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Association between maternal periconceptional dietary patterns and occurrence of orofacial clefts

Erin G. Sley^{*,1}, Tania A. Desrosiers¹, Daniela Sotres-Alvarez², Suzan L. Carmichael^{3,4}, Joanna Maselko^{1,5}, Mollie E. Wood¹, Elizabeth C. Ailes⁶, Wendy N. Nembhard⁷, Wei Yang⁸, Andrew F. Olshan¹, The National Birth Defects Prevention Study

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

²Department of Biostatistics, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States

³Department of Pediatrics, Stanford University School of Medicine, Stanford, CA, United States

⁴Department of Obstetrics and Gynecology, Stanford University School of Medicine, Stanford, CA, United States

⁵Carolina Population Center, University of North Carolina at Chapel Hill, Chapel Hill, NC, United States

⁶National Center on Birth Defects and Developmental Disabilities, Centers for Disease Control and Prevention, Atlanta, GA, United States

⁷Department of Epidemiology, College of Public Health, University of Arkansas for Medical Sciences and Arkansas Reproductive Health Monitoring System (ARHMS), Little Rock, AR, United States

⁸Division of Neonatology and Developmental Medicine, Department of Pediatrics, Stanford University School of Medicine, Stanford, CA, United States.

Abstract

Orofacial clefts (OFC) are a common birth defect with few known risk factors (eg, smoking). Maternal diet is associated with birth defects, though the relationship with OFC is less clear as studies typically only investigate single nutrients. We assessed the association between periconceptional maternal diet and OFC in the United States, using the National Birth Defects Prevention Study (1997-2011), including 3649 cases (2480 cleft lip with/without palate [CL/P] and 1169 cleft palate [CP]) and 10 584 controls (infants without a birth defect). Using latent class

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*Corresponding author: Erin G. Sley, Department of Epidemiology, Gillings School of Global Public Health, University of North Carolina at Chapel Hill, 135 Dauer Dr, 2101 McGavran-Greenberg Hall, CB #7435, Chapel Hill, NC 27599 (eringsley@gmail.com).

Conflict of interest

The authors declare no conflicts of interest.

Disclaimer

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

analysis, we derived dietary patterns based on relative consumption of self-reported food items via food frequency data. We used logistic regression to estimate adjusted odds ratios (aORs) and 95% CIs for the effect of dietary patterns on OFC. Four patterns were identified: Prudent (reference), Western, Low-Calorie Western, and Mexican. The Western diet had increased odds of CL/P (aOR: 1.3 [95% CI, 1.2-1.5]) and CP (aOR: 1.2 [95% CI, 1.1-1.4]). Low-Calorie Western (CL/P aOR: 1.2 [95% CI, 1.0-1.4]; CP aOR: 1.0 [95% CI, 0.9-1.2]) and Mexican diets (CL/P aOR: 1.1 [95% CI, 0.9-1.3]; CP aOR: 0.8 [95% CI, 0.6-1.1]) had a weaker or null association. Findings underscore the importance of further investigation into the effect of periconceptional diet on OFC occurrence.

Keywords

orofacial clefts; maternal diet; dietary exposures; preconception; birth defects; maternal health; dietary patterns; pregnancy

Introduction

Orofacial clefts (OFC) are a commonly diagnosed birth defect in the United States. For every 10 000 livebirths, approximately 10 infants are diagnosed with cleft lip with or without palate (CL/P) and 6 are diagnosed with cleft palate alone (CP), though the prevalence varies by race/ethnicity.^{1,2} The critical development window for OFC occurs within the first 9 weeks of pregnancy, often before pregnancy is recognized.^{3,4} These anomalies can cause complications in feeding, speech, hearing, and psychological well-being, which are associated with increased morbidity across the life-span.⁵⁻⁷ Optimal OFC care consists of extensive medical interventions and includes a coordinated interdisciplinary care consisting of medical, surgical, dental, and psychological professionals.⁸

The overall etiology of most OFC is largely unknown, and likely differs to some degree between CL/P and CP given differences in prevalence by race/ethnicity, risk factors, and sensitive periods of development for the lip and palate.^{3,9} An estimated 8% of cases are chromosomal.^{10,11} Current research suggests that occurrence is likely due to an interaction between genetic, environmental, and lifestyle factors. Prenatal smoking, often evaluated in the first trimester, is the most widely recognized risk factor for both CL/P and CP.¹²⁻¹⁸ Thus, it is important to continue assessing the effect of other modifiable exposures on OFC risk, such as maternal diet.

Maternal diet during the preconception and prenatal period has a substantial influence on fetal growth and development. Periconceptional nutrition, in the year prior to pregnancy, aids in the creation of a favorable preimplantation environment for the placenta and fetus¹⁹⁻²¹ and is often correlated with nutrition during early pregnancy, the critical development window for OFC.^{3,22} Optimal periconceptional diet quality has been associated with a decreased risk of multiple types of birth defects.²³⁻²⁶ The majority of the published scientific literature has assessed the effect of individual nutrients or single food items on the risk of OFC.²⁷⁻³³ Current findings suggest that adequate consumption of nutrients such as zinc, magnesium, calcium, and vitamins B, C, and E may decrease the risk of OFC. It has also been suggested that, like neural tube defects (NTDs), OFC risk may decrease with maternal

folic acid and multivitamin supplementation.^{34,35} However, few studies have holistically evaluated the association between dietary patterns and diet quality on OFC occurrence.³⁶⁻³⁸

A focus on overall dietary intake explores the realistic, complex, and synergistic effect of nutrient interactions, since nutrients are rarely consumed in isolation.^{39,40} To further explore the relationship between periconceptional diet and OFC, we measured the association between maternal dietary patterns, defined *a posteriori* with a latent class analysis (LCA), and the occurrence of CL/P and CP using data from a large multisite case-control study of birth defects.

Methods

Study population

The National Birth Defects Prevention Study (NBDPS) is a multisite, population-based case-control study designed to identify unknown causes of major structural birth defects in the United States among pregnancies. The NBDPS ascertained information on pregnancies from 1997 to 2011. Cases with OFC included liveborn infants along with terminations and stillbirths, dependent on state and year. Statewide surveillance systems identified cases in Arkansas, Iowa, New Jersey, and Utah and county-specific systems were used in California, Georgia, Massachusetts, New York, North Carolina, and Texas. Upon ascertainment, cases of CL/P and CP were clinically confirmed by a clinical geneticist.⁴¹ Controls (liveborn infants without major birth defects) were selected from vital or birth records within the same region and enrollment period of cases.⁴² The NBDPS eligibility requirements included fluency in English or Spanish and legal custody of the index infant at time of interview. Exclusion criteria included incarceration and, for some NBDPS sites, maternal age under 18.⁴² Eligible mothers were interviewed up to 2 years after their estimated delivery date and participated in an hour-long computer-assisted telephone interview. The interview ascertained information on maternal and paternal demographics, reproductive health, nutrition, health behaviors, and home and work environment.⁴² The NBDPS study protocol and data collection were approved by the Institutional Review Board (IRB) at the Centers for Disease Control (CDC) and at each of the participating state centers.

Characterization of maternal diet

Maternal diet was measured through a modified 58-question version of the validated Willett food frequency questionnaire (FFQ) administered during the NBDPS interview in which participants recalled their frequency of consumption for specific food items during the year prior to conception.⁴³ In conjunction with the FFQ, the interview ascertained coffee, tea, cereal, and soda intake, which allowed for the measurement of 64 food items in total (Table S1). We classified cereals by folic acid fortification status (highly fortified vs not) using the reported cereal brand, and soft drinks were classified as diet or regular. Soft drinks with an unknown diet status were excluded from the analysis. A total of 16 frequency responses were available for each food (ranging from “6 or more servings”/day to “less than 1 serving or no consumption”/month). Grams/day for each food were calculated by multiplying the frequency of consumption by the number of grams/serving in each food. Total grams consumed/day was calculated by summing daily grams of all food items. Food

and vitamin supplements were not included in these calculations. Nutrients were assigned to food items using the Department of Agriculture National Database, SR27.⁴⁴ Dietary folate equivalents (DFE) were calculated by upweighting synthetic folic acid by 1.7 and adding this to naturally occurring folate, to account for the greater bioavailability of synthetic folic acid.⁴⁵

Statistical analyses

Dietary patterns among controls were derived through Latent Class Analysis (LCA), a data reduction method that identifies underlying “classes” or group patterns in a population. Individuals are assumed to belong to 1 unknown class of individuals with similar indicators.⁴⁶ Our analysis is strengthened by the use of LCA which, unlike other data reduction methods such as principal component analysis, estimates class membership probabilities. These probabilities allow us to better understand how well a participant fits into their assigned dietary pattern. The LCA has been previously recommended for the assessment of maternal diet, especially for understanding the effect of exclusive classes (dietary patterns) on outcomes of interest.⁴⁷

The use of LCA for NBDPS dietary assessment has previously been used.²³ In short, we used a multinomial model, adjusted for energy intake (kcal/day), to derive dietary patterns from the relative consumption of 64 food items among controls. To assess relative consumption of each food item, we divided the daily intake of each food item (grams/day) by the total grams/day consumed to better understand the percentage of total daily intake attributed to each food. As an example, this relative percentage would highlight differences in consumption patterns between 2 individuals who consumed the same grams of a specific food (eg, 112 g/day of fish) but had a significantly different energy intake (eg, 1000 vs 2000 kcal/day). We categorized relative consumption of each food into 4 levels, tertiles of consumption among consumers and an additional nonconsumption level. Foods with notably low intake (<20% report any consumption), including liver, organ meat, low-calorie soda, and cereal fortified with folic acid, were dichotomized (any versus none) since higher tertiles still represented a substantively low number of grams consumed. To avoid sparse nonconsumption levels, foods consumed by most of the population (at least 90%), including rice/pasta, cheddar cheese, eggs, and potatoes, only had 3 intake levels with the small number of nonconsumers combined with the lowest tertile.

To identify the optimal number of patterns specific to these consumption values, we conducted the multinomial model multiple times with different seeds and specified 2-6 classes. We then compared the Akaike Information Criteria (AIC), Bayesian Information Criteria (BIC), entropy value, and interpretability of each model. The final model, determined by these 4 criteria, produced regression coefficients that estimated class membership (for each dietary pattern and energy intake) and the conditional probability of food item consumption given a specific class. These 2 probabilities were combined, using Bayes’ theorem, to predict each participant’s probability of class membership dependent on reported food consumption and energy intake.⁴⁸ Participants were assigned to the class in which they had the highest probability of membership.

Of the 4792 OFC cases and 11692 controls available in the NBDPS, we excluded deliveries with multiple birth defects ($n = 703$ cases), nonsingleton pregnancies ($n = 225$ cases, 372 controls), and pregnancies using donor embryos ($n = 19$ cases, 33 controls) due to chromosomal or biological etiologies that likely differ from other OFC cases. Mothers with any type of pregestational diabetes ($n = 121$ cases, 150 controls) were also excluded since diet may differentially impact OFC occurrence among this population. Finally, participants with extreme caloric intake compared to reported diet ($n = 233$ cases, 614 controls) or those missing more than 1 answer on the FFQ ($n = 167$ cases, 484 controls) were excluded to ensure a more valid diet measurement among all participants in our analytic sample. Some individuals were excluded based on multiple restrictions. Our final analytic sample consisted of 3649 cases and 10 584 controls. To investigate potential differences in risk between types of OFC⁴⁹, we analyzed CL/P cases ($n = 2480$) and CP cases ($n = 1169$) separately whenever possible.

After dietary patterns were derived, we estimated maternal demographic characteristics and mean nutrient intake among controls by class. We also examined the distribution of sociodemographic and pregnancy-related factors by case-control status. We then used multivariable logistic regression models to assess the effect of dietary patterns on CL/P and CP. Crude and adjusted odds ratios (aORs) were estimated, along with corresponding 95% CIs. For adjusted models, a minimally sufficient set was identified through a Directed Acyclic Graph (DAG) and included maternal: age at conception calculated using self-reported date of birth and estimated date of conception (<20, 20-25, 26-35, or ≥ 36 years), race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, Other [including individuals who identify as Asian/Pacific Islander or Native American/Alaskan Native, and those who do not identify with any of the aforementioned categories]), intake of any folic acid-containing supplement (yes/no for the first 2 months of pregnancy), education level as a proxy for socioeconomic status (<12, 12, or >12 years), family history of OFC in a first degree relative or prior pregnancy (yes/no), gravidity (0, 1, or >1 pregnancies), and study center. Periconceptional body mass index was included in the DAG as a mediator in the relationship between maternal diet in the year before conception and risk of OFCs (Figure S1).

Three sensitivity analyses were also conducted. To evaluate the effect of low-quality membership classification on results, we excluded participants with a low probability of class membership ($n = 355$ cases and 939 controls), defined as lower than the probability of random assignment to their specific class ($< [K-1]/K$ for K classes). Next, to assess the influence of severe morning sickness on dietary changes and OFC risk, we excluded individuals who reported taking nausea medication or treatments ($n = 507$ cases and 1580 controls), under the assumption that this captured participants with the most severe nausea whose usual diet may have been altered in early pregnancy. Finally, since smoking was not identified as a confounder in our DAG⁵⁰ (Figure S1) but is the most recognized risk factor for OFC, we adjusted the final models by smoking to assess potential residual confounding (categorized as any/none within first 2 months of pregnancy). All analyses were completed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

Participants with a control infant were primarily non-Hispanic White (58.3%) with more than 12 years of education (59.4%) (Table 1). Most of the control group took a supplement containing folic acid (75.3%) and did not smoke (84.4%) or report exposure to secondhand smoke (78.5%) or binge drinking (62.8%) at the start of pregnancy. Compared to controls, a higher percentage of CL/P and CP cases reported prenatal smoking (controls: 15.6%, CL/P: 21.4%, CP: 19.9%), exposure to secondhand smoke (controls: 21.5%, CL/P: 27.1%, CP: 25.5%), and family history of OFC (controls: 0.3%, CL/P: 6.1%, CP: 5.7%).

LCA models that specified 4, 5, and 6 classes had similar AIC, BIC, and entropy values (Table S2). We selected the 4-class solution to improve interpretability. Dietary patterns were labeled as Prudent (31.4% of controls), Western (27.0% of controls), Low-Calorie Western (26.3% of controls), and Mexican (15.4% of controls). Pattern labels were based on classes with similar consumption probabilities from previous studies^{23,24} (Figure 1). Of note, the Western diet class was more reflective of a diet found in North America, rather than other Western countries. Participants in the Prudent class, our referent group, had a relatively high probability of consuming higher amounts of dairy, nuts, and fish along with a low probability of not consuming vegetables, fruits, and dark breads. Individuals in the prudent diet also had a relatively low probability of “no consumption” for most foods, which may suggest a more diverse diet compared to other patterns. Aside from a higher probability of consuming salsa, chili peppers, and tortillas, the Mexican Diet class (primarily Hispanic participants) closely followed the Prudent diet class (primarily non-Hispanic White participants). This pattern was labeled “Mexican” as it closely follows consumption patterns of individuals living in Mexico. Although similar in food intake, there were notable differences in education between participants in these 2 dietary classes. Among controls, 86.4% of participants in the Prudent diet class, compared to 21.7% of participants in the Mexican diet class, reported more than 12 years of education (Table S3).

The other 2 classes, Western and Low-Calorie Western, tended to have a relatively high probability of consuming white bread, meat, and chips, and no consumption of vegetables and yogurt (Figure 1). Unlike the Western class, the Low-Calorie Western class was associated with a decrease in class membership probability as energy intake increased, a relatively low likelihood of caffeine intake, and extreme probabilities of relative intake for most food items (high and low). The consistently high probability of no consumption for most foods may suggest a more restrictive diet among the Low-Calorie Western class (Figure 1). Along with differences in consumption, differences in caloric intake and macronutrients by class were also observed (Table S4).

After adjustment, membership in the Western diet class was associated with higher odds of CL/P (aOR: 1.3 [95% CI, 1.2-1.5]) and CP (aOR: 1.2 [95% CI, 1.1-1.4]), compared to the Prudent diet. Associations between OFCs and the Low-Calorie Western and Mexican diets were weaker with wider confidence intervals. Specifically, the aORs for the Low-Calorie Western diet (vs Prudent) were 1.2 (95% CI, 1.0-1.4) and 1.0 (95% CI, 0.9-1.2) for CL/P and CP, respectively. Similarly, aORs associated with the Mexican diet were 1.1 (95% CI, 0.9-1.3) for CL/P and 0.8 (95% CI, 0.6-1.1) for CP (Table 2). Similar results were observed

when we excluded 1294 participants with a low probability of class membership ($<75\%$, since $K = 4$ classes) or 2087 participants with severe morning sickness (Tables S5 and S6). The inclusion of smoking in our adjusted models did not have a material difference on final estimates (Table S7).

Discussion

Specific periconceptional dietary patterns found in this study population were associated with a modest, yet significant, increase in risk of CL/P and CP, even after controlling for folic acid supplementation and other potential confounding factors including race/ethnicity. Compared to the Prudent diet (high in dairy, fish, dark breads, vegetables, and fruits), the Western diet (high in white bread, chips, and soda) was associated with a significant increase in the odds of both CP and CL/P. The more restrictive Low-Calorie Western diet (similar to Western with a lower energy intake), compared to the more diverse Prudent diet, was associated with a weaker, nonsignificant, increase in CL/P but had a null effect for CP. The Mexican diet (similar to Prudent but also high in salsa, peppers, and tortillas) had a mostly null effect on both phenotypes, when compared to Prudent.

Only 2 studies have evaluated the effect of comprehensive dietary measures on OFC by considering the intake and interaction of multiple food items.^{36,38} These studies showed that, after adjustment for folic acid intake, a healthier overall diet quality decreased OFC risk. Our results, although smaller in magnitude, align with these findings. Vujkovic *et al.* evaluated this association in the Netherlands by deriving dietary patterns using a factor analysis *a posteriori*.³⁶ Similarly, the highest tertile of their “Western” pattern, which overlaps with our “Western” definition (high in red or processed meat, potatoes, and legumes and low in fruits) was associated with a significant increase in the odds of any OFC (aOR: 1.9 [95% CI, 1.2-3.1]) compared to the lowest tertile of this pattern. Carmichael *et al.* assessed the effect of diet on OFC in a slightly smaller subset of our NBDPS population from 1997 to 2005 using 2 diet quality indices.³⁸ These indices positively scored dietary components like grains, fruits, vegetables, and several nutrients and negatively scored items such as meat and sweets.^{51,52} Higher (healthier) quartiles of the indices decreased the odds of OFC when compared to the lowest quartiles. Hispanic participants were more likely to be in these higher quartiles, similar to the dietary patterns we derived. Although we observed an increased risk of OFC associated with both Western diets, the Mexican diet had a null effect on OFC occurrence, when compared to the Prudent diet. These results remained consistent after controlling for potential confounders. To our knowledge, this is the only prior study to assess the effect of maternal diet on OFC in the United States, which is important to consider since diet is closely linked to geographic residence.⁵³

Our results demonstrate the use of holistic measures of dietary patterns and diet quality, as a complement to the investigation of individual nutrients. Like dietary indices used previously in the NBDPS data,³⁸ our newly derived patterns were more strongly associated with OFC risk compared to single-nutrient estimates previously reported in the NBDPS.³¹ To date, this is the largest single study to assess the impact of maternal diet on OFC occurrence. The NBDPS provides a diverse, population-based study sample with clinically verified cases of OFC and robust dietary information. Given the known etiologic heterogeneity

between CL/P and CP, our ability to analyze each phenotype separately is a strength of this study. Our ability to derive dietary patterns, compared to individual nutrients, allowed for a more comprehensive assessment of the ways in which food items are consumed and their interaction with one another. The LCA is optimal for deriving maternal dietary patterns due to its ability to identify complex patterns while adjusting for covariates, such as energy intake.⁴⁷

In terms of possible limitations, our results are potentially susceptible to selection bias due to nonparticipation. Though over 65% of eligible subjects agreed to participate in the NBDPS, it is possible that these individuals were inherently different than those who opted out of the study; yet, it has been noted that selection bias from differential participation in NBDPS may be minimal.⁵⁴ Another potential source of selection bias is missing data; however, this is likely minimal in our study given that 1) our analytic sample included 99% of eligible cases and controls within NBDPS; 2) a comparison of the analytic sample and eligible population showed no differences in maternal and infant characteristics (data not shown); and the frequency of missing data for covariates included in our analysis was minimal (0 to <1%).

Retrospective data collection inherent in a case-control study, such as NBDPS, introduces the potential for exposure misclassification. Self-reported exposures may have been influenced by case/control status, which could lead to differential misclassification. The NBDPS interview ascertained exposures, including dietary intake via the FFQ, retrospectively up to 2 years after the EDD. This extended time between delivery and interview could lead to recall error, which could result in differential or nondifferential misclassification.⁵⁵ However, we see no strong rationale for differential recall between cases and controls in terms of remembering general patterns of food consumption in the year prior to pregnancy, which has been previously correlated with early pregnancy diet.²² Thus, the impact of the longer recall period is likely nondifferential exposure misclassification due to recall error rather than differential recall bias. The semiquantitative nature of our FFQ warrants cautious interpretation of actual nutrient intake values but is a good tool for our purpose of assessing relative dietary patterns.^{56,57} Self-reported dietary intake reported through the FFQ is vulnerable to intake-related bias, in which individuals with high consumption report lower than actual consumption and vice versa, and social desirability bias, in which individuals attempt to align their responses to broader social norms.⁵⁸⁻⁶⁰ Additionally, the LCA assumes that dietary intake is similar within each class, which may be a strong assumption. However, results were robust to the exclusion of participants that had a lower likelihood of class membership, due to their individual intake differing from that of their assigned class. It is also important to note that the labels used for these dietary patterns were selected for ease of comparison with existing literature and do not perfectly represent the frequency of food items consumed by participants in each class. We encourage readers to not solely rely on these labels but rather look closely at the foods consumed within each pattern, provided in Figure 1. Finally, residual confounding is likely as several factors that influence both OFC risk and maternal diet were unmeasured in the NBDPS database, such as household income and other socioeconomic measures that impact the risk of OFC and access to healthy foods.

Dietary patterns that are more likely to include white bread, chips, and soda, compared to diets comprised of dairy, fish, dark breads, vegetables, and fruits, were associated with increased odds of CL/P and CP in our study population. These results remained robust after controlling for factors such as folic acid supplementation and add to the body of literature that suggests that a varied and healthy diet may improve pregnancy and birth outcomes, including a possible reduction in the risk of birth defects.^{20,22} Confirmation of these findings is important as periconceptional and prenatal diet is modifiable. Further research could also influence dietary recommendations and food assistance program practices for pregnant women, or those considering pregnancy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability

Information pertaining to accessing data used in this study is available here: NBDPS and BD-STEPS Public Access Procedures.

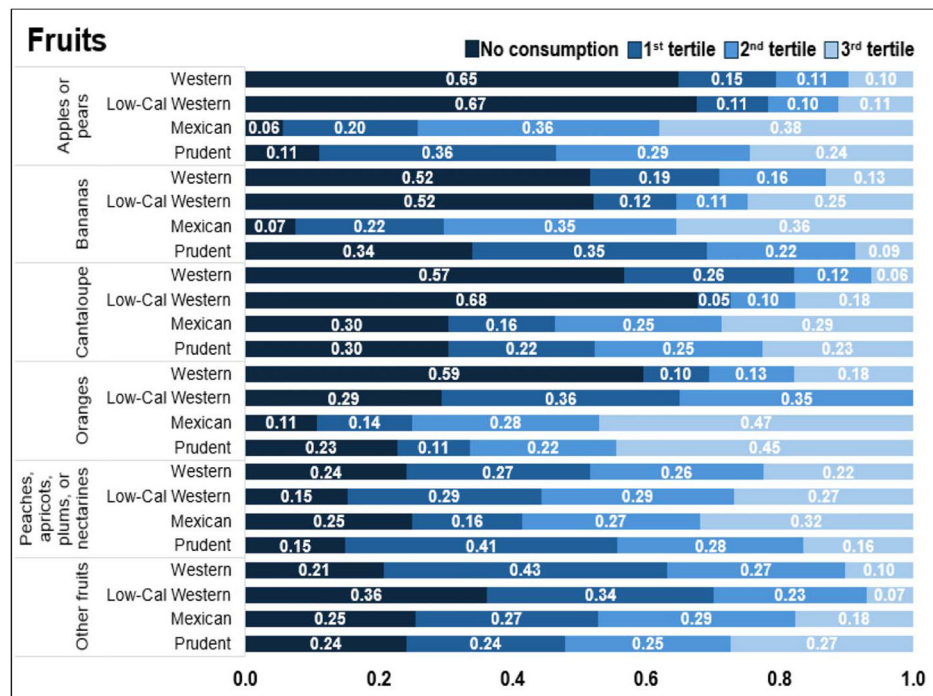
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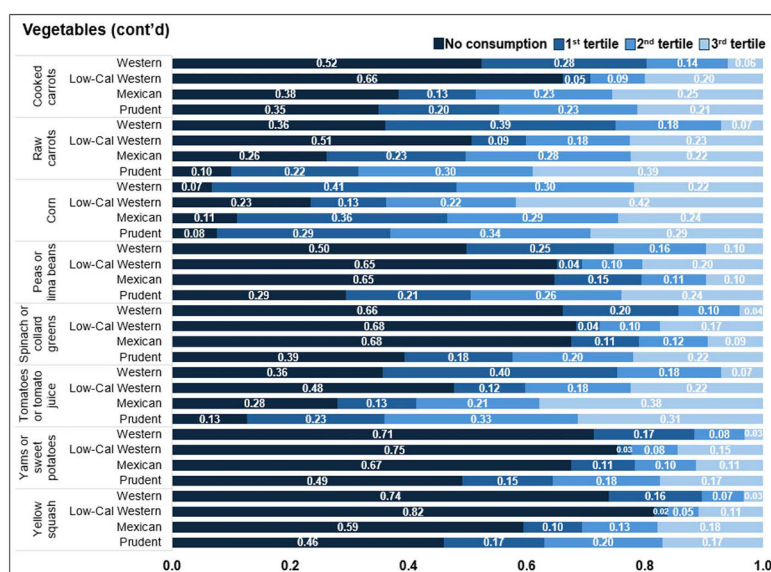
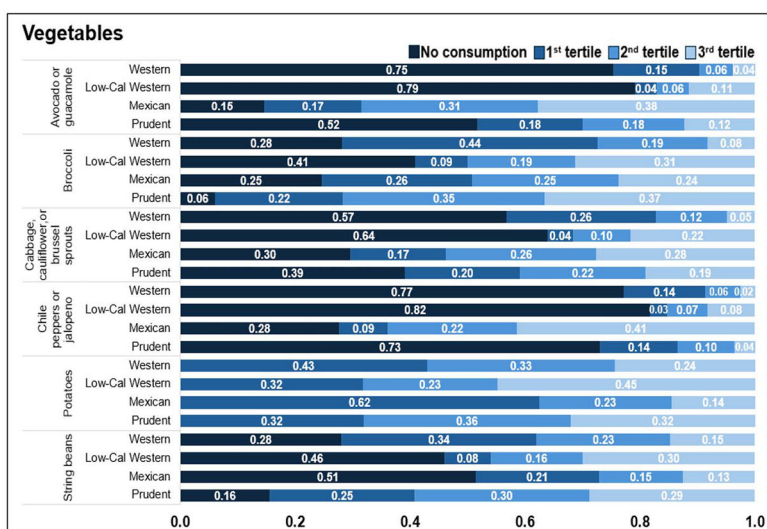
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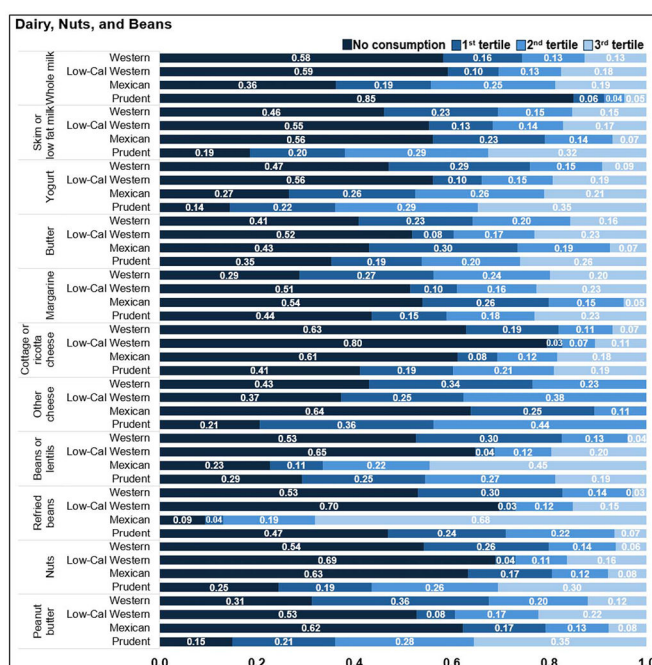
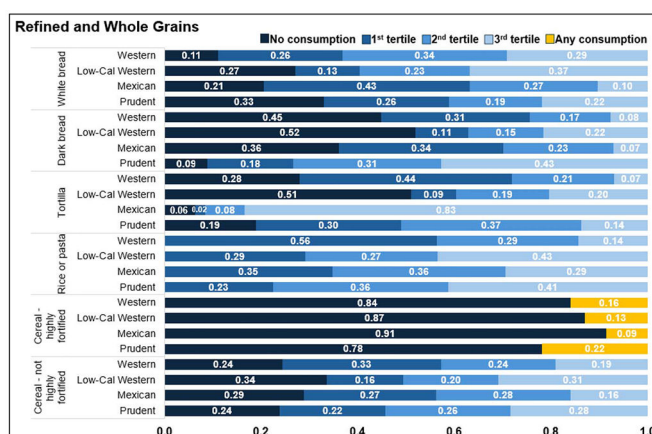
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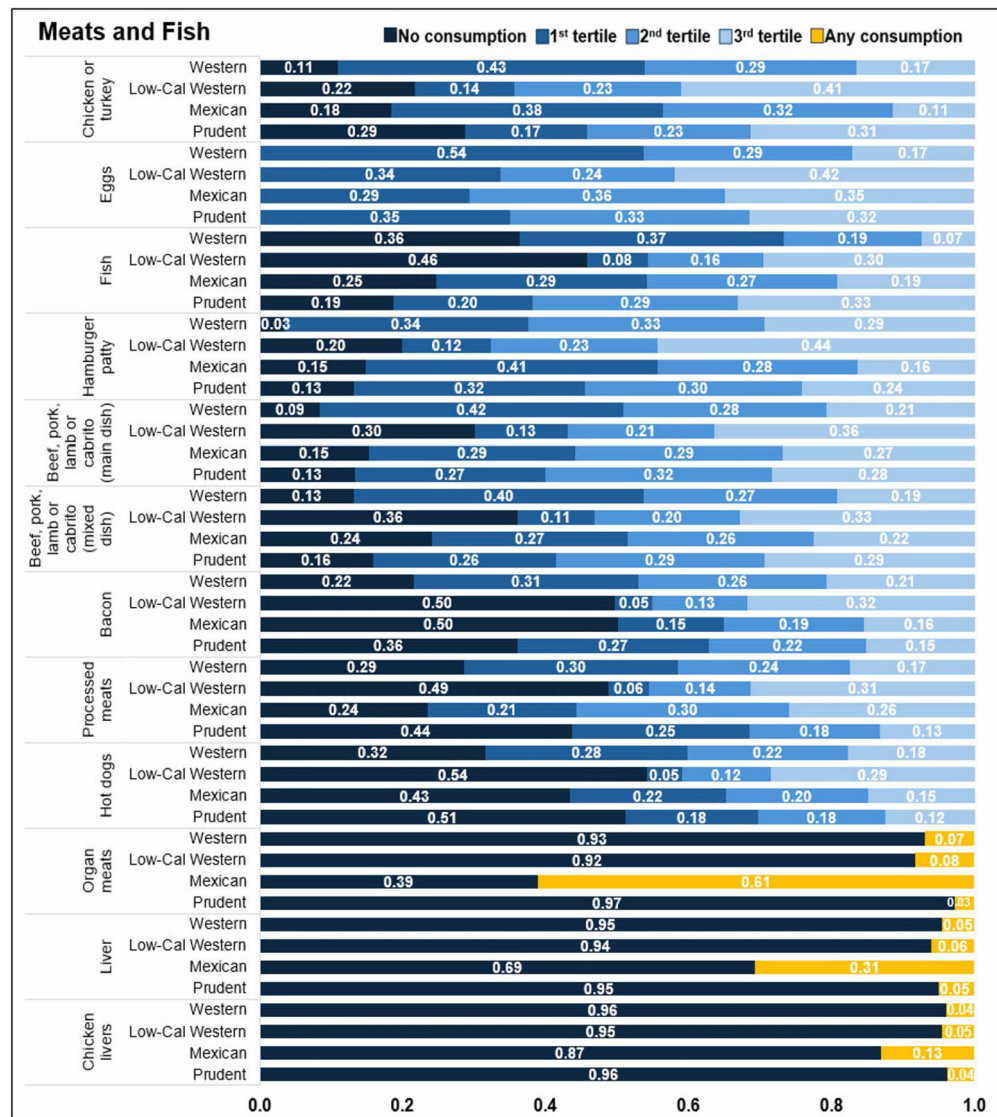
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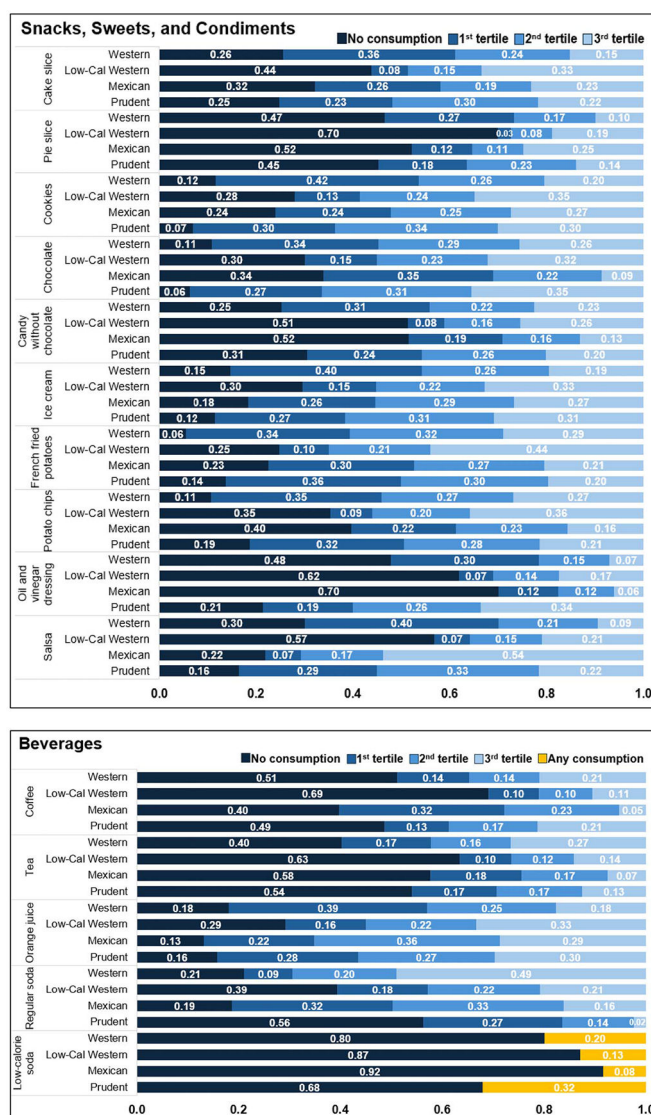
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**Figure 1.**

Probability of consumption for all food items by dietary patterns using latent class analysis among controls in the National Birth Defects Prevention Study, 1997-2011.* The probability of intake in the year prior to pregnancy, dependent on dietary class and adjusted for energy intake. The sum of consumption probabilities for each food item may not equal 100% due to rounding.

*The probability of intake in the year prior to pregnancy, dependent on dietary class and adjusted for energy intake. The sum of consumption probabilities for each food item may not equal 100% due to rounding.

Table 1.

Maternal and infant characteristics among cases with cleft lip with or without palate (CL/P) or cleft palate (CP) and controls without a birth defect, National Birth Defects Prevention Study, 1997-2011.

	Controls (n = 10 584) n (%)	CL/P (n = 2480) n (%)	CP (n = 1169) n (%)
Age at conception, y			
<20	1368 (12.9)	344 (13.9)	124 (10.6)
20-25	3037 (28.7)	772 (31.1)	318 (27.2)
26-35	5307 (50.1)	1180 (47.6)	600 (51.3)
36+	872 (8.2)	184 (7.4)	127 (10.9)
Missing	0	0	0
Race/ethnicity			
non-Hispanic White	6168 (58.3)	1551 (62.5)	777 (66.5)
non-Hispanic Black	1147 (10.8)	127 (5.1)	74 (6.3)
Hispanic	2577 (24.4)	625 (25.2)	235 (20.1)
Other ^a	688 (6.5)	177 (7.1)	83 (7.1)
Missing	4 (0.04)	0	0
Maternal education			
<12 y	1744 (16.6)	493 (20.0)	171 (14.7)
12 y	2522 (24.0)	660 (26.8)	296 (25.4)
>12 y	6241 (59.4)	1311 (53.2)	697 (59.9)
Missing	77 (0.7)	16 (0.7)	5 (0.4)
Prepregnancy BMI (kg/m ²)			
Underweight (<18.5)	557 (5.5)	148 (6.3)	68 (6.0)
Normal (18.5-24.9)	5442 (53.6)	1259 (53.4)	573 (50.3)
Overweight (25.0-29.9)	2327 (22.9)	507 (21.5)	273 (24.1)
Obese (≥30)	1829 (18.0)	445 (18.9)	220 (19.4)
Missing	429 (4.1)	121 (4.9)	35 (3.0)
Maternal smoking ^b			
Any	1644 (15.6)	528 (21.4)	232 (19.9)
None	8899 (84.4)	1940 (78.6)	936 (80.1)
Missing	41 (0.4)	12 (0.5)	1 (0.1)

	Controls (n = 10 584) n (%)			CL/P (n = 2480) n (%)			CP (n = 1169) n (%)		
Secondhand smoke ^b									
Yes	2262 (21.5)			668 (27.1)			297 (25.5)		
No	8253 (78.5)			1795 (72.9)			867 (74.5)		
Missing	69 (0.7)			17 (0.7)			5 (0.4)		
Maternal alcohol ^c									
Binge (≥4 drinks)	1326 (12.7)			327 (13.3)			143 (12.4)		
Some	2560 (24.5)			581 (23.7)			321 (27.7)		
None	6568 (62.8)			1543 (63.0)			693 (59.9)		
Missing	130 (1.2)			29 (1.2)			12 (1.0)		
Prior pregnancies									
0	3132 (29.6)			720 (29.1)			315 (27.0)		
1	3019 (28.5)			731 (29.5)			352 (30.1)		
>1	4430 (41.9)			1027 (41.4)			502 (42.9)		
Missing	3 (0.03)			2 (0.1)			0		
Folic acid-containing supplement ^b									
Any	7967 (75.3)			1845 (74.5)			900 (77.1)		
None	2612 (24.7)			633 (25.5)			268 (23.0)		
Missing	5 (0.1)			2 (0.1)			1 (0.1)		
Any prenatal care									
Yes	10 477 (99.1)			2443 (98.6)			1156 (99.0)		
No	101 (1.0)			35 (1.4)			12 (1.0)		
Missing	6 (0.1)			2 (0.1)			1 (0.1)		
Infant sex									
Female	5183 (49.0)			842 (34.0)			676 (57.9)		
Male	5391 (51.0)			1635 (66.0)			492 (42.1)		
Missing	10 (0.1)			3 (0.1)			1 (0.1)		
Family history of OFC									
Yes	32 (0.3)			152 (6.1)			66 (5.7)		
No	10 552 (99.7)			2328 (93.9)			1103 (94.4)		
Missing	0			0			0		
Folate-antagonistic medication									

	Controls (n = 10 584) n (%)	CL/P (n = 2480) n (%)	CP (n = 1169) n (%)
Yes	77 (0.7)	21 (0.9)	13 (1.1)
No	10 497 (99.3)	2456 (99.2)	1155 (98.9)
Missing	10 (0.1)	3 (0.1)	1 (0.1)
Maternal residence			
Arkansas	1377 (13.0)	296 (11.9)	138 (11.8)
California	1187 (11.2)	404 (16.3)	147 (12.6)
Georgia	1053 (10.0)	249 (10.0)	128 (11.0)
Iowa	1216 (11.5)	261 (10.5)	121 (10.4)
Massachusetts	1217 (11.5)	278 (11.2)	181 (15.5)
New Jersey	542 (5.1)	93 (3.8)	57 (4.9)
New York	932 (8.8)	202 (8.2)	108 (9.2)
North Carolina	926 (8.8)	186 (7.5)	103 (8.8)
Texas	1217 (11.5)	254 (10.2)	92 (7.9)
Utah	917 (8.7)	257 (10.4)	94 (8.0)

Abbreviations: BMI, body mass index; CL/P, cleft lip with or without palate; CP, cleft palate; OFC, orofacial clefts.

^a Includes individuals who identify as Asian/Pacific Islander or Native American/Alaskan Native, and those who do not identify with any of the aforementioned categories.

^b First 2 months of pregnancy

^c One month prior to conception through 3 months after conception.

Table 2.
Association between maternal dietary patterns and orofacial clefts, National Birth Defects Prevention Study (*n* = 14 233), 1997-2011.

	<i>n</i> cases	%	<i>n</i> controls	%	aOR ^a	(95% CI)	aOR ^b	(95% CI)
CL/P								
Prudent	692	27.9	3396	32.1	REF		REF	
Western	740	29.8	2744	25.9	1.3	(1.2-1.5)	1.3	(1.2-1.5)
Low-Calorie Western	643	25.9	2802	26.5	1.1	(1.0-1.3)	1.2	(1.0-1.4)
Mexican	405	16.3	1642	15.5	1.2	(1.1-1.4)	1.1	(0.9-1.3)
CP								
Prudent	380	32.5	3396	32.1	REF		REF	
Western	356	30.5	2744	25.9	1.2	(1.0-1.4)	1.2	(1.1-1.5)
Low-Calorie Western	293	25.1	2802	26.5	0.9	(0.8-1.1)	1.0	(0.9-1.2)
Mexican	140	12.0	1642	15.5	0.8	(0.6-0.9)	0.8	(0.6-1.1)

Abbreviation: OR, odds ratio.

^a Odds ratio adjusted for energy intake.

^b Odds ratio adjusted for energy intake, age, race/ethnicity, education, supplement with folic acid, gravidity, family history of orofacial cleft, and state.