosner B, Bain C, Witschi J,… Speizer FE (1985). REPRODUCIBILITY AND VALIDITY OF A SEMIQUANTITATIVE FOOD FREQUENCY QUESTIONNAIRE. American Journal of Epidemiology, 122(1), 51–65 [PubMed: 4014201]

Williams J, Mai CT, Mulinare J, Isenburg J, Flood TJ, Ethen M,… Centers for Disease Control and Prevention. (2015). Updated estimates of neural tube defects prevented by mandatory folic Acid fortification - United States, 1995–2011. MMWR Morb Mortal Wkly Rep, 64(1), 1–5 [PubMed: 25590678]

Yazdy MM, Mitchell AA, Tinker SC, Parker SE, & Werler MM (2013). Periconceptional use of opioids and the risk of neural tube defects. Obstet Gynecol, 122(4), 838–844 [PubMed: 24084542]

Table 1.

Characteristics of control and case infants and birth mothers, National Birth Defects Prevention Study, 1997–2011

Characteristic	Controls (n= 11,251)		All NTDs Combined (n=1,922)		Anencephaly[a] (n=541)		Spina Bifida (n=1,173)		Encephalocele[b] (n=208)	
	N	%	N	%	N	%	N	%	N	%
Child										
Phenotype										
Isolated	NA	NA	1,682	87.5	485	89.7	1,044	89.0	153	73.6
Multiple	NA	NA	240	12.5	56	10.4	129	11.0	55	26.4
Sex[c]										
Male	5,718	50.9	917	49.3	222	45.7	599	51.2	96	47.1
Female	5,523	49.1	931	50.7	265	54.3	559	48.8	107	52.9
Missing	10		74		54		15		5	
First-degree family history of NTDs[d,e,f]										
Yes	21	0.2	23	1.2	3	0.6	16	1.4	4	1.9
No	11,230	99.8	1,899	98.8	538	99.5	1,157	98.6	204	98.1
Missing	0		0		0		0		0	
NBDPS site[c,d,e]										
Arkansas	1,410	12.5	240	12.5	69	12.8	143	12.2	28	13.5
California	1,214	10.8	366	19.0	122	22.6	214	18.2	30	14.4
Georgia	1,208	10.7	236	12.3	65	12.0	142	12.1	29	13.9
Iowa	1,240	11.0	200	10.4	46	8.5	135	11.5	19	9.1
Massachusetts	1,366	12.1	104	5.4	21	3.9	71	6.1	12	5.8
New Jersey	562	5.0	67	3.5	10	1.9	49	4.2	8	3.9
New York	932	8.3	100	5.2	14	2.6	72	6.1	14	6.7
Texas	1,282	11.4	234	12.2	78	14.4	133	11.3	23	11.1
North Carolina	947	8.4	179	9.3	65	12.0	89	7.6	25	12.0
Utah	1,090	9.7	196	10.2	51	9.4	125	10.7	20	9.6
Maternal										
Race/Ethnicity[c,d,e,f]										
Non-Hispanic white	6,558	58.3	967	50.3	255	47.1	627	53.5	85	40.9
Non-Hispanic black	1,220	10.9	178	9.3	45	8.3	94	8.0	39	18.8
Hispanic	2,735	24.3	655	34.1	201	37.2	387	33.0	67	32.2
Other	736	6.5	122	6.4	40	7.4	65	5.5	17	8.2
Missing	2		0		0		0		0	
Age at delivery (years)										
<20	1,093	9.7	211	11.0	68	12.6	115	9.8	28	13.5
20–34	8,577	76.2	1,454	75.7	409	75.6	896	76.4	149	71.6
≥35	1,581	14.1	257	13.4	64	11.8	162	13.8	31	14.9

Characteristic	Controls (n= 11,251)		All NTDs Combined (n=1,922)		Anencephaly[a] (n=541)		Spina Bifida (n=1,173)		Encephalocele[b] (n=208)	
	N	%	N	%	N	%	N	%	N	%
Missing	0		0		0		0		0	
Education at delivery (years) [c,d,e]										
Less than high school	1,863	16.6	401	21.0	132	24.5	219	18.8	50	24.2
High school graduate	2,650	23.6	528	27.6	145	26.9	320	27.4	63	30.4
Some college or higher	6,696	59.7	983	51.4	262	48.6	627	53.8	94	45.4
Missing	42		10		2		7		1	
Pre-pregnancy BMI (kg/m^2) [d,e]										
Underweight (<18.5)	578	5.4	71	4.0	26	5.1	39	3.6	6	3.1
Normal weight (18.5–24.9)	5,804	53.8	848	47.2	256	50.1	483	44.3	109	56.2
Overweight (25- <30.0)	2,445	22.7	431	24.0	122	23.9	275	25.2	34	17.5
Obese (≥30.0)	1,957	18.2	446	24.8	107	20.9	294	27.0	45	23.2
Missing	467		126		30		82		14	
Gravidity [c,d,e]										
0	3,326	29.6	500	26.0	147	27.2	293	25.0	60	28.9
1–2	5,459	48.5	914	47.6	241	44.6	576	49.2	97	46.6
≥3	2,464	21.9	507	26.4	153	28.3	303	25.9	51	24.5
Missing	2		1		0		1		0	
Pregnancy intention [d,e]										
Intended	5,466	59.7	859	54.9	251	57.4	510	53.8	98	54.8
Mistimed	1,848	20.2	330	21.1	82	18.8	211	22.3	37	20.7
Ambivalent	1,035	11.3	231	14.8	59	13.5	148	15.6	24	13.4
Unwanted	815	8.9	144	9.2	45	10.3	79	8.3	20	11.2
Missing	2,087		358		104		225		29	
Pre-pregnancy hypertension [c,d]										
Yes	1,063	9.5	146	7.6	34	6.3	92	7.9	20	9.6
No	10,161	90.5	1,773	92.4	507	93.7	1,078	92.1	188	90.4
Missing	27		3		0		3			
Caffeine intake (mg/day) [d,g]										
0–9	2,051	18.3	304	15.9	94	17.5	183	15.7	27	13.2
10–99	4,014	35.8	730	38.2	210	39.1	432	37.0	88	42.9
100–199	2,575	23.0	473	24.8	132	24.6	294	25.2	47	22.9
200–299	1,405	12.5	221	11.6	61	11.4	135	11.6	25	12.2
≥300	1,169	10.4	183	9.6	40	7.5	125	10.7	18	8.8
Missing	37		11		4		4		3	

Characteristic	Controls (n= 11,251)		All NTDs Combined (n=1,922)		Anencephaly[a] (n=541)		Spina Bifida (n=1,173)		Encephalocele[b] (n=208)	
	N	%	N	%	N	%	N	%	N	%
Cigarette smoke exposure[c,d,e,f,h]										
No Active or Passive Smoking	7,928	70.7	1,306	68.7	382	71.8	792	68.1	132	63.8
Active Smoking Only	852	7.6	118	6.2	22	41	81	7.0	15	7.3
Passive Smoking Only	1,326	11.8	311	16.4	96	18.1	175	15.1	40	19.3
Active and Passive Smoking	1,105	9.9	167	8.8	32	6.0	115	9.9	20	9.7
Missing	40		20		9		10		1	
Use of folic acid-containing supplements[d,f,h]										
Yes	9,755	87.8	1,609	85.5	458	86.4	983	85.5	168	82.8
No	1,356	12.2	274	14.6	72	13.6	167	14.5	35	17.2
Missing	140		39		11		23		5	
Daily folate intake (μg/day)[d,g]										
<600	7,880	70.1	1,386	72.1	396	73.2	836	71.3	154	74.0
≥600	3,362	29.9	536	27.9	145	26.8	337	28.7	54	26.0
Missing	9		0		0		0		0	

BMI, body mass index; CDC, Centers for Disease Control and Prevention; kg, kilograms; mg, milligrams; NA, not applicable; NTD, neural tube defect; μg, micrograms.

Because of rounding, percentages may not total to 100.

[a] Includes anencephaly and craniorachischisis cases.

[b] Includes encephalocele, cranial meningocele, and encephalomyelocele cases.

[c] $p<0.05$ for anencephaly.

[d] $p<0.05$ for all NTDs combined.

[e] $p<0.05$ for spina bifida.

[f] $p<0.05$ for encephalocele.

[g] During the year before conception.

[h] During the periconceptional period (one month before conception through the first month of pregnancy).

Table 2.

Reported patterns of maternal periconceptional alcohol consumption and type of alcohol consumed, National Birth Defects Prevention Study, 1997–2011

Periconceptional Alcohol Consumption	Controls (N=11,251)		All NTDs combined (N=1,922)		Anencephaly[a] (N=541)		Spina Bifida (N=1,173)		Encephalocele[b] (N=208)	
	N	%	N	%	N	%	N	%	N	%
Any consumption										
No	7,268	64.6	1,394	72.5	427	78.9	818	69.7	149	71.6
Yes	3,983	35.4	528	27.5	114	21.1	355	30.3	59	28.4
Months										
B1 only	1,858	16.5	237	12.3	58	10.7	144	12.3	35	16.8
B1+P1	1,713	15.2	216	11.2	40	7.4	157	13.4	19	9.1
P1 only	412	3.7	75	3.9	16	3.0	54	4.6	5	2.4
Binge episodes										
None	7,268	64.9	1,394	72.8	427	79.2	818	70.3	149	71.6
No binge episodes	2,625	23.4	327	17.1	70	13.0	215	18.4	42	20.2
One or more binge episodes	1,312	11.7	194	10.1	42	7.8	135	11.6	19	8.2
Missing	46		7		2		5		0	
Average number of drinks per month										
0	7,268	65.0	1,394	72.9	427	79.2	818	70.2	149	71.6
1–4	1,772	15.8	250	13.1	55	10.2	164	14.1	31	14.9
5–15	1,348	12.1	178	9.3	32	5.9	128	11.0	18	8.7
16–30	555	5.0	56	2.9	16	3.0	34	2.9	6	2.9
>30	247	2.2	35	1.8	9	1.7	22	1.9	4	1.9
Missing	61		9		2		7		0	
Type of alcohol										
None	7,266	64.7	1,394	72.7	427	79.2	818	69.9	149	71.6
Beer only	744	6.6	130	6.8	28	5.2	90	7.7	12	5.8
Wine only	1,121	10.0	107	5.6	29	5.4	67	5.7	11	5.3
Distilled spirits only	689	6.1	102	5.3	19	3.5	69	5.9	14	6.7
Any combination	1,418	12.6	185	9.7	36	6.7	127	10.9	22	10.6
Missing	13		4		2		2		0	

B1, one month before conception; NTD, neural tube defect; P1, one month after conception.

[a] Includes anencephaly and craniorachischisis cases.

[b] Includes encephalocele, cranial meningocele, and encephalomyelocele cases.

Table 3

Associations for maternal periconceptional alcohol consumption and neural tube defects, National Birth Defects Prevention Study, 1997–2011

Periconceptional Alcohol Consumption	All NTDs combined OR (95% CI)	Anencephaly[a] OR (95% CI)	Spina Bifida OR (95% CI)	Encephalocele[b] OR (95% CI)
Any consumption				
None	Reference	Reference	Reference	Reference
Any	0.8 (0.7, 0.9)[c]	0.6 (0.5, 0.7)[c]	0.8 (0.7, 0.9)[d]	0.9 (0.6, 1.2)[e]
Binge episodes				
None	Reference	Reference	Reference	Reference
No binge episodes	0.7 (0.6, 0.8)[c]	0.6 (0.5, 0.8)[f]	0.8 (0.7, 1.0)[c]	1.0 (0.7, 1.4)[e]
One or more binge episodes	0.8 (0.7, 1.0)[c]	0.7 (0.5, 1.0)[f]	1.0 (0.8, 1.2)[c]	0.8 (0.4, 1.2)[e]
Average number of drinks per month				
0	Reference	Reference	Reference	Reference
1–4	0.8 (0.7, 0.9)[c]	0.6 (0.5, 0.8)[g]	0.9 (0.7, 1.1)[c]	1.0 (0.7, 1.6)[h]
5–15	0.8 (0.7, 0.9)[c]	0.5 (0.4, 0.8)[g]	0.9 (0.8, 1.1)[c]	0.9 (0.5, 1.5)[h]
16–30	0.6 (0.5, 0.8)[c]	0.6 (0.4, 1.1)[g]	0.6 (0.4, 0.9)[c]	0.7 (0.3, 1.6)[h]
>30	0.8 (0.6, 1.1)[c]	0.9 (0.4, 1.7)[g]	0.9 (0.6, 1.3)[c]	0.9 (0.3, 2.6)[h]
Type of alcohol				
None	Reference	Reference	Reference	Reference
Beer only	1.0 (0.8, 1.2)[c]	0.7 (0.5, 1.0)[i]	1.1 (0.9, 1.4)[j]	0.9 (0.5, 1.7)[i]
Wine only	0.6 (0.5, 0.7)[c]	0.6 (0.4, 0.9)[i]	0.7 (0.5, 0.9)[j]	0.7 (0.4, 1.3)[i]
Distilled Spirits only	0.8 (0.7, 1.0)[c]	0.5 (0.3, 0.9)[i]	0.9 (0.7, 1.2)[j]	1.0 (0.6, 1.9)[i]
Any combination	0.7 (0.6, 0.9)[c]	0.5 (0.4, 0.7)[i]	0.9 (0.7, 1.1)[j]	1.0 (0.6, 1.6)[i]

CI, confidence interval; NTD, neural tube defect; OR, odds ratio.

[a] Includes anencephaly and craniorachischisis cases.

[b] Includes encephalocele, cranial meningocele, and encephalomyelocele cases.

[c] Adjusted for NBDPS site.

[d] Crude OR.

[e] Adjusted for maternal race/ethnicity and education at delivery.

[f] Adjusted for NBDPS site, maternal education at delivery, and periconceptional cigarette smoke exposure.

[g] Adjusted for NBDPS site and maternal periconceptional cigarette smoke exposure.

[h] Adjusted for NBDPS site, maternal race/ethnicity, and periconceptional cigarette smoke exposure.

[i] Adjusted for NBDPS site, maternal race/ethnicity, and education at delivery.

[j] Adjusted for NBDPS site and maternal pre-pregnancy BMI.