HHS Public Access

Author manuscript

Int J Pediatr Otorhinolaryngol. Author manuscript; available in PMC 2020 July 01.

Published in final edited form as:

Int J Pediatr Otorhinolaryngol. 2019 July ; 122: 18–26. doi:10.1016/j.ijporl.2019.03.026.

Sociodemographic, health behavioral, and clinical risk factors for anotia/microtia in a population-based case-control study

Marisa A. Ryan, MD, MPH[1,2,3], **Andrew F. Olshan, PhD**[1], **Mark A. Canfield, PhD**[4], **Adrienne T. Hoyt, MS, MPH**[4], **Angela E. Scheuerle, MD**[4,5], **Suzan L. Carmichael, PhD**[6], **Gary M. Shaw, PhD**[6], **Martha M. Werler, PhD**[7], **Sarah C. Fisher, MPH**[8], **Tania A. Desrosiers, PhD, MPH**[1], and **National Birth Defects Prevention Study**

[1]Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC

[2]Division of Head and Neck Surgery & Communication Sciences, Department of Surgery, Duke University Hospital, Durham, NC

[3]Department of Otolaryngology–Head and Neck Surgery, Johns Hopkins University, Baltimore, MD (current affliliation)

[4]Birth Defects Epidemiology and Surveillance Branch, Texas Department of State Health Services, Austin, TX

[5]Department of Pediatrics, Division of Genetics and Metabolism, University of Texas Southwestern Medical Center, Dallas, TX

[6]Department of Pediatrics, Division of Neonatal and Developmental Medicine, Stanford University School of Medicine, Palo Alto, CA

[7]Department of Epidemiology, Boston University School of Public Health, Boston, MA

[8]Congenital Malformations Registry, New York State Department of Health, Albany, NY

Abstract

Objective: Anotia and microtia are congenital malformations of the external ear with few known risk factors. We conducted a comprehensive assessment of a wide range of potential risk factors using data from the National Birth Defects Prevention Study (NBDPS), a population-based case-control study of non-chromosomal structural birth defects in the United States.

Methods: Mothers of 699 infants with anotia or microtia (cases) and 11,797 non-malformed infants (controls) delivered between 1997 and 2011 were interviewed to obtain information about sociodemographic, health behavioral, and clinical characteristics. Adjusted odds ratios (aORs) and 95% confidence intervals (CIs) were estimated with logistic regression.

Corresponding author: Tania A. Desrosiers, PhD, MPH, Department of Epidemiology, Campus Box 7435, Gillings School of Global Public Health, University of North Carolina, Chapel Hill, NC 27599, tania.desrosiers@unc.edu.

Conflicts of interest: None.

Results: Infants with anotia/microtia were more likely to be male (aOR, 1.29; 95% CI, 1.10–1.50) and from a multifetal pregnancy (aOR, 1.68; 95% CI, 1.16–2.42). Cases were also more likely to have parents of Hispanic ethnicity (maternal aOR, 3.19; 95% CI, 2.61–3.91; paternal aOR, 2.11; 95% CI, 1.54–2.88), and parents born outside the United States (maternal aOR, 1.29; 95% CI, 1.06–1.57; paternal aOR, 1.92; 95% CI, 1.53–2.41). Maternal health conditions associated with increased odds of anotia/microtia included obesity (aOR, 1.31; 95% CI, 1.06–1.61) and pre-pregnancy diabetes (type I aOR, 9.89; 95% CI, 5.46–17.92; type II aOR, 4.70; 95% CI, 2.56–8.63). Reduced odds were observed for black mothers (aOR, 0.57; 95% CI, 0.38–0.85) and mothers reporting daily intake of folic acid-containing supplements (aOR, 0.59; 95% CI, 0.46–0.76).

Conclusion: We identified several risk factors for anotia/microtia, some which have been previously reported (e.g., diabetes) and others which we examined for perhaps the first time (e.g., binge drinking) that warrant further investigation. Our findings point to some potentially modifiable risk factors and provide further leads toward understanding the etiology of anotia/microtia.

Keywords

birth defect; congenital malformation; anotia; microtia; ear

1. INTRODUCTION

Microtia is a birth defect characterized by a small and/or malformed ear(s). The most severe form of microtia is anotia, in which the external ear is completely absent. The prevalence of anotia/microtia varies substantially by geographic region [1–6], with the highest prevalence of 17.4 per 10,000 newborns reported in Quito, Ecuador [7]. Within the United States, the average prevalence between 2011 and 2015 across 30 states with population-based birth defects surveillance programs was 1.8 per 10,000 infants [8]. However, a two-fold higher prevalence of 2.6 per 10,000 infants was observed in the subset of 12 states with active case-finding methodology (vs. passive surveillance)[8].

The functional, medical, and psychosocial costs of anotia/microtia are substantial [9–11]. Hearing loss is present in 90% of cases [12–13], and rehabilitation can be challenging. Often, rehabilitation cannot be accomplished through surgery alone and requires hearing aids [14]. The aesthetic component of the reconstruction process typically requires multiple surgical stages, and occurrence of complications can exceed 70% [14–15].

Anotia/microtia is sometimes associated with craniofacial syndromes, including Fraser, Treacher-Collins, and Goldenhaar Syndromes, as well as the chromosomal trisomies [6,16], but there are no confirmed single-gene mutations for non-syndromic cases. Other birth defects that may co-occur with anotia/microtia include vertebral anomalies, macrostomia, oral clefts, facial asymmetry, renal abnormalities, heart defects, microphthalmia, holoprosencephaly, and polydactyly [5,6,16–18]. However, 25–45% of cases are neither associated with a syndrome nor another defect [2,16]. The majority of these non-syndromic, isolated cases are presumed to be sporadic [6,19].

Few risk factors for anotia/microtia have been identified. Relatively well-established factors include male sex [2,4,5,16], Hispanic ethnicity [2,3,20,21], and maternal diabetes [6,22–24]. Other risk factors that have been suggested include advanced maternal age [2,4,5], high parity [5,7], multifetal gestation [24], low maternal educational achievement [2,3,16,21,25], American Indian/Alaskan Native [20] or Asian/Pacific Islander [4,20,26] ethnicity, and birth outside the US specifically among Hispanic mothers [21,23]. Teratogenic medications known to cause anotia/microtia include thalidomide, isotretinoin, and mycophenolate mofetil [27–29]. Pre-pregnancy obesity [21,30,31] and low periconceptional folic acid/folate intake [30,32] are among the few potentially modifiable risk factors.

We conducted a comprehensive assessment of potential sociodemographic, health behavioral, and clinical risk factors for anotia/microtia in a population-based study.

2. METHODS

2.1 Study population

The National Birth Defects Prevention Study (NBDPS) was a case-control study of over 30 types of major structural birth defects. Ten Centers for Birth Defects Research and Prevention (henceforth, “centers”) participated in the NBDPS, which was sponsored by the Centers for Disease Control and Prevention (CDC). Details of the NBDPS design are published [33]. Briefly, cases with an eligible birth defect were identified by population-based birth defects surveillance registries with active case ascertainment approaches in Arkansas, California, Iowa, Massachusetts, New Jersey, New York, Texas, Georgia, North Carolina, and Utah. Cases were ascertained among live-born infants, stillborn fetuses (≥ 20 weeks), and elective terminations. Infants without any major birth defect were selected as controls through random sampling of birth certificates or birth hospital records at each center from the same time- and geographic-frame as cases [34]. All cases and controls had an estimated delivery date (“due date”) between November 1997 and December 2011. Pregnancies with donor gamete(s) or embryos (3 cases and 32 controls) were excluded from our study sample.

2.2 Case classification

Cases of anotia/microtia (British Paediatric Association (BPA) codes 744.010–14 and 744.210–14) diagnosed at postnatal examination, surgical repair, or autopsy were ascertained up to one or (for some centers) two years after delivery by each center’s birth defects registry. Abstracted medical records for each infant with anotia or microtia were reviewed by a clinical geneticist at each center and again by a study-wide clinician (AES) to confirm that the case definition for eligibility was met, and to ensure consistent classification across all centers. Details of the NBDPS classification scheme are published [35].

Eligible cases of anotia/microtia included type 2 (moderately anomalous ear), type 3 (rudimentary soft tissue structure with no cartilage), and type 4 (anotia). Cases with type 1 microtia (normally shaped, but smaller ear) or those described only as “small ears” were excluded, as were cases with only abnormal external auditory canals. Also excluded from the NBDPS were any cases with known chromosomal abnormalities, single-gene disorders,

or syndromes. Eligible cases of anotia/microtia were further classified by the presence or absence of cooccurring defects: cases were classified as *isolated* if anotia/microtia occurred alone or with a minor defect (e.g., tongue tie, stenosis of lacrimal duct, or flat nasal bridge), or *non-isolated* if another major structural birth defect was present. Laterality (unilateral/bilateral) was also documented.

2.3 Risk factor assessment

Maternal self-reported information about demographics, health conditions and behaviors, paternal factors, and pregnancy characteristics were collected through a structured, computer-assisted telephone interview. Mothers were interviewed in English or Spanish between 6 weeks and 24 months after the estimated date of delivery; the average time-to-interview for cases and controls was 11 and 9 months, respectively. Among mothers of eligible cases of anotia/microtia, 68% participated in the interview (64% among mothers of controls); non-interviewed cases and controls were excluded from this analysis.

All potential risk factors assessed in this analysis were ascertained during the maternal interview. Maternal demographic factors of interest included age at delivery (<25, 25–34, >35 years), race/ethnicity (white, non-Hispanic; black, non-Hispanic; Hispanic; other [Asian, Pacific Islander, Native American, Alaskan Native, or self-identified other]), birthplace (US, non-US), and education level (<high school, high school, >high school). Health behaviors of interest were folic acid supplementation with a single vitamin, prenatal vitamin or multivitamin containing folic acid during the first trimester and month before pregnancy (no use, non-daily use [less than daily use], and daily use), cigarette use during the first trimester (none, 1–4 cigarettes/day, ≥5 cigarettes/day [equivalent to ≥1/2 a pack/day]), alcohol use during the first trimester and month before pregnancy (none; binge drinking of ≥4 drinks on one occasion with each drink defined as one glass of wine, beer, mixed drink or shot of liquor; drinking, but not binge drinking), substance abuse in the three months before pregnancy until delivery (no, yes, including any recreational or illicit drug use), and caffeine intake (<10, 10–99, 100–199, 200–299, <300 milligrams, derived from a continuous variable based on maternal consumption of coffee, tea, soda, and chocolate and categorized based on one cup of coffee intervals since each cup contains approximately 100 milligrams). Clinical factors of interest included self-reported first-degree family history of anotia/microtia (no, yes), number of prior live births (0, 1, 2, ≥3), pre-pregnancy body mass index (BMI) (<18.5, 18.5–25, 25–30, >30 kg/m^2 according to the National Institute of Health categories), history of asthma (no, yes for any history of an asthma diagnosis), and history of diabetes (no, any history of type I, type II, or gestational). We also assessed several paternal factors including age at delivery, race/ethnicity, birthplace, education level, and substance abuse. Lastly, we assessed the following pregnancy characteristics: infant sex (female, male), plurality (singleton, multifetal gestation), and gestational age at delivery (<32 weeks or very preterm, 32–36 weeks or preterm, ≥37 weeks or term).

2.4 Statistical analysis

Univariate and bivariate analyses were performed to explore the relationships between case status and the potential risk factors described above. Logistic regression was used to estimate odds ratios (ORs), adjusted odds ratios (aORs) and 95% confidence intervals (CIs)

for each factor of interest. To assess the potential for confounding, we constructed directed acyclic graphs (DAG) informed by previous studies and biologic plausibility [36,37]. Potential maternal confounders were age, race/ethnicity, birthplace, education level, number of prior live births, pre-pregnancy BMI, smoking, alcohol use, substance abuse, caffeine intake, and diabetes. Potential paternal confounders were age, race/ethnicity, birthplace, and education level. For each potential risk factor of interest, we began with a fully adjusted model and, using backward selection, retained only covariates that changed the magnitude of the estimated association by at least 10%.

In models estimating the association between folic acid-containing supplementation and anotia/microtia, we further assessed effect measure modification by obesity, maternal race/ethnicity, and birthplace with multiplicative interaction terms. These factors were chosen based on substantial biologic rationale and evidence from previous studies [30,38,39]. Greater than 10% differences in stratum specific estimates were considered substantially different. The likelihood ratio tests (LRT) and Wald p-values of the interaction terms were evaluated at an alpha-level of 0.05 to determine benefit to the model from their inclusion.

In a series of secondary analyses, we estimated adjusted ORs stratified by the presence of co-occuring defects (isolated vs. non-isolated), laterality (unilateral vs. bilateral), and infant sex. We also repeated analyses excluding mothers with pre-gestational type I or type II diabetes, given the previously reported strong association between pre-existing diabetes and anotia/microtia [6,22–24].

The NBDPS is approved by the Institutional Review Boards (IRB) of the CDC and all participating centers. Recruited participants provided informed consent to participate in the NBDPS prior to the maternal interview. For this analysis, additional IRB approval was obtained by the University of North Carolina at Chapel Hill (study #16–2460). Data were analyzed using SAS statistical software version 9.4 (SAS institute, Inc., Cary, NC, USA).

3. RESULTS

Our study sample consisted of mothers of 699 anotia/microtia cases and 11,797 controls. Among the cases, 480 (69%) had isolated anotia/microtia and 219 (31%) were non-isolated. There were 608 (87%) unilateral defects, 88 (13%) bilateral defects, and 3 (<1%) cases with unspecified laterality. The majority of anotia/microtia cases were livebirths (>98%); 3 and 7 of the cases were stillbirths and terminations, respectively.

The distribution of maternal, paternal, and pregnancy characteristics by case/control status is presented in Table 1. Infants with anotia/microtia were more likely to be male, part of a multi-fetal pregnancy, and delivered preterm. The proportion of cases and controls with a first-degree family history of anotia/microtia was similar. Mothers of cases were more likely to have a lower annual household income (≤$50,000), though the proportion of participants with missing information for income was relatively high (nearly 10%). The proportion of cases differed across the ten centers, as did the distribution of race/ethnicity.

3.1 Pregnancy characteristics

Associations between pregnancy characteristics and anotia/microtia are presented in Table 2. Increased odds were observed for males (OR, 1.29; 95% CI, 1.10–1.50) and non-singletons (OR, 1.68; 95% CI, 1.16–2.42). Cases were also more likely to be delivered preterm (OR, 2.46; 95% CI, 1.99–3.03) or very preterm (OR, 3.63; 95% CI, 2.42–5.45), particularly those with non-isolated anotia/microtia.

3.2 Maternal factors

Crude and adjusted ORs for selected maternal sociodemographic, clinical, and health behavioral factors are presented in Table 3 for all cases of anotia/microtia combined, as well as stratified by isolated/non-isolated classification. Increased odds were identified for maternal Hispanic race/ethnicity (aOR, 3.19; 95% CI, 2.61–3.91), 'other' race/ethnicity (aOR, 1.79; 95% CI, 1.30–2.46), and maternal birth outside the US (aOR, 1.2; 95% CI, 1.06–1.57). The strong association with maternal Hispanic race/ethnicity was observed for both isolated and non-isolated cases, whereas the association with non-US birthplace appeared to be only among cases with isolated anotia/microtia. Reduced odds of anotia/microtia were observed for black mothers (aOR, 0.57; 95% CI, 0.38–0.85), particularly among isolated cases, as compared with white, non-Hispanic mothers.

Mothers with high pre-pregnancy BMI (obese) were more likely to have an infant with anotia/microtia (OR, 1.31; 95% CI, 1.06–1.61), though this association was attenuated to null in sensitivity analyses excluding all women with a history of diabetes (data not shown). We observed ten-fold and five-fold increased odds for type I (aOR, 9.89; 95% CI, 5.46–17.92) and type II (aOR, 4.70; 95% CI, 2.56–8.63) diabetes, respectively, though the confidence intervals were wide. The associations with type I and II diabetes were substantially stronger for non-isolated cases. We observed an association for gestational diabetes among non-isolated cases (aOR, 1.62; 95% CI, 1.04–2.52), but not for isolated cases or for all cases combined.

Reduced odds were also observed for any use of periconceptional folic acid supplementation compared to no supplementation, particularly for daily use (aOR, 0.59; 95% CI, 0.46–0.76). There was effect measure modification of this association by maternal birth outside the US (p=0.003); among mothers born outside the US, the protective effect of daily supplement intake was stronger in magnitude (aOR, 0.33; 95% CI, 0.19–0.58). For mothers born in the US, there was no association with folic acid-containing supplement intake for any frequency of use (daily or non-daily). We observed no association with maternal alcohol use, with the possible exception of binge drinking and bilateral anotia/microtia (aOR, 1.84; 95% CI, 1.06–3.21) (Supplemental Table). Smoking ≥5 cigarettes/day was associated only with non-isolated cases of anotia/microtia. There were no significant associations with maternal age at delivery, education, number of prior live births, history of asthma, substance abuse, or caffeine intake.

The aORs estimated separately for unilateral vs. bilateral defects and male vs. female cases are presented in the Supplemental Table. The strong association with maternal Hispanic race/ethnicity persisted in all subgroups evaluated. The increased odds with maternal birth

outside the US was attenuated for bilateral defects. The increased odds with type I and II diabetes were both higher for bilateral compared to unilateral defects. There was no significant association for gestational diabetes for all cases together, however, there were significantly elevated aORs for gestational diabetes in the bilateral and female cases.

3.3 Paternal factors

Crude and adjusted ORs for selected paternal characteristics are presented in Table 4 for all cases of anotia/microtia combined, as well as stratified by isolated/non-isolated classification. For all anotia/microtia cases combined, an increased association was observed for paternal Hispanic race/ethnicity even after adjustment for maternal race/ethnicity (aOR, 2.11; 95% CI, 1.54–2.88). As with maternal Hispanic race/ethnicity, this strong association persisted in all subgroups evaluated (see also Supplemental Table). Increased odds were also observed for paternal birth outside the US (aOR, 1.92; 95% CI, 1.53–2.41). No associations were observed for paternal age, education, or substance abuse.

4. DISCUSSION

The relatively low prevalence of anotia/microtia in the general population has limited the epidemiologic study of potential risk factors for this major structural defect. The large number of cases in NBDPS and rich interview data affords a unique opportunity for a comprehensive assessment of a broad range of risk factors for non-syndromic anotia/microtia. The analysis updates and extends previous analyses conducted in a subset of our NBDPS study population [21,22,24,30,32,40,41]. Our study expands upon these earlier studies by including four additional years (2008–2011) and almost 200 additional cases. Our study also includes previously uninvestigated risk factors such as maternal binge drinking, substance use, number of prior live births, and maternal history of asthma, as well as paternal age, race/ethnicity, and education.

The increased risk we confirmed for male infants has been already well established in various populations [2,4,5,16]. This analysis also confirms prior findings that the association with male sex is driven mostly by unilateral and isolated rather than the bilateral and non-isolated cases, which are more evenly distributed by sex [5].

Our results are also consistent with previous studies that have reported increased risk of anotia/microtia with Hispanic maternal ethnicity [2,3,20,21], American Indian/Alaskan Native/Asian/Pacific Islander/other maternal ethnicity [4,20,26], maternal birth outside the US [2,21], multifetal gestation [24], diabetes [6,22–24], and lower folic acid/folate intake [30, 32]. Our study is also consistent with previous reports of lower odds of anotia/microtia among black mothers [2,20]. Notably, our analysis identified new potential risk factors for further investigation including paternal Hispanic race/ethnicity (independent of maternal race/ethnicity), smoking of ≥5 cigarettes/day (for non-isolated cases), and binge drinking (for bilateral defects).

The association with Hispanic ethnicity may be related to lifestyle or immigration and acculturation. In the NBDPS study population, the majority of parents born outside the US are Hispanic (69% of both mothers and fathers). Previous NBDPS analyses have shown that

maternal birth outside the US increases risk of anotia/microtia among Hispanic mothers [21,39]. Specifically, in an analysis of 163 cases, Ramadhani et al. (2009) found that Hispanic immigrants have a higher risk of having a child with anotia/microtia than Hispanic-Americans born in the US (aOR, 1.60; 95% CI, 1.06–2.42)[39]. Hoyt et al. (2014) showed that maternal emigration from Mexico after age 5 (aOR, 4.88; 95% CI, 2.93–8.11) portends a particularly high risk [21]. Both of these analyses were of an earlier subset of the NBDPS population and our results show a similar increased risk in mothers born outside the US. We also found an increased risk for fathers born outside the US, even after accounting for maternal nativity. Similar to race/ethnicity, parental nativity may influence the risk of anotia/microtia through both environmental and lifestyle factors. However, we did not account for heterogeneity in birthplace among non-US born parents, and further investigation is required.

A major strength of our study is the rigorous case verification and systematic classification scheme. Stratification by isolated and non-isolated occurrences of anotia/microtia allowed us to independently evaluate a more etiologically homogenous group of isolated cases, as severe cases with multiple cooccurring defects may have different underlying pathogenesis [35]. Notably, the decreased odds with black maternal race and folic acid-containing supplementation as well as the increased odds with maternal birth outside the US and male sex were stronger for isolated cases.

Further, owing to the detailed classification information in NBDPS, we could estimate associations stratified by laterality, which is important since bilateral cases may introduce phenotypic heterogeneity and may also be more likely related to an unknown syndrome [2,6]. However, the relatively few bilateral defects in our study group (n=88, 12.6%) limited analytic precision. The moderately increased risk with maternal binge drinking for bilateral defects was not present overall or in any other subgroup, and requires further investigation. The stronger association noted for bilateral cases and maternal diabetes, particularly for pre-pregnancy type I/II diabetes, supports the diabetic embryopathy theory proposed by Van Bennekom et al. (2013) that hyperglycemia induced disruption of ear development may contribute more to the development of bilateral defects [24]. The strength of the association with all types of diabetes also increased for non-isolated defects and this may have been due to the wide fluctuations in blood glucose in diabetes that lead to varied structural defects during different time points in embryologic development [42]. Those with gestational diabetes can still be euglycemic during the first trimester, which could explain the weaker association compared to pre-existing type I/II diabetes.

The diabetic embryopathy etiology also suggests that obese mothers would have a higher risk of offspring with anotia/microtia, since glucose intolerance is more common with obesity even in the absence of a diabetes diagnosis. The 1.31 times higher odds of anotia/microtia in obese mothers (95% CI, 1.06–1.61) is similar to analyses in earlier subsets of the NBDPS population including those by Ma et al. (2010) (1997–2005; OR, 1.27; 95% CI, 0.96–1.67) and Waller et al. (2007) (1997–2002; aOR, 1.10; 95% CI, 0.74–1.65) [30,31].

Because of the known strong association with type I/II diabetes, a sensitivity analysis excluding mothers with pre-gestational diabetes was performed. This exclusion slightly

attenuated the already weak association with obesity, suggesting that this association may be related to concomitant diabetes or elevated glucose levels in those mothers rather than independent changes caused by the pathophysiology of obesity.

There may be an interplay between folate levels and diabetes. Folate is essential to normal embryogenesis and cell proliferation. Folic acid supplementation reduced malformations in animal embryos exposed to high glucose concentrations that simulate diabetes [43,44]. Folate status in pregnant women is influenced by both dietary folate and supplemental folic acid intake. In an earlier subset of the NBDPS data, Ma et al. (2012) found an association between anotia/microtia and low dietary folate intake (OR, 1.57; 95% CI, 1.09–2.25)[32]. Ma et al. (2010) also showed a decreased odds with periconceptional folic acid-containing supplementation (OR, 0.81; 95% CI, 0.59–1.10) in an analysis of 420 cases [30]. Our analysis of folic acid-containing supplementation, which included additional NBDPS participants, had a smaller aOR with a narrower CI. Further, the analysis by Ma et al. (2010) found a decreased odds with folic acid-containing supplementation in non-obese women (aOR, 0.63; 95% CI, 0.44–0.91), but not in obese women (aOR, 1.51; 95% CI, 0.69–3.28), suggesting a different biologic effect of folic acid based on BMI [30]. However, there was no statistical evidence of effect measure modification of folic acid-containing supplementation by obesity in our analysis.

There was effect measure modification of folic acid-containing supplementation by maternal nativity in our analysis. After stratifying by maternal nativity, the significantly reduced odds only persisted in women not born in the US who also took daily supplements. This may be due to recall error about supplementation or could possibly reflect differences in dietary sources of folate between mothers based on nativity. Serum folate levels are lower in Hispanic compared to non-Hispanic white women in the US [38]. This may in part be due to lower consumption of cereals and enriched grains, which are required to be fortified with folic acid in the US, and higher consumption of staple foods made with corn flour (masa), which was not fortified during the study period. To address folate insufficiency and neural tube defects (NTDs) in this population, the U.S Food and Drug Administration recently authorized voluntary fortification of corn flour in 2016 [45]. Many other countries do not have any mandatory folate fortification. Women who lived in countries without fortification or who had a corn flour-based diet during the periconceptional period may experience a larger benefit from folic acid supplementation. US-born women who eat a fortified grain-based diet and have adequate folate stores may receive less added protection from additional folic acid supplementation. Anotia/microtia could decrease along with NTDs as more countries fortify their grain products and as more corn flour is fortified in the US.

The suggestion that poor quality periconceptional diets and lack of folic acid have contributed to the excess of NTDs and anotia/microtia found in mothers born outside the US has been previously suggested by Ramadhani et al. (2009), who found similarly elevated odds of anotia/microtia (aOR, 1.60; 95% CI, 1.06–2.42) and spina bifida (aOR, 1.53; 95% CI; 1.06–2.35) in NBDPS mothers born in Central America or Mexico [39]. The critical period of external ear development occurs later than neural tube closure, starting after the first month of pregnancy and extending through the third month of pregnancy [46].

Adequate nutrition and folate levels may be most important during this period to prevent anotia/microtia.

Our results were not consistent with previously reported associations with advanced maternal age [2,4,5], high parity [5,7], and low educational achievement [2,3,16,21,25]. In our analysis, the elevated OR for less than a high school maternal education compared to high school education did not persist after adjustment for race/ethnicity.

Despite the rigorous case classification scheme in the NBDPS, there are some limitations to the available clinical data. Given the population-based case-control design, the source of clinical information about cases in NBDPS is abstracted medical records, which come from a large number of independent health care providers across 10 states over a period of approximately 15 years. Subsequently, there is variation across records in terminology and diagnostic criteria, making it challenging to systematically and accurately differentiate between subtle subtypes across the continuum of microtia. Thus, in this analysis, we do not distinguish between Types 2–4 of microtia/anotia. The available information was sufficient to exclude cases with the least severe phenotype, Type 1 microtia, but it is possible that a few additional cases would have been excluded if more uniform information were available. Cases with known chromosomal anomalies or single gene disorders are also excluded from NBDPS. However, cases were only ascertained up to two years of age and some genetic conditions may have been diagnosed after that time, or the relevant information may not have been available in the accessible medical record at the time of abstraction. Cases with genetic causes may also be more common in the non-isolated and bilateral defect groups [2,6], thereby biasing the apparent effect of risk factors in those subgroups when there is an underlying genetic etiology.

The percentage of eligible mothers who participated in the interview was less than 70% and there is the potential for selection bias due to factors associated with non-participation. Retrospectively collected information from mothers is susceptible to recall errors and potentially differential recall between cases and controls, which could bias estimates towards or away from the null. This bias was limited in the NBDPS by using trained interviewers and structured questionnaires with recall aids. Some of the associations were based on low numbers of exposed mothers, especially asthma, recreational substance use, first-degree family history of anotia/microtia; likewise, some analyses were based on case subgroups (e.g., bilateral cases only), which limited the precision of those analyses.

The strengths of the NBDPS include its large population-based study design, which leverages case ascertainment from active surveillance programs to limit referral bias. The multi-state study population is geographically and ethnically diverse, and has been shown to represent the underlying US population relatively well [34]. As noted earlier in Section 2.2, confirmation of case diagnosis and eligibility as well as systematic classification is a critical strength that reduces phenotypic – and thus likely etiologic – heterogeneity. Lastly, the maternal interview yields rich information about a comprehensive set of socio-demographic, health behavioral, and clinical factors before and during pregnancy for mothers as well as fathers. Findings from this analysis strengthen the existing evidence and point to additional

possible risk factors for anotia/microtia that should be further investigated in future analyses and in different populations.

Future analyses should consider the effect of risk factors during the critical period of external ear development in the second and third month of pregnancy, especially folate levels as grain/flour/masa fortification policies change. Though guidelines for periconceptional folic acid supplementation to prevent NTDs and anencephaly already exist, including those published by the CDC, US Preventive Services Task Forces, American College of Obstetricians and Gynecologists, American Academy of Family Physicians, and American Academy of Pediatrics [47], future updates of these recommendations could also include anotia/microtia. The interaction between folate and oxidating risk factors such as diabetes, alcohol and cigarettes should be further explored. Given the heterogeneity of the populations at highest risk of anotia/microtia (Hispanic, Asian, and Pacific Islander) further evaluation of birthplace and racial/ethnic sub-groups of those mothers and fathers is also warranted. Ultimately, prevention recommendations can be targeted to those groups at highest risk for anotia/microtia as their underlying risk factors become more fully understood.

5. CONCLUSIONS

We identified several possible risk factors for anotia/microtia, some which have been previously observed (e.g., diabetes) and others which we investigated for the first time and warrant further investigation (e.g., binge drinking). Our findings point to some potentially modifiable risk factors and provide further leads toward understanding the etiology of anotia/microtia.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements:

We thank the California Department of Public Health, Maternal Child and Adolescent Health Division for providing surveillance data from California for this study. We thank the participating families, scientists, and staff from all of the NBDPS sites. We thank Nina Forestieri for replicating the statistical analyses presented herein.

Funding: This study was supported by cooperative agreements with the Centers for Disease Control and Prevention and the North Carolina Center for Birth Defects Research and Prevention at the University of North Carolina, Chapel Hill (5U01DD000488, 5U01DD001036). This project was also supported in part by a National Institute on Deafness and other Communication Disorders training grant (T32 DC013018–03). The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Center for Disease Control and Prevention, the National Institute on Deafness and other Communication Disorders, or the California Department of Public Health.

REFERENCES

[1]. Mai CT, Isenburg J, Langlois PH, Alverson CG, Gilboa SM, Rickard R, Canfield MA, Anjohrin SB, Lupo PJ, Jackson DR, Stallings EB, Scheuerle AE, Kirby RS, National Birth Defects Prevention Network. Population-based birth defects data in the United States, 2008 to 2012: Presentation of state-specific data and descriptive brief on variabiliy in prevalence. Birth Defects Research (2015) 103(11):972–93. [PubMed: 26611917]

[2]. Canfield MA, Langlois PH, Nguyen LM, Scheuerle AE. Epidemiologic features and clinical subgroups of anotia/microtia in Texas. Birth Defects Research (2009) 85:905–913. [PubMed: 19760683]

[3]. Husain T, Langlois PH, Sever LE, Gambello MJ. Descriptive epidemiologic features shared by birth defects thought to be related to vascular disruption in Texas, 1996–2002. Birth Defects Research (2008) 82:435–440. [PubMed: 18383510]

[4]. Forrester MB, Merz RD. Descriptive epidemiology of anotia and microtia, Hawaii, 1986–2002. Congenital Anomalies (2005) 45:119–124. [PubMed: 16359491]

[5]. Harris J, Kallen B, Robert E. The epidemiology of anotia and microtia. Journal of Medical Genetics (1996) 33:809–813. [PubMed: 8933331]

[6]. Mastroiacovo P, Corchia C, Botto LD, Lanni R, Zampino G, Fusco D. Epidemiology and genetics of microtia-anotia: a registry based study on over one million births. Journal of Medical Genetics (1995) 32:453–457. [PubMed: 7666397]

[7]. Castilla EE, Orioli IM. Prevalence rates of microtia in South America. International Journal of Epidemiology (1986) 15:364–368. [PubMed: 3771073]

[8]. Stallings EB, Isenburg JL, Mai CT, Liberman RF, Moore CA, Canfield MA, Salemi JL, Kirby RS, Short TD, Nembhard WN, Forestieri NE, Heinke D, Alverson CJ, Romitte PA, Huynh M, Denson LE, Judson EM, Lupo PJ, Birth Defects Prevention Network. Population-based birth defects data in the United States, 2011–2015: A focus on eye and ear defects. Birth Defects Research (2018) 110:1478–1486. [PubMed: 30444307]

[9]. Ryan MA, Khoury T, Kaylie DM, Crowson MG, Brown CS, McClennen J, Raynor EM. Osseointegrated implants for auricular prostheses: An alternative to autologous repair. The Laryngoscope (2018) 128:2153–2156. [PubMed: 29481697]

[10]. Fiorillo CE, Rashidi V, Westgate PM, Jacobs JA, Bush ML, Studts CR. Assessment of Behavioral Problems in Children With Hearing Loss. Otology & Neurotology (2017) 38:1456–1462. [PubMed: 28953604]

[11]. Johns AL, Lewin SL, Im DD. Teasing in younger and older children with microtia before and after ear reconstruction. Journal of Plastic Surgery and Hand Surgery (2017) 51:205–209. [PubMed: 27609237]

[12]. Ishimoto S, Ito K, Karino S, Takegoshi H, Kaga K, Yamasoba T. Hearing levels in patients with microtia: correlation with temporal bone malformation. Laryngoscope (2007) 117:461–465. [PubMed: 17334306]

[13]. Suutarla S, Rautio J, Ritvanen A, Ala-Mello S, Jero J, Klockars T. Microtia in Finland: comparison of characteristics in different populations. International Journal of Pediatric Otorhinolaryngoly (2007) 71:1211–1217.

[14]. Lipan MJ, Eshraghi AA. Otologic and audiology aspects of microtia repair. Seminars in Plastic Surgery (2011) 25:273–278. [PubMed: 23115533]

[15]. Long X, Yu N, Huang J, Wang X. Complication rate of autologous cartilage microtia reconstruction: a systematic review. Plastic and Reconstructive Surgery (2013) 1:e57. [PubMed: 25289252]

[16]. Shaw GM, Carmichael SL, Kaidarova Z, Harris JA. Epidemiologic characteristics of anotia and microtia in California, 1989–1997. Birth Defects Research (2004) 70:472–475. [PubMed: 15259037]

[17]. Carey JCPA, Muntz HR. External Ear In: Stevenson RE (Ed.), Human malformations and Related Anomalies. Oxford University Press, New York, 2006, pp. 329–338.

[18]. Koenig JL, Amoils M, Grade MM, Chang KW, Truong MT. Renal ultrasound abnormalities in children with syndromic and non-syndromic microtia. International Journal of Pediatric Otorhinolaryngology (2018) 113:173–176. [PubMed: 30173979]

[19]. Klockars T, Suutarla S, Kentala E, Ala-Mello S, Rautio J. Inheritance of microtia in the Finnish population. International Journal of Pediatric Otorhinolaryngology (2007) 71:1783–1788. [PubMed: 17868909]

[20]. Canfield MA, Mai CT, Wang Y, O'Halloran A, Marengo LK, Olney RS, Borger CL, Rutkowski R, Fornoff J, Irwin N, Copeland G, Flood TJ, Meyer RE, Rickard R, Alverson CJ, Sweatlock J,

Kirby RS. The association between race/ethnicity and major birth defects in the United States, 1999–2007. American Journal of Public Health (2014) 104:e14–23.

[21]. Hoyt AT, Canfield MA, Shaw GM, Waller DK, Polen KN, Ramadhani T, Anderka MT, Scheuerle AE. Sociodemographic and hispanic acculturation factors and isolated anotia/microtia. Birth Defects Research (2014) 100:852–862. [PubMed: 25074828]

[22]. Correa A, Gilboa SM, Besser LM, Botto LD, Moore CA, Hobbs CA, Cleves MA, Riehle-Colarusso TJ, Waller DK, Reece EA. Diabetes mellitus and birth defects. American Journal of Obstetrics and Gynecology (2008) 199:237.e231–239. [PubMed: 18674752]

[23]. Ewart-Toland A, Yankowitz J, Winder A, Imagire R, Cox VA, Aylsworth AS, Golabi M. Oculoauriculovertebral abnormalities in children of diabetic mothers. American Journal of Medical Genetics (2000) 90:303–309. [PubMed: 10710228]

[24]. Van Bennekom CM, Mitchell AA, Moore CA, Werler MM. Vasoactive exposures during pregnancy and risk of microtia. Birth Defects Research (2013) 97:53–59. [PubMed: 23180593]

[25]. Zhang QG, Zhang J, Yu P, Shen H. Environmental and genetic factors associated with congenital microtia: a case-control study in Jiangsu, China, 2004 to 2007. Plastic and Reconstructive Surgery (2009) 124:1157–1164. [PubMed: 19935299]

[26]. Yang J, Carmichael SL, Kaidarova Z, Shaw GM. Risks of selected congenital malformations among offspring of mixed race-ethnicity. Birth Defects Research (2004) 70:820–824. [PubMed: 15390318]

[27]. Hoeltzenbein M, Elefant E, Vial T, Finkel-Pekarsky V, Stephens S, Clementi M, Allignol A, Weber-Schoendorfer C, Schaefer C. Teratogenicity of mycophenolate confirmed in a prospective study of the European Network of Teratology Information Services. American Journal of Medical Genetics (2012) 158a:588–596. [PubMed: 22319001]

[28]. Okajima H, Takeichi Y, Umeda K, Baba S. Clinical analysis of 592 patients with microtia. Acta Otolaryngoly (1996) 525:18–24.

[29]. Lynberg MC, Khoury MJ, Lammer EJ, Waller KO, Cordero JF, Erickson JD. Sensitivity, specificity, and positive predictive value of multiple malformations in isotretinoin embryopathy surveillance. Teratology (1990) 42:513–519. [PubMed: 2278026]

[30]. Ma C, Carmichael SL, Scheuerle AE, Canfield MA, Shaw GM. Association of microtia with maternal obesity and periconceptional folic acid use. American Journal of Medical Genetics (2010) 152a:2756–2761. [PubMed: 20949601]

[31]. Waller DK, Shaw GM, Rasmussen SA, Hobbs CA, Canfield MA, Siega-Riz AM, Gallaway MS, Correa A. Prepregnancy obesity as a risk factor for structural birth defects. Archives of Pediatrics & Adolescent Medicine (2007) 161:745–750. [PubMed: 17679655]

[32]. Ma C, Shaw GM, Scheuerle AE, Canfield MA, Carmichael SL. Association of microtia with maternal nutrition. Birth Defects Research (2012) 94:1026–1032. [PubMed: 22821770]

[33]. Reefhuis J, Gilboa SM, Anderka M, Browne ML, Feldkamp ML, Hobbs CA, Jenkins MM, Langlois PH, Newsome KB, Olshan AF, Romitti PA, Shapira SK, Shaw GM, Tinker SC, Honein MA. The National Birth Defects Prevention Study: A review of the methods. Birth Defects Research (2015) 103:656–669. [PubMed: 26033852]

[34]. Cogswell ME, Bitsko RH, Anderka M, Caton AR, Feldkamp ML, Hockett Sherlock SM, Meyer RE, Ramadhani T, Robbins JM, Shaw GM, Mathews TJ, Royle M, Reefhuis J. Control selection and participation in an ongoing, population-based, case-control study of birth defects: the National Birth Defects Prevention Study. American Journal of Epidemiology (2009) 170:975–985. [PubMed: 19736223]

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

[36]. Hernan MA, Hernandez-Diaz S, Werler MM, Mitchell AA. Causal knowledge as a prerequisite for confounding evaluation: an application to birth defects epidemiology. American Journal of Epidemiology (2002) 155:176–184. [PubMed: 11790682]

[37]. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. Epidemiology (1999) 10:37–48. [PubMed: 9888278]

[38]. Tinker SC, Hamner HC, Qi YP, Crider KS. US women of childbearing age who are at possible increased risk of a neural tube defect-affected pregnancy due to suboptimal red blood cell folate concentrations, National Health and Nutrition Examination Survey 2007 to 2012. Birth Defects Research (2015) 103:517–526. [PubMed: 25884850]

[39]. Ramadhani T, Short V, Canfield MA, Waller DK, Correa A, Royle M, Scheuerle A. Are birth defects among Hispanics related to maternal nativity or number of years lived in the United States? Birth Defects Research (2009) 85:755–763. [PubMed: 19350653]

[40]. Miquel-Verges F, Mosley BS, Block AS, Hobbs CA. A spectrum project: preterm birth and small-forgestational age among infants with birth defects. Journal of Perinatology (2015) 35:198–203. [PubMed: 25275696]

[41]. Browne ML, Hoyt AT, Feldkamp ML, Rasmussen SA, Marshall EG, Druschel CM, Romitti PA. Maternal caffeine intake and risk of selected birth defects in the National Birth Defects Prevention Study. Birth Defects Research (2011) 91:93–101. [PubMed: 21254365]

[42]. Zabihi S, Loeken MR. Understanding diabetic teratogenesis: where are we now and where are we going? Birth Defects Research (2010) 88:779–790. [PubMed: 20706996]

[43]. Oyama K, Sugimura Y, Murase T, Uchida A, Hayasaka S, Oiso Y, Murata Y. Folic acid prevents congenital malformations in the offspring of diabetic mice. Endocrine Journal (2009) 56:29–37. [PubMed: 18781038]

[44]. Wentzel P, Eriksson UJ. A diabetes-like environment increases malformation rate and diminishes prostaglandin E(2) in rat embryos: Reversal by administration of vitamin E and folic acid. Birth Defects Research (2005) 73:506–511. [PubMed: 15959876]

[45]. Flores AL, Cordero AM, Dunn M, Sniezek JE, Arce MA, Crider KS, Tinker S, Pellegrini C, Carreon R, Estrada J, Struwe S, Boyle C. Adding folic acid to corn Masa flour: Partnering to improve pregnancy outcomes and reduce health disparities. Preventive Medicine (2018) 106:26–30. [PubMed: 29128408]

[46]. Moore K The Developing Human, Clinically Oriented Embryology, 10th. Ed Saunders/Elsevier, New York, 2016.

[47]. US Preventative Services Task Force, Bibbins-Domingo K, Grossman DC, Curry SJ, Davidson KW, Epling JW Jr, García FA, Kemper AR, Krist AH, Kurth AE, Landefeld CS, Mangione CM, Phillips WR, Phipps MG, Pignone MP, Silverstein M, Tseng CW. Folic Acid Supplementation for the Prevention of Neural Tube Defects: US Preventive Services Task Force Recommendation Statement. Journal of the American Medical Association (2017) 317:183–189. [PubMed: 28097362]

Table 1.

Maternal, paternal, and pregnancy characteristics of infants with anotia or microtia (cases) compared to infants without a major birth defect (controls), National Birth Defects Prevention Study, 1997–2011

	Cases (n = 699) n (%)	Controls (n = 11,797) n (%)
Pregnancy characteristics		
Infant sex		
Male	400 (57.2)	6004 (50.9)
Female	299 (42.8)	5781 (49.0)
Missing	*0*	*12 (<1.0)*
Plurality		
Singleton	666 (95.3)	11434 (96.9)
Multifetal gestation	33 (4.7)	338 (2.9)
Missing	*0*	*25 (<1.0)*
Gestational age at delivery		
<32 weeks, very preterm	29 (4.1)	155 (1.3)
32–36 weeks, preterm	118 (16.9)	931 (7.9)
≥37 weeks, term	552 (79.0)	10709 (90.8)
Missing	*0*	*2 (<1.0)*
Maternal socio-demographic factors		
Study center (residence at delivery)		
Arkansas	47 (6.7)	1463 (12.4)
California	165 (23.6)	1261 (10.7)
Iowa	43 (6.2)	1297 (11.0)
Massachusetts	57 (8.2)	1393 (11.8)
New Jersey	53 (7.6)	575 (4.9)
New York	43 (6.2)	987 (8.4)
Texas	136 (19.5)	1414 (12.0)
Georgia	43 (6.2)	1266 (10.7)
North Carolina	37 (5.3)	1014 (8.6)
Utah	75 (10.7)	1127 (9.6)
Age at delivery		
<25 years	249 (35.6)	3845 (32.6)
25–34 years	348 (49.8)	6308 (53.5)
>35 years	102 (14.6)	1644 (13.9)
Race/ethnicity		
White, non-Hispanic	242 (34.6)	6807 (57.7)
Black, non-Hispanic	27 (3.9)	1307 (11.1)
Hispanic	376 (53.8)	2906 (24.6)
Other	54 (7.7)	770 (6.5)
Missing	*0*	*7 (<1.0)*
Birthplace		
US	406 (58.1)	9070 (76.9)

	Cases (n = 699) n (%)	Controls (n = 11,797) n (%)
non-US	279 (39.9)	2392 (20.3)
Missing	*14 (2.0)*	*335 (2.8)*
Education level		
<high school	200 (28.6)	1905 (16.1)
high school	170 (24.3)	2724 (23.1)
>high school	314 (44.9)	6823 57.8)
Missing	*15 (2.1)*	*345 (2.9)*
Household income		
≤$50,000	476 (68.1)	6763 (57.3)
>$50,000	156 (22.3)	3862 (32.7)
Missing	*67 (9.6)*	*1172 (9.9)*
Maternal clinical factors		
First-degree family history of anotia/microtia		
No	689 (98.6)	11790 (99.9)
Yes	10 (1.4)	7 (0.1)
Number of prior live births		
0	258 (36.9)	4641 (39.3)
1	228 (32.6)	3837 (32.5)
2	118 (16.9)	2026 (17.2)
≥3	95 (13.6)	1242 (10.5)
Missing	*0*	*51 (<1.0)*
Body mass index, kg/m^2		
<18.5, underweight	29 (4.1)	598 (5.1)
18.5–25, normal weight	307 (43.9)	6029 (51.1)
25–30, overweight	145 (20.7)	2546 (21.6)
>30, obese	138 (19.7)	2070 (17.5)
Missing	*80 (11.4)*	*554 (4.7)*
History of diabetes		
None	590 (84.4)	10809 (91.6)
Type I	19 (2.7)	34 (0.3)
Type II	15 (2.1)	49 (0.4)
Gestational	68 (9.7)	822 (7.0)
Missing	*7 (1.0)*	*83 (<1.0)*
History of asthma		
No	695 (99.4)	11710 (99.3)
Yes	4 (0.6)	87 (0.7)
Maternal health behaviors		
Folic acid supplementation		
No use	224 (32.0)	2687 (22.8)
Some use, but not daily	336 (48.1)	5587 (47.4)
Daily use	123 (17.6)	3225 (27.3)
Missing	*16 (2.3)*	*298 (2.5)*

	Cases (n = 699) n (%)	Controls (n = 11,797) n (%)
Alcohol use		
None	468 (67.0)	7196 (61.0)
Drinking, but not binge	136 (19.5)	2773 (23.5)
Binge drinking	80 (11.4)	1429 (12.1)
Missing	*15 (2.1)*	*399 (3.4)*
Cigarette use		
None	596 (85.3)	9713 (82.3)
1–4 cigarettes/day	28 (4.0)	560 (4.7)
≥5 cigarettes/day	64 (9.2)	1210 (10.3)
Missing	*11 (1.6)*	*314 (2.7)*
Substance abuse		
No	649 (92.8)	10859 (92.0)
Yes	37 (5.3)	634 (5.4)
Missing	*13 (1.9)*	*304 (2.6)*
Daily caffeine intake		
<10 mg	123 (17.6)	2077 (17.6)
10–99 mg	233 (33.3)	4099 (34.7)
100–199 mg	170 (24.3)	2630 (22.3)
200–299 mg	86 (12.3)	1447 (12.3)
>300 mg	70 (10.0)	1218 (10.3)
Missing	*17 (2.4)*	*326 (2.8)*
Paternal factors		
Age at delivery		
<25 years	163 (23.3)	2477 (21.0)
25–34 years	353 (50.5)	6067 (51.4)
>35 years	157 (22.5)	2868 (24.3)
Missing	*26 (3.7)*	*385 (3.3)*
Race/ethnicity		
White, non-Hispanic	233 (33.3)	6498 (55.1)
Black, non-Hispanic	34 (4.9)	1402 (11.9)
Hispanic	364 (52.1)	2738 (23.2)
Other	47 (6.7)	684 (5.8)
Missing	*21 (3.0)*	*475 (4.0)*
Birthplace		
US	384 (54.9)	8823 (74.8)
non-US	296 (42.3)	2538 (21.5)
Missing	*19 (2.7)*	*436 (3.7)*
Education level		
<high school	205 (29.3)	1813 (15.4)
high school	204 (29.2)	3307 (28.0)
>high school	252 (36.1)	6001 (50.9)
Missing	*38 (5.4)*	*676 (5.7)*

	Cases (n = 699) n (%)	**Controls (n = 11,797) n (%)**
Substance abuse		
No	607 (86.8)	10210 (86.5)
Yes	72 (10.3)	1192 (10.1)
Missing	*20 (2.9)*	*395 (3.3)*

US: United States

Table 2.

Estimated associations between pregnancy characteristics and anotia/microtia, National Birth Defects Prevention Study, 1997–2011

	All cases (n=699)	Isolated anotia/microtia (n=480)	Non-isolated anotia/microtia (n=219)
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Infant sex			
Female	1	1	1
Male	1.29 (1.10, 1.50)	1.36 (1.13, 1.64)	1.15 (0.88, 1.50)
Plurality			
Singleton	1	1	1
Multifetal gestation	1.68 (1.16, 2.42)	1.24 (0.76, 2.04)	2.67 (1.58, 4.49)
Gestational age at delivery			
<32 weeks, very preterm	3.63 (2.42, 5.45)	1.49 (0.76, 2.94)	10.24 (6.24, 16.80)
32–36 weeks, preterm	2.46 (1.99, 3.03)	1.49 (1.11, 1.99)	5.45 (4.02, 7.40)
≥37 weeks, term	1	1	1

CI: confidence interval, OR: odds ratio

Table 3.

Estimated associations between anotia/microtia and selected maternal socio-demographic, clinical, and health behavioral factors, National Birth Defects Prevention Study, 1997–2011

	All cases - unadjusted model (n=699)	All cases - adjusted model	Isolated cases - adjusted (n=480)	Non-isolated cases - adjusted (n=219)
	OR (95% CI)	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)
Socio-demographic factors				
Age at deliver[a]				
<25 years	1.17 (0.99, 1.39)	0.93 (0.78, 1.12)	0.97 (0.78, 1.20)	0.84 (0.61, 1.16)
25–34 years	1	1	1	1
>35 years	1.12 (0.90, 1.41)	1.20 (0.96, 1.51)	1.18 (0.90, 1.56)	1.26 (0.85, 1.86)
Race/ethnicity[b]				
White, non-Hispanic	1	1	1	1
Black, non-Hispanic	0.58 (0.39, 0.87)	0.57 (0.38, 0.85)	0.37 (0.20, 0.69)	0.91 (0.53, 1.58)
Hispanic	3.64 (3.08, 4.30)	3.19 (2.61, 3.91)	3.49 (2.73, 4.46)	2.64 (1.87, 3.73)
Other	1.97 (1.46, 2.67)	1.79 (1.30, 2.46)	1.94 (1.33, 2.83)	1.52 (0.86, 2.69)
Birthplace[c]				
US	1	1	1	1
non-US	2.61 (2.22, 3.05)	1.29 (1.06, 1.57)	1.43 (1.14, 1.80)	1.00 (0.71, 1.42)
Education level[c]				
<high school	1.68 (1.36, 2.08)	1.14 (0.91, 1.42)	1.10 (0.85, 1.43)	1.24 (0.84, 1.82)
high school	1	1	1	1
>high school	0.74 (0.61, 0.89)	0.95 (0.77, 1.16)	1.00 (0.78, 1.27)	0.86 (0.61, 1.21)
Clinical factors				
Number of prior live births				
0	1	1	1	1
1	1.07 (0.89, 1.28)	NC[d]	0.99 (0.79, 1.23)[d]	1.31 (0.95, 1.80)[d]
2	1.05 (0.84, 1.31)	NC[d]	1.04 (0.80, 1.35)[d]	0.92 (0.60, 1.40)[d]
≥3	1.38 (1.08, 1.76)	NC[d]	1.09 (0.80, 1.47)[d]	1.40 (0.91, 2.15)[d]
Body mass index, kg/m^2				
<18.5, underweight	0.95 (0.64, 1.41)	NC[d]	0.96 (0.60, 1.53)[d]	0.94 (0.47, 1.86)[d]
18.5–25, normal weight	1	1	1	1
25–30, overweight	1.12 (0.91, 1.37)	NC[d]	0.96 (0.60, 1.53)[d]	0.88 (0.60, 1.29)[d]
>30, obese	1.31 (1.06, 1.61)	NC[d]	1.15 (0.89, 1.49)[d]	1.65 (1.18, 2.31)[d]
History of diabetes[c]				
None	1	1	1	1
Type I	10.24 (5.80, 18.06)	9.89 (5.46, 17.92)	4.93 (1.99, 12.18)	23.48 (12.03, 45.83)
Type II	5.61 (3.13, 10.06)	4.70 (2.56, 8.63)	1.31 (0.40, 4.28)	13.91 (7.17, 26.96)
Gestational	1.52 (1.17, 1.97)	1.26 (0.97, 1.64)	1.14 (0.83, 1.57)	1.62 (1.04, 2.52)

	All cases - unadjusted model (n=699)	All cases - adjusted model	Isolated cases - adjusted (n=480)	Non-isolated cases - adjusted (n=219)
	OR (95% CI)	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)
History of asthma[c]				
No	1	1	1	1
Yes	0.77 (0.28, 2.12)	0.96 (0.35, 2.65)	0.73 (0.18, 2.99)	1.45 (0.35, 5.94)
Health behaviors				
Folic acid supplementation				
No use	1	1	1	1
Some use, but not daily	0.72 (0.61, 0.86)	0.81 (0.67, 0.97)	0.73 (0.59, 0.90)	1.04 (0.75, 1.45)
Daily use	0.46 (0.37, 0.57)	0.59 (0.46, 0.76)	0.52 (0.39, 0.70)	0.80 (0.52, 1.24)
Alcohol use[c]				
None	1	1	1	1
Drinking, but not binge	0.75 (0.62, 0.92)	0.97 (0.79, 1.18)	1.01 (0.79, 1.28)	0.87 (0.61, 1.24)
Binge drinking	0.86 (0.67, 1.10)	1.06 (0.83, 1.36)	1.03 (0.76, 1.39)	1.13 (0.75, 1.71)
Cigarette use[c]				
None	1	1	1	1
1–4 cigarettes/day	0.81 (0.55, 1.20)	0.93 (0.63, 1.37)	0.91 (0.57, 1.46)	0.96 (0.49, 1.90)
≥5 cigarettes/day	0.86 (0.66, 1.12)	1.29 (0.98, 1.70)	1.07 (0.75, 1.54)	1.70 (1.12, 2.59)
Substance abuse[a]				
No	1	1	1	1
Yes	0.98 (0.69, 1.37)	NC[d]	0.84 (0.54, 1.29)[d]	1.29 (0.76, 2.20)[d]
Daily caffeine intake[c]				
<10 mg	1	1	1	1
10–99 mg	0.96 (0.77, 1.20)	0.92 (0.73, 1.15)	0.95 (0.72, 1.25)	1.09 (0.74, 1.59)
100–199 mg	1.09 (0.86, 1.39)	1.01 (0.79, 1.29)	1.09 (0.81, 1.45)	0.86 (0.56, 1.32)
200–299 mg	1.00 (0.76, 1.33)	1.07 (0.81, 1.43)	1.08 (0.76, 1.53)	1.08 (0.67, 1.75)
>300 mg	0.97 (0.72, 1.31)	1.14 (0.84, 1.56)	1.09 (0.74, 1.59)	1.24 (0.75, 2.05)

aOR: adjusted odds ratio, CI: confidence interval, NC: not calculated, OR: odds ratio, US: United States

[a]Multivariable models were adjusted for maternal education.

[b]Multivariable models were adjusted for maternal birthplace.

[c]Multivariable models were adjusted for maternal race/ethnicity.

[d]Adjusted estimates not calculated because no confounder(s) were identified for model inclusion.

Table 4.

Estimated associations between paternal characteristics and anotia/microtia in offspring, National Birth Defects Prevention Study, 1997–2011

	All cases - unadjusted model (n=699)	All cases - adjusted model	Isolated cases - adjusted (n=480)	Non-isolated cases - adjusted (n=219)
	OR (95% CI)	aOR (95% CI)	aOR (95% CI)	aOR (95% CI)
Age at delivery[a]				
<25 years	1.13 (0.93, 1.37)	0.86 (0.67, 1.10)	0.81 (0.61, 1.09)	0.98 (0.63, 1.51)
25–34 years	1	1	1	1
>35 years	0.94 (0.78, 1.14)	0.89 (0.71, 1.12)	0.83 (0.63, 1.10)	1.04 (0.71, 1.54)
Race/ethnicity[b]				
White, non-Hispanic	1	1	1	1
Black, non-Hispanic	0.68 (0.47, 0.97)	0.98 (0.56, 1.72)	0.71 (0.33, 1.52)	1.59 (0.69, 3.68)
Hispanic	3.71 (3.13, 4.40)	2.11 (1.54, 2.88)	1.81 (1.25, 2.63)	2.89 (1.70, 4.91)
Other	1.92 (1.39, 2.65)	1.45 (0.98, 2.14)	1.36 (0.85, 2.18)	1.62 (0.82, 3.19)
Birthplace[c]				
US	1	1	1	1
non-US	2.68 (2.29, 3.14)	1.92 (1.53, 2.41)	2.06 (1.57, 2.69)	1.66 (1.11, 2.47)
Education level[d]				
<high school	1.83 (1.50, 2.24)	1.18 (0.95, 1.45)	1.31 (1.02, 1.69)	0.91 (0.63, 1.33)
high school	1	1	1	1
>high school	0.68 (0.56, 0.82)	0.87 (0.71, 1.06)	0.93 (0.73, 1.19)	0.77 (0.55, 1.07)
Substance abuse				
No	1	1	1	1
Yes	1.02 (0.79, 1.31)	NC[e]	0.91 (0.66, 1.24)[e]	1.26 (0.84, 1.90)[e]

aOR: adjusted odds ratio, CI: confidence interval, NC: not calculated, OR: odds ratio, US: United States

[a]Multivariable models were adjusted for maternal age and paternal education.

[b]Multivariable models were adjusted for maternal race/ethnicity.

[c]Multivariable models were adjusted for maternal birthplace.

[d]Multivariable models were adjusted for paternal race/ethnicity.

[e]Adjusted estimates not calculated because no confounder(s) were identified for model inclusion.