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Evaluating Differences in Nonsyndromic Orofacial Clefts by Infant Sex: National Birth Defects Prevention Study, 1997-2011

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Abstract

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Declaration of Competing Interest

The authors report no conflicts of interest.

Objective: To investigate nongenetic factors that may contribute to observed differences in nonsyndromic orofacial clefts by infant sex.

Study design: Using data for 1997-2011 deliveries from the National Birth Defects Prevention Study, a case-control study, we separately examined associations between 23 maternal factors and cleft lip with or without cleft palate (CL/P) and cleft palate alone (CP) using multivariable logistic regression stratified by infant sex.

Results: We compared 2986 infants with CL/P and 1557 with CP to 11 271 control infants without birth defects. After adjusting for maternal age at conception and education, lower odds of nonsyndromic orofacial clefts were observed among male infants of non-Hispanic Black mothers (CL/P adjusted odds ratio [aOR]: 0.36; 95% confidence interval [CI]: 0.28-0.45; CP aOR: 0.56; 95% CI: 0.41-0.76) and of Hispanic mothers (CL/P aOR: 0.84; 95% CI: 0.73-0.96; CP aOR: 0.57; 95% CI: 0.45-0.72) compared with non-Hispanic White mothers. Similar, though attenuated, lower odds of nonsyndromic orofacial clefts were observed among female infants of non-Hispanic Black mothers, but no association was observed among female infants of Hispanic mothers. Differences in associations between maternal education and nutrient intake (carbohydrate, energy, total lipids/fat, vitamin E, and zinc) and CL/P, as well as maternal vitamin C intake and CP, were also observed by infant sex.

Conclusions: Associations between nonsyndromic orofacial clefts and minority racial and ethnic groups were attenuated or nonexistent among female infants compared with male infants. Sex-specific differences of CL/P appear more susceptible to environmental factors (eg, maternal education and nutrient intake) than sex-specific differences of CP.

Orofacial clefts are a major congenital structural anomaly, comprising cleft lip with or without cleft palate (CL/P) and cleft palate alone (CP), and are relatively common birth defects that occur due to a syndromic cause (eg, genetic or chromosomal) or, more often, in the absence of a known etiology. Infants born with orofacial clefts have higher rates of mortality within the first year of life, compared with those without orofacial clefts,¹ and often encounter significant morbidity – hearing, dental, speech, and mental health complications – that impact the psychosocial and socioeconomic wellbeing of affected children and caregivers.^{2–6} Among racial and ethnic groups in the United States, the birth prevalence of CL/P and CP among offspring is lowest for non-Hispanic Black mothers (CL/P: ~1 in 1500 births; CP: ~1 in 2500 births) and higher for non-Hispanic White mothers (CL/P: ~1 in 900 births; CP: ~1 in 1500 births).⁷ Nonsyndromic orofacial cleft etiology likely involves a complex interaction of genetic and environmental factors, including maternal smoking and diabetes.^{8–12}

Sex ratio differences of nonsyndromic orofacial cleft phenotypes have been recognized for decades – while a preponderance of males is observed among infants with CL/P, an excess of females is observed among infants with CP.^{13–16} Most research to date has focused on simply describing these differences overall rather than more specifically investigating what factors may underlie them. It has been hypothesized that sex-specific differences in fetal survival may play a role,¹⁷ though this mechanism has been challenging to evaluate. As a next step to understanding sex-specific differences in nonsyndromic orofacial cleft

occurrence, better characterizing similarities and differences between male and female infants with clefts may shed further light on the potential sex-specific mechanisms involved.

Thus, this study aimed to investigate nongenetic factors that may contribute to observed differences in nonsyndromic orofacial clefts by infant sex. Study objectives were to (1) better understand known sex-specific differences in nonsyndromic orofacial cleft occurrence by characterizing sex-specific associations between maternal characteristics and nonsyndromic orofacial clefts and (2) shed light on how fetal survival may play a role by determining if exclusion of fetal deaths impacts sex-specific associations.

Methods

National Birth Defects Prevention Study

This study evaluated data from the National Birth Defects Prevention Study (NBDPS), a large, population-based, multicenter case-control study on potential causes of major structural birth defects in the United States that included data for pregnancies ending on or after October 1, 1997 to those with an expected date of delivery ending on or before December 31, 2011. Ten states with population-based surveillance systems and legislative authority for active case-finding of all major structural birth defects participated in the NBDPS: Arkansas (AR), California (CA), Georgia (GA), Iowa (IA), Massachusetts (MA), North Carolina (NC), New Jersey (NJ), New York (NY), Texas (TX), and Utah (UT).¹⁸ Information on the NBDPS is available on the study website (www.nbdps.org) and study methods have been described.¹⁸

NBDPS cases were identified using standard criteria from each participating birth defect surveillance system, and controls were randomly selected among live born infants from the same study region as cases, using vital records (AR [2001-2011], GA [2001-2011], IA, MA, NC, NJ, UT) and hospital records (AR [1997-2000], CA, GA [1998-2000], NY, TX) from 1997 to 2011.¹⁸ Case notes from abstracted medical records of potential case infants were systematically reviewed and classified by clinical geneticists to establish eligibility prior to inclusion in the NBDPS.¹⁸ Potential cases with a chromosomal or single gene condition, or who were stillborn infants ≤ 20 weeks gestational age or < 500 g, were excluded from participating in the NBDPS, and we further excluded cases without CL/P or CP, of multiple gestation pregnancies, with missing birth outcome, or with unknown or ambiguous infant sex.¹⁸ Thus, eligible cases included infants with CL/P or CP who were live born (AR, CA, GA, IA, MA, NJ, NY, NC, TX, UT), stillborn after 20 weeks gestational age or ≥ 500 g (AR, CA, GA, IA, MA, NY, NC, TX, UT), or electively terminated at any gestational age or weight (AR, CA, GA, IA, NY, NC, TX, UT).¹⁸ Potential control infants were not eligible for inclusion in the NBDPS if they had a major structural birth defect, were adopted or in foster care, or were stillborn.¹⁸ Potential cases and controls were additionally not eligible for inclusion in the NBDPS if a mother did not speak English or Spanish, previously participated in the NBDPS, was incarcerated or deceased, or resided outside the geographic area covered by a participating birth defect surveillance system at the time of delivery.¹⁸

Measures

Two binary (yes, no) outcomes were examined in this study: CL/P and CP. Maternal demographic factors of interest obtained during study interviews included: race and ethnicity (Hispanic, non-Hispanic Black, non-Hispanic White, Other); age at conception (<20 years, 20-24 years, 25-29 years, 30-34 years, > 35 years); education (< high school, high school graduate, > high school); and household income (<\$20K, \$20-\$50K, >\$50K). Maternal health factors of interest included: smoking status from 3 months before pregnancy to the end of pregnancy (yes, no); prepregnancy diabetes (yes, no); history of seizures (yes, no); maternal alcohol consumption from 3 months before pregnancy to the end of pregnancy (yes, no); substance (marijuana, cocaine, or other) abuse from 3 months before pregnancy to the end of pregnancy (yes, no); prepregnancy body mass index (underweight: <19.8; normal: 19.8-26.0; overweight: 26.1-29.0; obese: >29.0); pre-existing hypertension (yes, no); pregnancy intention (wanted to get pregnant, wanted to wait until later, didn't care, didn't want to become pregnant at all); previous miscarriage (yes, no); maternal or paternal fertility procedures (yes, no); first degree relative with clefts (yes, no); and folic acid supplementation from 3 months before pregnancy to the end of pregnancy (yes, no). In addition, the following maternal nutrient intake factors were examined as quartile values (first, second, third, or fourth quartile): carbohydrate (g); energy (KJ); total lipids/fat (g); folate (mg); protein (g); vitamin E (mg); vitamin C (mg); and zinc (mg). Nutrient intake information was estimated from a survey of dietary intake the year before pregnancy.¹⁸ Quartile threshold values were calculated using control data and applied to case data.

Statistical Analysis

Frequencies and proportions of the maternal demographic factors and maternal health factors were calculated, stratified by infant sex. Unadjusted logistic regression analyses were conducted between each outcome of interest (CL/P, CP) and 23 maternal factors described above. These comparisons were repeated in multivariable logistic regression analyses, adjusting for three maternal demographic factors (race and ethnicity; age at conception; education) selected *a priori* based on previously reported associations with birth outcomes.^{7,19,20} Unadjusted and adjusted odds ratios (ORs, aORs), 95% confidence limits, and global (type 3) *P* values were obtained from infant sex-stratified models (male, female). Joint effect (factor*sex interaction) *P* values were obtained from nonstratified models to examine potential combined effects of infant sex and each maternal factor on CL/P or CP occurrence. To shed light on the possibility that known differences in nonsyndromic orofacial cleft occurrence may reflect differences in fetal survival by infant sex, regression analyses were repeated after restricting to live births. Using SAS 9.4, we performed an available case analysis in which participants with missing values for any included variables were excluded automatically from the regression models.

Results

A total of 2986 study infants had CL/P (n = 1960 male; n = 1026 female), 1557 had CP (n = 673 male; n = 884 female), and 11 271 were controls without birth defects (n = 5756 male; n = 5515 female). This information and other sample characteristics are presented in Online Table A; available at www.jpeds.com.

CL/P

Results from unadjusted (Online Table B; available at www.jpeds.com) and adjusted (Table I) logistic regression models were similar. The joint effect terms between infant sex and two maternal demographic factors, race and ethnicity and education, were significantly associated with CL/P (P value < .05) (Table I). Lower odds of CL/P were observed among male infants born to non-Hispanic Black mothers (aOR: 0.36; 95% confidence interval [CI]: 0.28-0.45) and to Hispanic mothers (aOR: 0.84; 95% CI: 0.73-0.96), compared with male infants born to non-Hispanic White mothers. Lower odds of CL/P were also observed among female infants born to non-Hispanic Black mothers (aOR: 0.70; 95% CI: 0.54-0.90), though the magnitude of this effect estimate was less than that among male infants (aOR: 0.70 vs 0.36, respectively). Further, Hispanic maternal race and ethnicity was not associated with CL/P among female infants. Among both male and female infants, higher odds of CL/P were observed among mothers with a high school education and mothers with less than a high school education compared with mothers with more than a high school education; however, the magnitude of these effect estimates was slightly larger among female infants than among male infants (eg, aOR: 1.72 vs 1.38, respectively, for less than high school education).

Significant joint effect terms between infant sex and maternal nutrient intake variables were observed for: carbohydrate, energy, total lipids/fat, vitamin E, and zinc (Table I). For example, higher odds of CL/P were observed among male infants born to mothers with moderately high maternal carbohydrate intake in the third vs second quartile (referent category) (aOR: 1.21; 95% CI: 1.05-1.41), but lower odds of CL/P (and of borderline significance) were observed among female infants (aOR: 0.83; 95% CI: 0.68-1.02).

CP

Unadjusted (Online Table C; available at www.jpeds.com) and adjusted (Table II) logistic regression results were generally similar. A significant joint effect term between infant sex and maternal race and ethnicity was associated with CP (Table II). Lower odds of CP were observed among male infants born to non-Hispanic Black mothers (aOR: 0.56; 95% CI: 0.41-0.76) and to Hispanic mothers (aOR: 0.57; 95% CI: 0.45-0.72), compared with male infants born to non-Hispanic White mothers. Lower odds were also observed among female infants of non-Hispanic Black mothers (aOR: 0.64; 95% CI: 0.48-0.84), but an association between CP and female infants born to Hispanic mothers was not observed.

A significant joint effect term between infant sex and maternal vitamin C intake was associated with CP (Table II). Lower odds of CP were observed among male infants born to mothers in the first (aOR: 0.77; 95% CI: 0.61-0.95), third (aOR: 0.75; 95% CI: 0.60-0.93), and fourth (aOR: 0.76; 95% CI: 0.60-0.96) quartiles of maternal vitamin C intake values compared with mothers in the second quartile (referent category); however, maternal vitamin C intake was not associated with CP among female infants.

Sensitivity Analysis

Results from the regression analyses restricted to live births yielded similar results as the primary analysis (which included live births and eligible fetal deaths) [data not shown].

Discussion

In this study, we sought to better characterize similarities and differences between male and female infants with nonsyndromic orofacial clefts to shed further light on the potential sex-specific mechanisms involved in the development of nonsyndromic orofacial clefts.

Lower odds of nonsyndromic orofacial clefts (CL/P and CP) were observed among male infants born to nonHispanic Black and Hispanic mothers compared with male infants born to non-Hispanic White mothers. Lower odds of nonsyndromic orofacial clefts (CL/P and CP) were also observed among female infants born to non-Hispanic Black mothers, though the strength of this association was weaker than that among male infants. These findings seem consistent with results from a previous analysis of NBDPS data examining sex ratios of birth defects (1997-2009), which reported differences in nonsyndromic orofacial cleft sex ratios by maternal race and ethnicity for infants with CL/P and CP, with the highest male to female sex ratios observed among offspring of non-Hispanic White women for both CL/P (2.05) and CP (0.81), though the prior study did not conduct association analyses.¹⁶

Interestingly, observed associations with maternal race and ethnicity seem to be inversely related to many other historical socioeconomic health disparities (eg, preterm birth) across racial/ethnic groups (ie, nonsyndromic orofacial clefts occur more frequently among offspring of non-Hispanic White women). Population specific genetic risk factors for nonsyndromic orofacial clefts have been reported among individuals with different ancestries.²¹ Though genetic risk factors for nonsyndromic orofacial clefts may vary by ancestral groups,²² the observed statistical interaction between maternal race and ethnicity and infant sex may represent other differences that were unaccounted for (eg, health behaviors, etc.). Observed associations with maternal race and ethnicity may also reflect some degree of under-ascertainment of nonsyndromic orofacial clefts among the participating state registries. Further, although we used a population-based sample, approximately one-third of eligible mothers did not participate in the NBDPS, and it is unknown if risk profiles of nonparticipants differed from that of participants.¹⁸ Although increased nonsyndromic orofacial cleft occurrence has also been reported among other maternal racial/ethnic groups (American Indian and Asian), there were insufficient numbers to conduct sex-stratified analyses among these NBDPS groups.

For CP only, both low and high levels of maternal vitamin C intake were inversely associated among male but not female infants, suggestive of an inverted U-shaped pattern. Vitamin C has not been well studied in relation to birth defects and intake below or higher than the recommended daily allowance is not known to increase risk for birth defects. However, some studies have observed inverse associations with higher maternal vitamin C intake for select birth defects.^{23,24} For CL/P, differences in effect estimate directions were observed among male vs female infants for associations with select maternal nutrient intake values. For example, higher odds of CL/P were observed with moderately high maternal carbohydrate intake among males (aOR: 1.21; 95% CI: 1.05-1.41), but the opposite was observed among females (aOR: 0.83; 95% CI: 0.68-1.02). Although the latter association was of borderline significance and the magnitudes of both associations were fairly weak, interaction between infant sex and carbohydrate intake was further supported by a significant

association between a sex-carbohydrate intake joint effect term and CL/P, suggestive of a combined effect of infant sex and maternal carbohydrate intake on CL/P occurrence. To our knowledge, our study is the first to report significant joint effect terms for nonsyndromic orofacial clefts between infant sex and any type of maternal nutrient intake.

Observed male-female differences in associations with CL/P and/or CP may be consistent with the notion that nonsyndromic orofacial cleft development involves a complex landscape of factors, and that some degree of differences in the various causal mechanisms involved might reflect sex-specific mechanisms. For instance, sex-specific differences in occurrence may partially reflect differences in risk for defect development between male and female embryos, including the impact of genetic factors and/or other nongenetic teratogenic exposures. In addition, sex-selective embryonic or fetal death may contribute to observed male-female difference in orofacial cleft occurrence.¹⁷ However, it remains unclear to what extent infant sex may relate directly to nonsyndromic orofacial cleft development as opposed to reflecting sex-specific differences in fetal survival-to-term. The low proportion of fetal deaths among case infants (8.3%) inhibited our ability to determine if sex-specific associations differed by live birth status, and there were insufficient numbers to specifically evaluate the nonlive born group. However, similar results were observed between the primary analysis (cases with live births or fetal deaths; controls with live births only) and the sensitivity analysis (cases and controls with live births only). Further research is needed to disentangle the complex interactions of genetic and environmental factors that may influence fetal risk of nonsyndromic orofacial cleft development by infant sex. It is also unclear if associated factors modify the effect of infant sex on nonsyndromic orofacial cleft development, if infant sex modifies the effect of associated factors on nonsyndromic orofacial cleft development, or both.

Several potential limitations are present in our study. The NBDPS does not include data allowing for assessment of differences in early fetal loss (<20 weeks), though nonsyndromic orofacial clefts are generally thought to have lower stillbirth and termination rates compared with many other birth defects.^{25,26} Although each case was reviewed by clinical geneticists and considered nonsyndromic, it is possible that not all cases had comprehensive genetic testing (ie, exome/genome sequencing) to identify monogenic causes of orofacial clefts. When examining maternal nutrient intake, the analysis was not stratified by maternal body mass index (due to insufficient numbers), which could account for variations in dietary intake. Although several associations differed between male and female infants with CL/P or CP in our study, results should also be interpreted in light of multiple comparisons (eg, 23 factors evaluated $\times$ 2 phenotypes = 46 main comparisons), particularly for results that were inconsistent across cleft types; these “hypothesis-generating” results (eg, nutrient intake associations) should be confirmed in future studies.

Despite these limitations, this study has several strengths. The relatively large sample of NBDPS infants allowed for sex-specific analyses. Misclassification bias was reduced by high-quality phenotype data, a focus on nonsyndromic cases, and the systematic review and classification of birth defect cases by clinical geneticists. Control mothers who participated in the NBDPS are representative of their state populations regarding maternal age, smoking, and diabetes, with minor differences in maternal race and ethnicity and education level.¹⁸

In conclusion, observed male-female differences in associations with nonsyndromic orofacial clefts suggest a complex landscape of factors related to differing etiologies by infant sex. For instance, associations between nonsyndromic orofacial clefts (CL/P and CP) and minority racial/ethnic groups were attenuated or nonexistent among female infants compared with male infants. Sex-specific differences of CL/P appear more susceptible to environmental factors (eg, maternal education and nutrient intake) than sex-specific differences of CP. Further research examining differences in nonsyndromic orofacial cleft occurrence by infant sex is necessary to confirm observed associations and to identify more specific mechanisms.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Disclaimers

The findings and conclusions in this publication are those of the author(s) and do not necessarily represent the views of the North Carolina Department of Health and Human Services, Division of Public Health, and do not necessarily represent the official position of the California Department of Public Health. n

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Data Statement

Data sharing statement available at www.jpeds.com.

Glossary

aOR	Adjusted odds ratio
CI	Confidence interval
CL/P	Cleft lip with or without cleft palate
CP	Cleft palate alone
NBDPS	National Birth Defects Prevention Study

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Table 1.

Adjusted Odds Ratios with 95% Confidence Intervals and Joint Effect *P* Values for Nongenetic Factors and Cleft Lip with or without Cleft Palate by Infant Sex, National Birth Defects Prevention Study (1997-2011)

Nongenetic factor	Male			Female			Joint effect (factor*sex) <i>P</i> value
	aOR*	95% CI	Global type 3 <i>P</i> value ^c	aOR*	95% CI	Global type 3 <i>P</i> value ^c	
Maternal race and ethnicity			<.0001			0.04	0.0002 ^d
Hispanic	0.84	(0.73, 0.96)		1.00	(0.84, 1.19)		
Non-Hispanic Black	0.36	(0.28, 0.45)		0.70	(0.54, 0.90)		
Other	0.94	(0.76, 1.17)		1.06	(0.81, 1.39)		
Non-Hispanic White (ref)	(ref)	(ref)		(ref)	(ref)		
Maternal age at conception			0.09			0.59	0.55
<20 years	0.98	(0.81, 1.18)		0.97	(0.77, 1.22)		
20-24 years	1.14	(0.98, 1.31)		0.97	(0.80, 1.17)		
25-29 years (ref)	(ref)	(ref)		(ref)	(ref)		
30-34 years	0.91	(0.79, 1.06)		0.87	(0.72, 1.06)		
35+ years	1.03	(0.85, 1.24)		1.06	(0.83, 1.34)		
Maternal education			<.0001			<.0001	0.03 ^d
<High school	1.38	(1.17, 1.63)		1.72	(1.40, 2.12)		
High school graduate	1.31	(1.14, 1.50)		1.41	(1.19, 1.68)		
>High school (ref)	(ref)	(ref)		(ref)	(ref)		
Maternal smoking [‡] (Y vs N)	1.19	(1.05, 1.36)	0.01	1.41	(1.19, 1.67)	<.0001	0.29
Maternal alcohol consumption [‡] (Y vs N)	1.07	(0.96, 1.20)	0.20	0.99	(0.86, 1.14)	0.87	0.08
Maternal diabetes (Y vs N)	1.23	(1.02, 1.48)	0.03	1.48	(1.19, 1.86)	0.0006	0.13
Maternal history of seizures (Y vs N)	1.09	(0.79, 1.49)	0.61	1.40	(0.98, 2.00)	0.07	0.34
Maternal substance abuse [‡] (Y vs N)	1.03	(0.82, 1.29)	0.82	1.08	(0.80, 1.44)	0.62	0.72
Prepregnancy BMI			0.38			0.02	0.05
Underweight (<19.8)	0.99	(0.79, 1.24)		1.49	(1.13, 1.95)		
Normal (19.8-26.0)	(ref)	(ref)		(ref)	(ref)		
Overweight (26.1-29.0)	0.96	(0.84, 1.10)		1.15	(0.97, 1.37)		
Obese (>29.0)	1.11	(0.96, 1.29)		1.15	(0.95, 1.39)		

Nongenetic factor	Male			Female			Joint effect (factor*sex) P value
	aOR*	95% CI	Global type 3 P value*	aOR*	95% CI	Global type 3 P value*	
Pre-existing maternal hypertension [§] (Y vs N)	1.16	(0.91, 1.49)	0.23	1.46	(1.07, 1.97)	0.02	0.22
Pregnancy intention [§]			0.03			0.04	0.62
Wanted to get pregnant then (ref)	(ref)	(ref)		(ref)	(ref)		
Wanted to wait until later	1.06	(0.91, 1.25)		1.00	(0.82, 1.23)		
Didn't care	1.06	(0.86, 1.30)		1.17	(0.89, 1.52)		
Didn't want to become pregnant at all	1.33	(1.11, 1.59)		1.36	(1.08, 1.70)		
Previous miscarriage (Y vs N)	1.13	(1.00, 1.28)	0.05	1.25	(1.06, 1.46)	0.01	0.39
Mother/father had fertility procedure(s) (Y vs N)	1.22	(0.80, 1.86)	0.36	1.76	(1.04, 2.97)	0.03	0.43
First degree relative(s) with clefts (Y vs N)	14.36	(9.19, 22.43)	<.0001	27.54	(14.66, 51.70)	<.0001	0.13
Folic acid supplementation (any type) [‡] (Y vs N)	0.92	(0.73, 1.16)	0.48	0.80	(0.60, 1.05)	0.11	0.23
Carbohydrate intake (g)			0.01			0.04	0.0016 [‡]
1st quartile	1.22	(1.05, 1.42)		1.06	(0.88, 1.29)		
2nd quartile (ref)	(ref)	(ref)		(ref)	(ref)		
3rd quartile	1.21	(1.05, 1.41)		0.83	(0.68, 1.02)		
4th quartile	1.05	(0.90, 1.23)		1.07	(0.88, 1.30)		
Energy intake (KJ)			0.41			0.0003	0.0002 [‡]
1st quartile	1.04	(0.90, 1.21)		1.31	(1.08, 1.59)		
2nd quartile (ref)	(ref)	(ref)		(ref)	(ref)		
3rd quartile	1.07	(0.92, 1.24)		0.90	(0.73, 1.10)		
4th quartile	0.94	(0.81, 1.10)		1.23	(1.01, 1.50)		
Total lipids/fat intake (g)			0.88			<.0001	0.0021 [‡]
1st quartile	1.06	(0.91, 1.23)		1.25	(1.04, 1.51)		
2nd quartile (ref)	(ref)	(ref)		(ref)	(ref)		
3rd quartile	1.01	(0.87, 1.17)		0.80	(0.65, 0.99)		
4th quartile	1.02	(0.88, 1.90)		1.20	(0.99, 1.45)		
Folate intake (μ g)			0.04			0.04	0.09
1st quartile	1.08	(0.93, 1.25)		1.09	(0.90, 1.31)		
2nd quartile (ref)	(ref)	(ref)		(ref)	(ref)		

Nongenetic factor	Male			Female			Joint effect (factor*sex) P value
	aOR*	95% CI	Global type 3 P value*	aOR*	95% CI	Global type 3 P value*	
3rd quartile	1.07	(0.93, 1.25)		0.84	(0.69, 1.02)		
4th quartile	0.89	(0.76, 1.03)		0.90	(0.74, 1.09)		
Protein intake (g)						0.02	0.11
1st quartile	1.09	(0.94, 1.27)	0.62	1.29	(1.07, 1.57)		
2nd quartile (ref)	(ref)	(ref)		(ref)	(ref)		
3rd quartile	1.06	(0.91, 1.23)		1.00	(0.82, 1.22)		
4th quartile	1.02	(0.87, 1.18)		1.15	(0.94, 1.40)		0.02 [†]
Vitamin E intake (mg)			0.0022			0.04	
1st quartile	0.90	(0.78, 1.04)		1.25	(1.03, 1.51)		
2nd quartile (ref)	(ref)	(ref)		(ref)	(ref)		
3rd quartile	0.79	(0.68, 0.91)		1.03	(0.85, 1.25)		
4th quartile	0.78	(0.67, 0.91)		0.97	(0.80, 1.18)		
Vitamin C intake (mg)			0.001			0.80	0.05
1st quartile	0.96	(0.83, 1.11)		1.06	(0.88, 1.28)		
2nd quartile (ref)	(ref)	(ref)		(ref)	(ref)		
3rd quartile	0.77	(0.66, 0.90)		1.00	(0.82, 1.21)		
4th quartile	0.80	(0.69, 0.94)		0.96	(0.78, 1.17)		0.02 [‡]
Zinc intake (mg)			0.99			0.002	
1st quartile	1.02	(0.88, 1.19)		1.40	(1.15, 1.69)		
2nd quartile (ref)	(ref)	(ref)		(ref)	(ref)		
3rd quartile	1.00	(0.86, 1.16)		1.04	(0.85, 1.28)		
4th quartile	1.00	(0.86, 1.17)		1.22	(1.00, 1.48)		

* Adjusted for maternal race/ethnicity, maternal age at conception, and maternal education.

[†] $P \leq .05$ for test for effect modification by sex (interaction term).

[‡] From 3 months before pregnancy to the end of pregnancy.

[§] Greater than 10% missingness.

Table II.

Adjusted Odds Ratios with 95% Confidence Intervals and Joint Effect *P* Values for Nongenetic Factors and Cleft Palate Alone by Infant Sex, National Birth Defects Prevention Study (1997-2011)

Nongenetic factor	Male			Female			Joint effect (factor*sex) <i>P</i> value
	aOR*	95% CI	Global type 3 <i>P</i> value*	aOR*	95% CI	Global type 3 <i>P</i> value*	
Maternal race and ethnicity			<.0001			0.01	0.03 [†]
Hispanic	0.57	(0.45, 0.72)		0.92	(0.76, 1.12)		
Non-Hispanic Black	0.56	(0.41, 0.76)		0.64	(0.48, 0.84)		
Other	0.89	(0.64, 1.23)		1.17	(0.89, 1.54)		
Non-Hispanic White (ref)	(ref)	(ref)		(ref)	(ref)		
Maternal age at conception			0.62			0.0013	0.39
<20 years	0.80	(0.59, 1.09)		0.79	(0.60, 1.04)		
20-24 years	0.96	(0.76, 1.21)		0.84	(0.68, 1.03)		
25-29 years (ref)	(ref)	(ref)		(ref)	(ref)		
30-34 years	1.03	(0.82, 1.28)		1.03	(0.85, 1.26)		
35+ years	1.02	(0.77, 1.35)		1.38	(1.09, 1.74)		
Maternal education			0.01			0.01	0.93
<High school	1.39	(1.07, 1.82)		1.23	(0.97, 1.57)		
High school graduate	1.33	(1.09, 1.64)		1.34	(1.11, 1.61)		
>High school (ref)	(ref)	(ref)		(ref)	(ref)		
Maternal smoking [‡] (Y vs N)	1.09	(0.89, 1.34)	0.43	1.26	(1.04, 1.51)	0.02	0.92
Maternal alcohol consumption [‡] (Y vs N)	0.98	(0.83-1.16)	0.82	1.01	(0.87-1.17)	0.93	0.90
Maternal diabetes (Y vs N)	1.31	(0.99, 1.73)	0.06	1.68	(1.34, 2.11)	<.0001	0.07
Maternal history of seizures (Y vs N)	1.40	(0.91, 2.16)	0.13	1.47	(1.01, 2.15)	0.05	0.96
Maternal substance abuse [‡] (Y vs N)	1.09	(0.77, 1.53)	0.64	1.09	(0.79, 1.50)	0.62	0.76
Prepregnancy BMI			0.57			0.47	0.94
Underweight (<19.8)	1.11	(0.78, 1.57)		1.14	(0.83, 1.57)		
Normal (19.8-26.0)	(ref)	(ref)		(ref)	(ref)		
Overweight (26.1-29.0)	1.14	(0.92, 1.40)		1.05	(0.87, 1.27)		
Obese (>29.0)	1.13	(0.90, 1.41)		1.16	(0.95, 1.42)		

Nongenetic factor	Male			Female			Joint effect (factor*sex) P value
	aOR*	95% CI	Global type 3 P value*	aOR*	95% CI	Global type 3 P value*	
Pre-existing maternal hypertension [§] (Y vs N)	0.84	(0.56, 1.28)	0.42	0.97	(0.67, 1.40)	0.85	0.63
Pregnancy intention [§]			0.30			0.0005	0.11
Wanted to get pregnant then (ref)	(ref)	(ref)		(ref)	(ref)		
Wanted to wait until later	0.88	(0.68, 1.13)		1.46	(1.14, 1.86)		
Didn't care	1.22	(0.91, 1.63)		1.47	(1.13, 1.90)		
Didn't want to become pregnant at all	0.96	(0.71, 1.31)		0.94	(0.75, 1.18)		
Previous miscarriage (Y vs N)	1.10	(0.91, 1.33)	0.33	1.07	(0.90, 1.27)	0.45	0.98
Mother/father had fertility procedure(s) (Y vs N)	1.75	(1.02, 2.99)	0.04	1.80	(1.09, 2.98)	0.02	0.86
First degree relative(s) with clefts (Y vs N)	13.37	(7.98, 22.41)	<.0001	20.02	(10.37, 38.64)	<.0001	0.39
Folic acid supplementation (any type) [‡] (Y vs N)	0.86	(0.60, 1.24)	0.42	0.93	(0.67, 1.30)	0.68	0.84
Carbohydrate intake (g)			0.89			0.31	0.97
1st quartile	1.03	(0.82, 1.29)		1.08	(0.88, 1.32)		
2nd quartile (ref)	(ref)	(ref)		(ref)	(ref)		
3rd quartile	0.95	(0.75, 1.19)		0.98	(0.80, 1.21)		
4th quartile	0.95	(0.75, 1.21)		0.87	(0.70, 1.09)		
Energy intake (KJ)			0.46			0.09	0.66
1st quartile	0.96	(0.77, 1.20)		1.16	(0.95, 1.41)		
2nd quartile (ref)	(ref)	(ref)		(ref)	(ref)		
3rd quartile	0.83	(0.66, 1.05)		0.89	(0.72, 1.10)		
4th quartile	0.91	(0.72, 1.15)		0.99	(0.80, 1.22)		
Total lipids/fat intake (g)			0.52			0.04	0.83
1st quartile	1.15	(0.92, 1.44)		1.19	(0.98, 1.45)		
2nd quartile (ref)	(ref)	(ref)		(ref)	(ref)		
3rd quartile	0.98	(0.78, 1.24)		0.90	(0.73, 1.11)		
4th quartile	1.07	(0.85, 1.35)		0.96	(0.78, 1.19)		
Folate intake (μg)			0.84			0.16	0.79
1st quartile	0.97	(0.77, 1.21)		1.05	(0.86, 1.29)		
2nd quartile (ref)	(ref)	(ref)		(ref)	(ref)		
3rd quartile	0.99	(0.79, 1.25)		0.89	(0.72, 1.08)		

Nongenetic factor	Male			Female			Joint effect (factor*sex) P value
	aOR*	95% CI	Global type 3 P value*	aOR*	95% CI	Global type 3 P value*	
4th quartile	0.91	(0.72, 1.14)		0.85	(0.69, 1.05)		
Protein intake (g)			0.92			0.05	0.61
1st quartile	1.07	(0.85, 1.35)		1.25	(1.03, 1.53)		
2nd quartile (ref)	(ref)	(ref)		(ref)	(ref)		
3rd quartile	1.06	(0.84, 1.33)		0.98	(0.80, 1.21)		
4th quartile	1.01	(0.80, 1.28)		1.01	(0.82, 1.25)		
Vitamin E intake (mg)			0.99			0.11	0.69
1st quartile	0.99	(0.79, 1.25)		1.21	(0.99, 1.48)		
2nd quartile (ref)	(ref)	(ref)		(ref)	(ref)		
3rd quartile	0.99	(0.79, 1.25)		0.98	(0.80, 1.21)		
4th quartile	1.02	(0.81, 1.30)		0.97	(0.79, 1.20)		
Vitamin C intake (mg)			0.02			0.06	0.02 [†]
1st quartile	0.77	(0.61, 0.95)		1.14	(0.94, 1.40)		
2nd quartile (ref)	(ref)	(ref)		(ref)	(ref)		
3rd quartile	0.75	(0.60, 0.93)		1.09	(0.89, 1.33)		
4th quartile	0.76	(0.60, 0.96)		0.86	(0.69, 1.07)		
Zinc intake (mg)			0.28			0.04	0.07
1st quartile	0.94	(0.75, 1.17)		1.30	(1.07, 1.60)		
2nd quartile (ref)	(ref)	(ref)		(ref)	(ref)		
3rd quartile	0.80	(0.63, 1.00)		1.14	(0.93, 1.40)		
4th quartile	0.92	(0.73, 1.15)		1.03	(0.83, 1.27)		

* Adjusted for maternal race/ethnicity, maternal age at conception, and maternal education.

[†] $P \leq .05$ for test for effect modification by sex (interaction term).

[‡] From 3 months before pregnancy to the end of pregnancy.

[§] Greater than 10% missingness.