Published in final edited form as:
Arch Pediatr Adolesc Med. 2012 February ; 166(2): 121–126. doi:10.1001/archpediatrics.2011.185.

Higher diet quality reduces risks of neural tube defects and orofacial clefts

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Abstract

Objective—To examine whether better maternal diet quality was associated with reduced risk for selected birth defects.

Design—A multi-center, population-based case-control study, the National Birth Defects Prevention Study.

Setting—Ten participating centers in the United States.

Patients/Participants—Eligible subjects' estimated due dates were from October, 1997 through December, 2005. Telephone interviews were conducted with 72% of case and 67% of control mothers. Analyses included 936 cases with neural tube defects (NTDs), 2,475 with orofacial clefts, and 6,147 non-malformed controls.

Main exposures—Food-frequency data were used to calculate the Mediterranean Diet Score (MDS) and Diet Quality Index (DQI), modeled after existing indices.

Main outcome measures—Adjusted odds ratios.

Results—After covariate adjustment, increasing diet quality based on either index was associated with reduced risks for the birth defects studied. The strongest association was between anencephaly and DQI; the odds ratio (OR) for highest versus lowest quartile was 0.49 (95% CI 0.31, 0.75). ORs for cleft lip+/−cleft palate and cleft palate and DQI were also notable, with ORs = 0.66 (0.54, 0.81) and 0.74 (0.56, 0.96), respectively.

Conclusions—Healthier maternal dietary patterns, as measured by diet quality scores, were associated with reduced risks of NTDs and clefts. These results suggest that dietary approaches could lead to further reduction in risks of major birth defects and complement existing efforts to fortify foods and encourage periconceptional multivitamin use.

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INTRODUCTION

Discovery and demonstration of the effect of folic acid supplementation and food fortification in preventing neural tube defects (NTDs) is an important public health success [1]. However, folic acid does not prevent all NTDs, and in countries that have implemented folic acid fortification, NTD prevalence may be resistant to further reduction from folic acid [2,3]. Furthermore, other aspects of nutritional status may also contribute to NTD etiology, including other nutritional factors related to one-carbon metabolism, oxidative stress, and glycemic control [4–7]. It is therefore important to continue to improve our understanding of the complex contribution of nutritional status to NTD etiology. It is also important to expand such investigations to other birth defects, such as orofacial clefts, whose risk might also be affected by nutritional status[8–10].

Nutrition research on birth defects has tended to focus on one nutrient (or nutritional factor) at a time. The focus on single nutrients is a reasonable starting point. However, the reality of nutrition is much more complex. People typically eat foods, which represent composites of nutrients. These nutrients are highly correlated, making it difficult, if not impossible, to isolate truly independent effects of single nutrients outside of highly controlled trials. An exclusive focus on single nutrients also ignores the biologic interaction of nutrients inherent to most metabolic pathways.

A more holistic approach is to examine diet quality. Many indices of diet quality attempt to characterize the overall diet, typically with respect to a known set of dietary recommendations or dietary pattern. Most indices involve some combination of intake of nutrients and food groups. Historically, diet quality indices have been informative for various complex disease phenotypes. For example, indices that quantify adherence to a Mediterranean diet pattern, the DASH diet (Dietary Approaches to Stop Hypertension), or U.S. dietary recommendations have been associated with reduced risk of hypertension, cardiovascular disease, and cancer [11–15]. The association of diet quality with birth defects also merits investigation.

For the current analysis, we developed two diet quality indices that were modeled after the Mediterranean Diet Score [16,17] and the Diet Quality Index for Pregnancy [18], which focus on overall diet quality from the perspective of the Mediterranean diet and the USDA Food Guide Pyramid, respectively. We examined these indices in relation to risks for non-syndromic NTDs and orofacial clefts, using data from the National Birth Defects Prevention Study (NBDPS).

METHODS

Study design

The NBDPS is a multi-state, population-based case-control study of clinically well-defined birth defects. The study began with deliveries that had estimated due dates in October, 1997. Recruitment and data collection are on-going. The study is an approved activity of the Institutional Review Boards of the participating study centers and the Centers for Disease Control and Prevention. Detailed study methods and descriptions of surveillance systems in the ten states that contributed data to this analysis have been published[19]. In brief, seven states included liveborn, stillborn (fetal deaths >20 weeks gestation), and prenatally diagnosed and electively terminated cases (AR, CA, GA, IA, NC, TX, UT), one state included only liveborn and stillborn cases (MA), one included only liveborn cases (NJ), and one included liveborn cases from 1997–1999 and added stillborn cases in 2000 (NY).

Case review and classification

Case information was obtained from hospital reports and medical records and entered into a standardized database for clinician review and classification. Cases included infants or fetuses with anencephaly, spina bifida, cleft lip with or without cleft palate (CLP) or cleft palate alone (CP), as confirmed by clinical, surgical, or autopsy reports. Cases resulting from known single gene or chromosomal abnormalities (syndromic cases) were ineligible, given their presumed genetic determinants. Each case was also classified as isolated if there was no additional major unrelated defect or as non-isolated if there was at least one unrelated major birth defect [20]. Infants whose clefts were believed to be secondary to another defect (e.g., holoprosencephaly) were ineligible for the study.

Control selection

Each participating center randomly selected approximately 100 liveborn controls without birth defects per study year from birth certificates (AR 2000-current, GA 2001-current, IA, MA, NC, NJ, UT) or from birth hospitals (AR 1997–1999, CA, GA 1997–2000, NY, TX) to represent the population from which the cases were derived.

Maternal interviews

Maternal interviews were conducted using a standardized, computer-based questionnaire, primarily by telephone, in English or Spanish, no earlier than six weeks after the infant's estimated date of delivery and no later than 24 months after the estimated due date. Exposures to many factors were assessed, relative to the woman's estimated date of conception, which was derived by subtracting 266 days from the expected due date. Expected due date was based on self-report; if unknown, it was estimated from information in the medical record (<2%of subjects).

The current analysis included 3,824 cases and 6,807 controls with due dates from October 1997 to December 2005. Interviews were conducted with mothers of 72% of cases and 67% of controls. Median time from actual date of delivery to interview was 9.1 months for cases (interquartile range 7.3 months) and 7.5 months for controls (interquartile range 6.4 months).

Food frequency questionnaire

Mothers reported their average intake of foods using a 58-item food frequency questionnaire developed by Willett and colleagues for The Nurses Health Study [21]. Participants reported how often, on average, they consumed food items in the year before they became pregnant. For seasonal foods, such as fruits and vegetables, they averaged their intake over the six months prior to pregnancy. Foods eaten less than once a month were recorded as "never or none." Intake of breakfast cereals, sodas, food supplements and caffeinated tea and coffee were assessed by separate, more detailed questions, which covered intake during the three months before pregnancy. Because few women (mothers of 10% of cases and 10% of controls) consumed food supplements (which included items such as powdered drink supplements) and nutrient data were not available for many of these products, food supplements were not included in nutrient calculations. The USDA nutrient database (version 19) was the source of nutrient values (14), except for choline, for which USDA version 20 was used because it is more complete [22,23]. Dietary folate intake was expressed as dietary folate equivalents (DFEs), calculated by multiplying the amount of folic acid from fortified foods by 1.7 (to account for greater bioavailability), and then adding that amount to natural folate from foods.

Diet quality indices

The Mediterranean Diet Score (MDS) reflects how closely an individual's diet fits a typical Mediterranean diet as defined by Trichopoulou et al. [16,17]. The MDS is a summary of intake of six positively scored components (legumes, grains, fruits and nuts, vegetables, fish, and the ratio of mono-unsaturated to saturated fatty acid intake) and three negatively scored components (dairy, meat, and sweets). The MDS used in these analyses is different from the original in that it excludes the ethanol component but adds a sweets component, sums servings rather than grams per day to score the components, and scores components in quartiles rather than medians.

The Diet Quality Index (DQI) examines intake of specific food groups and nutrients and incorporates pregnancy-specific nutritional recommendations [18,24]. The original DQI was based on the year 2000 Dietary Guidelines for Americans and the 1992 Food Guide Pyramid [25,26]. The DQI is the summary score of six positively scored components (grains, vegetables, fruits, folate, iron, and calcium) and two negatively scored components (percent of calories from fat, and sweets). The DQI used in these analyses differs from the original in that it excludes the meal pattern component but includes a sweets component and it scores each component based on quartiles rather than absolute values.

A detailed description of the food items included in each component, how the indices differ from the originals, and how they were calculated is included in eTable 1. The objective was to mimic the original indices as closely as possible. In brief, we calculated servings per day of each food-based component, ranked each component by quartile based on the distribution among controls, and then summed the components to provide a final value for each index.

Analyses

Descriptive analyses were conducted to examine the association of the diet quality indices with each other, their components, and selected nutrients. Multivariable linear regression analyses were conducted to examine the association of the indices with selected covariates. The covariates were maternal race-ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, other); education (<, =, or > high school); prepregnancy body mass index (kg/m^2); any periconceptional alcohol drinking, smoking, or intake of folic acid-containing vitamin/mineral supplements; energy intake; and study center.

Multivariable logistic regression analyses were conducted to estimate odds ratios and 95 percent confidence intervals reflecting the association of each diet quality index with specific phenotypes. Each diet quality index was examined in categorical (quartile) and continuous form. Analyses were first adjusted for energy intake only and then also for the potential covariates listed above.

Mothers with energy intake <500 or >5,000 kcals and mothers with more than one food item missing (i.e., not queried) from the food frequency questionnaire (112 cases, 206 controls) were excluded from all analyses. Cases with both anencephaly and spina bifida were analyzed with the anencephaly group (n=3). Cases with both a NTD and an orofacial cleft were analyzed in the NTD group (n=20). We further excluded 57 cases and 40 controls whose mothers had pre-gestational diabetes from the logistic regression analyses, given that diet-phenotype associations could differ for women with diabetes. After these exclusions and restriction to subjects with complete covariate data, 936 NTDs, 2,475 clefts, and 6,147 controls were available for analyses.

For some cases, the developmental critical period for the structural malformations being studied occurred in 1997, before mandatory fortification of grain products with folic acid. We therefore re-ran final analyses after excluding these subjects (i.e., 247 cases, 472

controls with estimated dates of conception before November 1, 1997). We also re-ran final analyses after excluding women who took food supplements (355 cases in total and 631 controls), and we examined separate analyses for isolated and non-isolated CLP and CP, given potential etiologic heterogeneity.

RESULTS

Most mothers of controls were non-Hispanic white and had more than a high school education; 19% smoked, 38% drank alcohol, and 78% took folic acid-containing supplements during early pregnancy; and 16% were obese (Table 1). Frequencies of these characteristics among cases are also in Table 1.

The 10^{th}, 25^{th}, 50^{th}, 75^{th} and 90^{th} percentiles were 8, 11, 13, 16 and 18 for the MDS and 5, 8, 12, 16 and 19 for the DQI. The respective ranges were 2–25 and 0–24. The mean (SD) of the MDS was 13.2 (3.8), and for the DQI it was 12.0 (5.2). The correlation of the two indices with each other was 0.53. Correlations of each index with its components were in the expected directions (eTable 2). They ranged from −0.26 to 0.48 for the MDS and from −0.36 to 0.69 for the DQI. Correlations with single nutrient categories tended to be substantially higher for the DQI than the MDS; e.g., the correlations with energy intake were 0.58 and 0.15, respectively.

Women who were Hispanic had substantially higher values for the DQI and the MDS, whereas values were lower among women with less education and women who smoked, did not take supplements, or were obese, even after adjusting all these factors for each other (eTable 3).

We observed reduced birth defect risks associated with higher dietary quality scores (Table 2). That is, after adjusting for all covariates, increasing diet quality based on either index was associated with reduced risk of each birth defect studied. The strongest associations were observed for anencephaly. The odds ratio for the highest versus lowest quartile was 0.64 (95% CI 0.45, 0.92) for the MDS and 0.49 (0.31, 0.75) for the DQI. Based on continuous specifications of the indices, the odds ratio reflecting a difference comparable to the 90^{th} versus 10^{th} percentiles of the MDS (i.e., 18 versus 8) was 0.70 (95% CI 0.49, 0.99), and for the DQI (i.e., 19 vs. 5) it was 0.45 (95% CI 0.30, 0.68). Odds ratios for the categorical and continuous specifications of both indices produced confidence intervals that excluded one for CLP but were closer to one than for anencephaly. Odds ratios for the continuous specification of the DQI and spina bifida and CP also had confidence intervals that excluded one.

Results were similar after excluding subjects with dates of conception before November 1, 1997 or subjects who consumed food supplements (data not shown). Results for non-isolated CLP and CP tended to be of a similar magnitude but less precise than results for isolated CLP and CP, likely due to smaller numbers of non-isolated cases. Odds ratios adjusted only for energy intake tended to be similar to or closer to 1.0 than odds ratios adjusted for all covariates (data not shown).

DISCUSSION

Based on two diet quality indices, higher maternal diet quality in the year before pregnancy was associated with lower risks for NTDs and orofacial clefts. This finding persisted even after adjusting for multiple potential confounders such as maternal intake of vitamin/mineral supplements. These results are notable because previous analyses from this same study, the NBDPS, which assessed single nutrient intakes in isolation, had not been informative. In particular, maternal intake of folic acid-containing vitamin/mineral supplements was not

associated in the NBDPS with a reduced risk of NTDs, and findings for dietary folate intake were inconsistent [2]. Similarly, maternal supplement intake was not associated with reduced risk of orofacial clefts, and findings did not suggest associations with multiple dietary nutrients that were examined, including folate [10]. Thus, the findings from this study suggest that overall diet quality is more predictive of birth defect risk than intake of single nutrients.

Few studies have examined diet quality as a predictor of birth defect risks. One small study suggested better diet quality based on food groups was protective against NTDs [27,28]. A more recent study suggested that better diet quality, using an index based on intake of several nutrients, was protective, independent of folic acid intake [29]. A study of Dutch women observed that healthier dietary patterns, which were derived from principal components analyses of food groups, were protective against spina bifida and orofacial clefts, independent of intake of folic acid-containing supplements [30,31].

For the current study, we defined indices of overall diet quality *a priori*, based on existing, validated indices [12,32]. An *a priori* approach has the advantage of being more easily replicated than a data-driven approach. The NBDPS used a version of the Willett food frequency questionnaire that was shortened and included few questions to differentiate types of fat and refined versus unrefined grain consumption, all of which may have reduced the ability of the indices to discriminate between better and worse diet quality. Our analyses, as well as previously published results, demonstrate the content validity of the indices, with higher values being associated with higher intake or serum levels of nutrients and other selected biomarkers [12]. However, there is no single “gold standard” for comparison, so fully assessing the validity of these indices is somewhat challenging. In addition, we could not specifically validate the modifications we made to the existing indices. A potential limitation of our indices is that each component gets the same weight; in the absence of knowledge regarding which components may deserve greater or lesser weight, we believe this is reasonable. Why Hispanic mothers tended to score higher in diet quality is unclear. Some studies have suggested better nutrient intakes among Hispanics, especially those who are less acculturated [33–35]. However, adjustment for race-ethnicity did not substantially alter the reported risk estimates.

Strengths of the current study include the rigorous, population-based design and careful case ascertainment. Potential limitations include recall bias, selection bias, and residual confounding. Previous studies suggest that for many chronic exposures, recall bias is likely to be minimal in studies of birth defects [36–38]. Also, it is unlikely that systematic recall bias would occur for a complex exposure like dietary intake. We were unable to validate women’s reported dietary intake. However, previous studies have demonstrated good validity and reliability of the instrument when used in other populations [21,39]. A comparison of characteristics of participants with non-participants was not possible, although a comparison using earlier data from this study suggested that controls were generally representative of the base population [40]. Women excluded from our analyses due to missing data were more likely to be Hispanic and have lower education, but this was true of cases and controls. We expect that our findings could be generalizable beyond our study population because of the study’s population-based design, active case ascertainment, and the racial-ethnic, geographic and socioeconomic diversity. Our analyses were adjusted for multiple potential confounders; adjustment for them did not markedly affect results, but at least a portion of the observed associations may be attributable to unmeasured confounders. Another limitation is that women reported diet during the year before pregnancy, which would not capture dietary changes in early pregnancy (e.g., due to nausea and vomiting). However, symptoms such as nausea and vomiting often do not start until several weeks after conception, at which time the neural tube would have closed. This limitation has greater

potential to impact cleft lip or cleft palate, which can occur through a longer period of development, 4–6 weeks after the neural tube closes.

The diet quality approach focuses on the combined effects of multiple nutrients and food constituents as evaluated through a single index. Our finding that maternal diet quality was more strongly associated with reductions in risks of NTDs and orofacial clefts than previous analyses from the NBDPS of maternal intake of single nutrients [2,10] supports the proposition that the combined effects may be greater than the sum of individual nutrient effects.

Although the focus on folic acid has enabled substantial reductions in the prevalence of NTDs and perhaps other birth defects, the population burden of birth defects remains extensive. If increased diet quality can indeed have a greater impact than individual nutrients, appropriate public health messages may need to be developed that convey this broader perspective.

Acknowledgments

We thank the California Department of Public Health Maternal Child and Adolescent Health Division for providing data. This project was partially supported by NIH R01 NS050249 and R03DE020112 and CDC 6U01-DD-000489 and 1U01-DD-0006982. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the California Department of Public Health.

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Table 1

Descriptive characteristics of case and control infants, National Birth Defects Prevention Study, 1997–2005.

	Percent[1]				
	Anencephaly (n=291)	**Spina Bifida (n=645)**	**CLP (n=1622)**	**CP (n=853)**	**Controls (n=6147)**
Race-ethnicity					
Non-Hispanic white	53	58	65	67	63
Black	8	9	6	8	12
Hispanic	31	28	23	18	19
Other	8	6	7	7	6
Education					
Less than high school	19	16	17	14	14
Equal to high school	28	29	28	28	25
Greater than high school	53	55	54	58	61
Smoking[2]					
None	87	81	74	76	81
Any	13	19	26	24	19
Drinking[2]					
None	70	66	61	59	62
Any	30	34	39	41	38
Folic acid-containing vitamin/mineral supplement use[2]					
None	21	24	23	22	22
Any	79	76	77	78	78
Body mass index (kg/m^2)					
Underweight (<18.5)	7	4	8	6	6
Normal weight (18.5–24.9)	54	46	53	52	56
Overweight (25.0–29.9)	23	24	22	23	22
Obesity (>=30.0)	17	26	17	19	16

[1] Numbers may not add to 100% due to rounding.

[2] From one month before through two months after conception.

Table 2

Association of neural tube defects and orofacial clefts with the Mediterranean Diet Score (MDS) and Diet Quality Index (DQI).

	Adjusted odds ratio (95 percent confidence interval)[1]			
MDS	**Anencephaly (n= 291)**	**Spina Bifida (n=645)**	**CLP (n=1622)**	**Cleft Palate (n=853)**
Quartile 1 (2–10)	Reference	Reference	Reference	Reference
Quartile 2 (11–12)	0.69 (0.48,1.00)	0.96 (0.75,1.23)	0.75 (0.64,0.89)	0.82 (0.66,1.01)
Quartile 3 (13–15)	0.83 (0.60,1.15)	1.05 (0.83,1.32)	0.89 (0.76,1.03)	1.06 (0.87,1.29)
Quartile 4 (16–25)	0.64 (0.45,0.92)	0.88 (0.68,1.13)	0.76 (0.64,0.90)	0.83 (0.67,1.04)
Continuous (90^{th} vs. 10^{th} percentile)[2]	0.70 (0.49,0.99)	0.93 (0.73,1.18)	0.79 (0.67,0.93)	0.92 (0.75,1.14)
DQI				
Quartile 1 (0–8)	Reference	Reference	Reference	Reference
Quartile 2 (9–12)	0.71 (0.51,0.99)	0.94 (0.75,1.18)	0.90 (0.77,1.04)	0.97 (0.80,1.19)
Quartile 3 (13–16)	0.68 (0.48,0.95)	0.89 (0.70,1.14)	0.79 (0.67,0.93)	1.01 (0.82,1.24)
Quartile 4 (17–24)	0.49 (0.31,0.75)	0.80 (0.60,1.08)	0.66 (0.54,0.81)	0.74 (0.56,0.96)
Continuous (90^{th} vs. 10^{th} percentile)[2]	0.45 (0.30,0.68)	0.72 (0.54,0.95)	0.64 (0.53,0.77)	0.77 (0.60,0.99)

[1] Adjusted for maternal energy intake, race-ethnicity (white, black, Hispanic, other), body mass index (kg/m2), education (<, =, or > high school), study center (AR, CA, GA, IA, MA, NC, NJ, NY, TX, UT), and any drinking, smoking, and intake of folic acid-containing vitamin/mineral supplements during the month before pregnancy or the first two months of pregnancy. Analyses included the 6,147 controls who did not have pre-gestational diabetes.

[2] The 90^{th} versus 10^{th} percentile represents a 10-unit change for the MDS (18 vs. 8) and a 14-unit change for the DQI (19 vs. 5).

CLP = cleft lip with or without cleft palate; CP=cleft palate