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Maternal Dietary Patterns and Risk of Isolated Cleft Birth Defects in Utah - A Case-Control Study

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MATERNAL DIETARY PATTERNS AND RISK OF ISOLATED CLEFT LIP WITH OR WITHOUT CLEFT PALATE IN UTAH: A CASE—CONTROL STUDY.

by

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ABSTRACT

MATERNAL DIETARY PATTERNS AND RISK OF ISOLATED CLEFT LIP WITH OR WITHOUT CLEFT
PALATE IN UTAH: A CASE—CONTROL STUDY.

By

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Inadequate maternal nutrition during pregnancy has been suggested as a risk factor for
oral cleft birth defects including the major groupings of cleft lip with or without cleft palate
(CL/P), and cleft palate alone (CP). Few studies have analyzed overall dietary patterns in
relation to development of oral clefts. The purpose of this study is to examine the statistical
associations between maternal dietary pattern scores and risk of oral clefts in Utah.

Data collected from the Utah Oral Cleft Study was used as a starting point. New
variables were formed to define maternal dietary patterns using the SPSS statistical analysis
program. Derived dietary pattern variables were compared among mothers of Utah children
with oral clefts (445 cases) and mothers of unaffected children (410 controls); these included
scores based on intake of the following groups of foods: fruits, vegetables, whole grains, low-fat
dairy foods, and an overall diet score based on the DASH dietary intervention studies. Logistic
regression analyses were used to estimate the risk of oral clefts by quintile of the food group
and DASH scores while controlling for the potential confounding effects of maternal age,
education, smoking and alcohol use during pregnancy, and multivitamin use during pregnancy.

Logistic regression analysis indicated a 40% reduction in risk of oral clefts (CL/P and CP
combined) (OR=0.60) in mothers in the highest vs. lowest quintile of whole grain intake. The

DASH dietary score was not significantly associated with risk of oral clefts. Periconceptional

exposure to tobacco smoke and education levels were also associated with risk of CL/P.

Periconceptional dietary intake of whole grains may significantly reduce incidence of

isolated CLP in the offspring.

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INTRODUCTION

Evidence is increasing that nutrition plays a significant role in the development and prevention of birth defects, including orofacial clefts (OFCs). In this respect, it is important to address that during pregnancy, specifically during the development of the lip and palate, the embryonic nutritional status is fully dependant on maternal food intake and metabolism. Due to increased needs, inadequate intake, decreased absorption, disturbances in embryonic transfer, or underlying genetic aberrations in the mother or embryo or both, maternal nutritional deficiencies during pregnancy may significantly affect the nutritional status of the embryo and gene expression and other developmental events in specific embryonic tissues (1).

BACKGROUND

Cleft Lip and Palate

OFCs including cleft lip and/or palate (CL/P) are congenital malformations occurring during the embryonic period of development, which results in a fissure in the lip and roof of the mouth (2). OFCs are among the most common birth defects with varying birth prevalence rates among populations, gender, and geographic region (3). Children born with this birth defect must undergo several treatments by various specialists, which can greatly affect their lives. OFCs generally require surgical repair, and often multiple surgeries are needed to reconstruct the lip and palate. Other health and medical problems are also associated with OFCs including feeding problems, ear infections, speech problems, and dental or orthodontic problems (4).

At the time of conception and during the first trimester, the mother's nutritional status is important in the development of the lip and palate, as well as other craniofacial structures of the fetus (5). During this critical stage of development, several key nutrients have been

implicated in the development of OFCs, some of which are folic acid, vitamin B-12, vitamin B-6, and zinc (5). In addition to adequate nutrition of the mother, environmental and behavioral factors such as poverty, smoking, and alcohol use have been shown to significantly increase the risk of birth defects, including OFCs (6).

Folic Acid

Folate, as a one-carbon donor, is involved in the biosynthesis of purines and pyrimidines and in homocysteine remethylation producing methyl groups for methylation of DNA, which is important for gene expression (7).   The methylenetetrahydrofolate reductase (MTHFR) gene involved in the metabolism of folate is an example of OFC risk modification. The MTHFR enzyme catalyzes the conversion of 5, 10-methylenetetrahydrofolate to 5-methyltetrahydrofolate, an irreversible step, which is the predominant form of folate and the methyl donor for the remethylation of homocysteine into methionine (Fig. 1). Polymorphisms in MTHFR lead to increased levels of homocysteine, which has been associated with increased risk of OFCs (8).

Humans are dependent on dietary sources of folate. Major contributors are bread, cereals, fruits, vegetables, and liver (7).

Vitamin B-12

The only dietary sources of vitamin B-12 for humans, other than supplements, are from animal or fortified products. Vitamin B-12 functions as an essential coenzyme in the conversion of homocysteine into methionine. Because the formation of 5-methyl THF is irreversible, a deficiency of vitamin B-12 traps body folate in the 5-methyl form, which is known as the methyl-folate trap hypothesis (Fig. 1). This trapping leads to increased homocysteine levels and

Figure 1—Re-methylation of homocysteine into methionine.
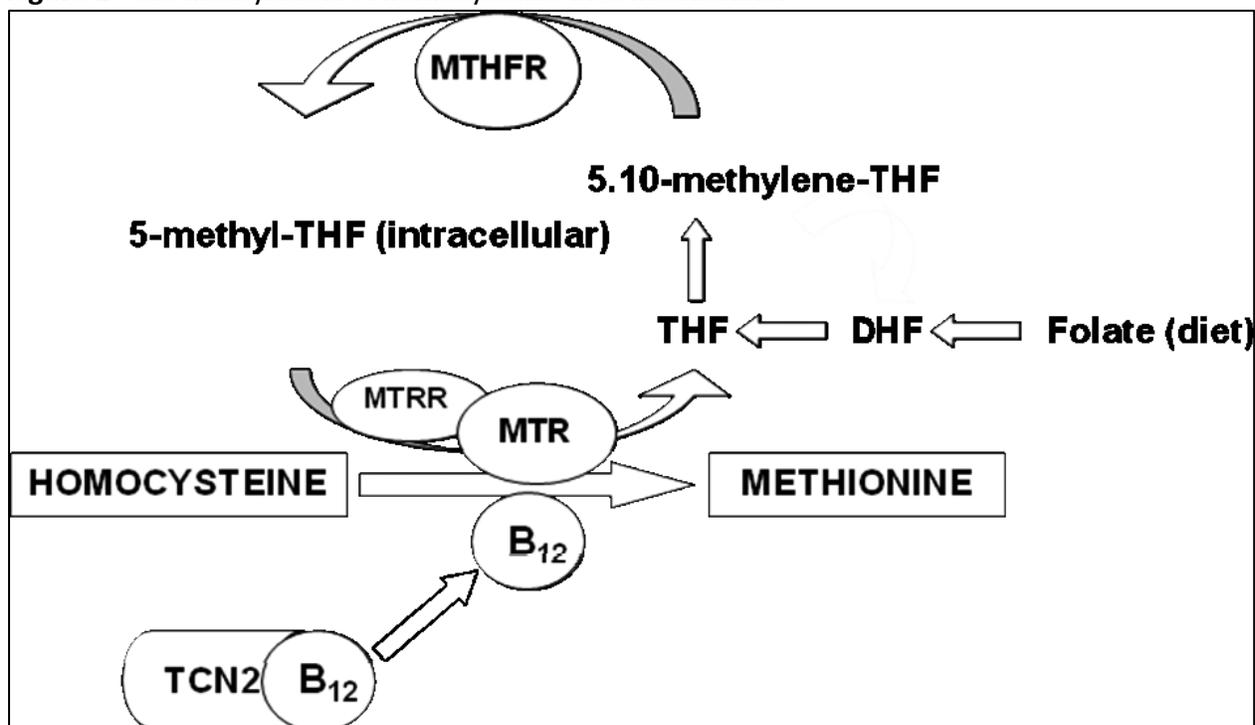
DHF, dihydrofolate; THF, tetrahydrofolate; MTHFR, 5,10-methylenetetrahydrofolate reductase; MTRR, methionine synthase reductase; MTR, methionine synthase; TCN2, transcobalamin II (10)

decreased methylation of DNA, which is important in the regulation of gene activity. An inadequate amount of methionine caused by lack of vitamin B-12 decreases the availability of S-adenosyl methionine (SAM). SAM is required for methylation reactions, which are also essential for myelin maintenance and thus neural function (9).

Vitamin B-6

Along with vitamin B-12, vitamin B-6 also plays a key role in the metabolism of folate and homocysteine. Vitamin B-6 is known to protect against OFCs induced in laboratory animals by teratogens, and deficiency alone was sufficient to cause OFCs in mice (5). A case-control study in the Philippines evaluated the association between the risk for CL/P and maternal vitamin B-6 status. The study concluded that inadequate vitamin B-6 status was associated

with an increased risk for CL/P (11). Food sources other than supplements rich in vitamin B-6 include meats, whole grain products, vegetables, some fruits, and nuts. Fortified cereals also represent a major contributor of vitamin B-6 in the diet (9).

Zinc

Zinc is of interest because of its role in the absorption of folate. A study in the Netherlands demonstrated that mothers of children of CL/P had lower erythrocyte zinc concentrations than control mothers (12).   Polyglutamate hydrolase is a zinc-dependant enzyme necessary for the digestion of folate in the gastrointestinal tract. In addition, zinc is involved in the conversion of 5-methyltetrahydrofolate into tetrahydrofolate by the zinc-dependant methionine synthase enzyme. Thus, poor zinc intake or status can diminish folate absorption (9). Zinc is typically associated with the protein fraction of foods. Therefore, rich sources of this nutrient are found in animal products, predominately red meats and seafood. However, whole grains and vegetables represent good plant sources of zinc (9).

Although single source nutrients have shown to be significant in the reduction of clefting in animal models, there have been very few studies of these associations in human studies and far fewer studies of overall diet patterns among mothers and the risk for development of OFCs in the child. Comprehensive dietary variables that are defined by the intake of many foods may show a greater effect on disease than any single nutritional component (13). For this reason, the identification of maternal dietary patterns has become of considerable interest and has been related to cardiovascular disease, type 2 diabetes, and cancer. However, data on maternal dietary patterns and birth defects are lacking (3).

Characteristics of the DASH Diet

The Dietary Approaches to Stop Hypertension (DASH)-sodium trail was a multicenter, randomized, controlled-feeding trial comparing the effects of three levels of sodium and two dietary patterns on blood pressure. Table 1 shows the food groups and the recommended servings emphasized in the DASH diet. The DASH diet demonstrated a diet that emphasizes fruits, vegetables, and low-fat dairy products, including whole grains, poultry, fish, and nuts; that contains only small amounts of red meat, sweets, and sugar-containing beverages; and that contains decreased amounts of total and saturated fat and cholesterol lowers blood pressure substantially both in people with hypertension and those without hypertension, as compared with a typical diet in the United States (14).

Table 1. DASH diet components

Food groups	Servings
Whole grains	6-8 a day
Fruits and vegetables	8-10 a day
Fat-free or low-fat dairy	2-3 a day
Lean meats, poultry and fish	6 or fewer a day
Nuts, seeds and beans	4-5 a week
Fats and oils	2-3 a day
Sweets	5 or fewer a week
Sodium	1500-2400 mg a day

Researchers from the American Dietetic Association analyzed the various food groups in the two dietary patterns used in the DASH-sodium trial: a control diet, which is similar to what many Americans eat and the DASH diet as described earlier. The aim of the analyses was to identify major food group sources of several essential nutrients of the two dietary patterns. These sources are summarized in Table 2 (15).

DASH Diet in Comparison to Control Diet

Energy

Whole grains, fruits and juices, and low-fat dairy products were the top three sources of energy in the DASH diet contributing to more than half of the total energy intake. In the control diet, the major source of energy came from refined grains; fats, oils, and dressings; and sweets and candies. These top three sources all together contributed more than two-thirds of the total energy intake (15).

Carbohydrate

Two-thirds of the total carbohydrate intake contributed to whole grains and fruits and juices and one-third came from low-fat dairy products, vegetables, and refined grains. In the control diet, refined grains made up nearly half of the total carbohydrate intake, followed by sweets and candies, fruit juices, and vegetables (15).

Zinc

The most important food group sources of zinc for the DASH diet were the whole grains; low-fat dairy products; vegetables; red meats; and nuts, seeds, and legumes. The most important food group sources of zinc for the control diet were red meats, refined grains, and poultry (15).

Table 2. Top food sources of energy, carbohydrates, zinc, and folate.

	CONTROL (top sources)	DASH (top sources)
Energy	Refined grains; fats, oils, dressings; sweets and candies.	Whole grains, fruits and juices, low-fat dairy products.
Carbohydrate	Refined grains; sweets and candies; fruits, and fruit juices; vegetables.	Whole grains, fruits and fruit juices.
Zinc	Red meats, refined grains, and poultry	Whole grains; low-fat dairy products; vegetables; red meats; nuts, seeds, legumes
Folate	Refined grains; vegetables; sweets and candies; red meats.	Vegetables, fruits and juices, whole grains.

Folate

For the DASH diet, the top three food group sources of folate were vegetables, fruits and juices, and whole grains, contributing to 78% of total intake. Low-fat dairy products, refined grains, nuts, seeds, and legumes also were important contributors of folate in the DASH diet. For the control diet, refined grains contributed more than half of the total intake, followed by vegetables, sweets and candies, and red meats (15).

Studying Dietary Patterns vs. Single Source Nutrients

In nutritional epidemiology, traditional analyses typically examine diseases in relation to a single or a few nutrients or foods. Although this type of analysis has been quite valuable, it has several limitations. First, people do not eat isolated nutrients. Instead, they eat meals consisting of a variety of foods with complex combinations of nutrients that are likely to be interactive or synergistic. Second, the high level of intercorrelation among nutrients makes it difficult to examine their separate effects. Third, the effect of a single nutrient may be too small to detect, but the cumulative effects of multiple nutrients in a dietary pattern may be

sufficiently large to be detectable. Finally, because nutrient intakes are commonly associated with certain dietary patterns, single nutrient analysis may be confounded by the effect of dietary patterns (16).

Turning the focus to studying diet patterns rather than single nutrients could provide professionals guidance for nutrition intervention while also resulting in important public health implications because the general patterns of dietary intake might be easier for the public to translate into diets.

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ABSTRACT

Inadequate maternal nutrition during pregnancy has been suggested as a risk factor for OFCs including the major groupings of cleft lip with or without cleft palate (CL/P), and cleft palate alone (CP). Few studies have analyzed overall dietary patterns in relation to development of OFCs. The purpose of this research is to examine the statistical associations between maternal dietary pattern scores and risk of OFCs.

Data collected from the Utah Oral Cleft Study was used as a starting point. New variables were formed to define maternal dietary patterns using the SPSS statistical analysis program. Derived dietary pattern variables were compared among mothers of Utah children with OFCs (411 cases) and mothers of unaffected children (636 controls); these included scores based on intake of the following groups of foods: fruits, vegetables, whole grains, low-fat dairy foods, sweets, and an overall diet score based on the DASH dietary intervention studies. Logistic regression analyses were used to estimate the risk of oral clefts by tertile of the food

group and DASH scores while controlling for the potential confounding effects of maternal age, education, smoking and alcohol use during pregnancy, and multivitamin use during pregnancy.

Logistic regression analysis indicated a 40% reduction in risk of OFCs (CL/P and CP combined) (OR=0.60) in mothers in the highest vs. lowest quintile of whole grain intake. The DASH dietary score was not significantly associated with risk of OFCs. Periconceptional exposure to tobacco smoke and education levels were also associated with risk of CL/P.

MATERIALS and METHODS

Participants

A starting point for this investigation began with collected data obtained from the Utah Oral Cleft Study, which was a case-control study conducted in Utah during 2000-2005 to identify genetic and environmental factors, including nutrition, which may be associated with the risk of OFCs. This study was conducted in collaboration with the Utah Birth Defects Network (UBDN), a state-wide birth defects registry operated by the Utah Department of Health.   This study was approved by the Institutional Review Boards of Utah State University, the University of Utah, and the University of Alabama at Birmingham. Each mother provided a written consent for contact by study investigators. Case-mothers were defined as Utah residents with a child liveborn or stillborn with an OFC between January 1995 and June 2005. OFCs and other malformations were classified after review of the UBDN records by a geneticist. Cases were categorized into: (1) isolated cleft lip with or without cleft palate (CL/P-I); (2) isolated cleft palate (CP-I); (3) CL/P with other malformations (CL/P-M); and (4) CP with other malformations (CP-M). In the present analyses only cases with isolated OFCs were evaluated because this is a more homogenous group than cases of OFCs in the presence of multiple birth

defects in other anatomic sites. Control mothers were randomly selected using Utah birth

certificate files by frequency matching births by month and year and child gender to cases.

Between June 2000 and November 2005, mothers were interviewed, and a food frequency

questionnaire (FFQ) based on the Nurse's Health Study was included in the interview along with

questions on demographic characteristics of the mother and history of supplement, tobacco,

and alcohol use.

Developing the DASH Scores

The development of the DASH Scores was provided by researchers from Utah State

University Nutrition and Food Science Department (17). Scores were based on nine food

categories selected to represent food groups targeted in the DASH diet: High fruit, vegetable

(no potatoes), nut/legume, whole grain, fish and low-fat dairy; and low sodium, meat, and

sweets and sweetened beverage (15). Individuals were assigned a food component score by

using quintiles cut-offs of the cohort-specific nutrient component distribution of intake. After

food groups in servings per day were calculated, the food groups were energy adjusted using

the willet regression method and then transformed into quintiles of intake (18). Food groups

were then assigned a point value. Low intake of fruits, vegetables, nuts/legumes, whole grains,

fish, low-fat dairy and high intake of sodium, meat, and sweets/sweetened beverages received

lower scores on a 1-5 point scales; and high intake of fruit, vegetables, nuts/legumes, whole

grains, low-fat dairy and low intake of sodium, red/processed meat, and sweetened beverages

received higher scores on 1-5 point scales. Scores for all nine groups were then totaled highest

possible points 45 and lowest 9. The total score was also binned or transformed into quintiles

and used to look at descriptive statistics and outcome of OFCs.

Statistical Analyses

New variables were formed to define maternal dietary patterns using the SPSS statistical analysis program (19). Derived dietary pattern variables were compared among mothers of Utah children with OFCs (411 cases) and mothers of unaffected children (636 controls); these included scores based on intake of the following groups of foods: fruits, vegetables, whole grains, low-fat dairy foods, sweets, and an overall diet score developed based on the Dietary Approaches to Stop Hypertension (DASH) intervention studies. The means of continuous variables were compared between cases and controls using analysis of variance, and categorical variables were evaluated with the chi-squared test. Tertiles of whole grain intake were defined by the distribution of values of isolated OFC cases and controls combined. Odd Ratios (OR) and 95% confidence interval (CI) were calculated in logistic-regression models with composition of potential confounding factors such as maternal age, education, smoking and alcohol use during pregnancy, and multivitamin use during pregnancy. Adjusted ORs for risk of OFCs were calculated across increasing whole grain intake tertiles with the lowest tertile as the reference. Analysis of risk of isolated OFCs by tertiles were stratified by whole grain intake (<20th percentile, 20th-80th percentile, >80th percentile) to evaluate whether risk of isolated OFCs varied over these intervals. The present analyses were limited to mothers of children with isolated OFCs because this group of birth defects is more homogenous than OFCs that occur with multiple birth defects in other sites.

RESULTS

Demographic information and food intake were available for (1) 313 CL/P-I case mothers; (2) 98 CP-I case mothers; (3) 411 CL/P-I and CP-I case mothers combined; and (4) 636

Table 3. Descriptive analysis (mean ± SD) of continuous variables of case mothers of children with CL/P-I, CP-I, and CL/P-I and CP-I, and control mothers.

	Controls n = 636	CL/P-I n = 313	CP-I n= 98	CL/P-I, CP-I n= 411
Maternal age at delivery, y	26.8 ± 5.2	26.9 ± 5.6	27.1 ± 5.6	26.8 ± 5.6
Maternal weight (kg)	66.5 ± 14.8	67.0 ± 15.4	66.3 ± 16.1	66.8 ± 15.53
Height of mother (cm)	165.6 ± 6.71	165.4 ± 7.5	164.3 ± 6.5	165 ± 7.27
BMI of mother at conception	24.3 ± 5.3	24.4 ± 4.9	24.6 ± 5.9	24.5 ± 5.12

control mothers. Average ethnic/racial composition of all subjects was 88% Caucasian and 6% Hispanic/Latino, and the remaining were Asians, Native Americans, and African Americans (Table 3). The overall maternal mean age at delivery of the child was similar for case and control mothers (26.8 years old). In general, all four groups of mothers showed similar characteristics including maternal weight, height, and body mass index (BMI) that could have affected outcome of pregnancy (20). Rates of smoking were higher in case mothers than in control mothers (p = .03), and alcohol use during pregnancy was not significantly different for cases and controls (p = .54). Maternal levels of education were significantly lower in case mothers than controls (p = <.01). Use of multivitamins during pregnancy was common but not significantly different between cases and controls (Table 4).

Mean intake of the fruit, vegetable, and low-fat dairy food groups were similar among cases and controls. However, intake from the whole grain food group were significantly lower among case mothers than in control mothers in CL/P-I (p = .02) and CL/P-I and CP-I combined (p = .007). Furthermore, intake from the sweets food group among cases were significantly higher than in controls for CL/P-I (p = .02) and CL/P-I and CP-I combined (p=.03). Overall DASH

score was not significantly different among mothers of CL/P-I and CP-I compared to control

mothers, however, case mothers in the CL/P-I and CP-I combined group had a lower DASH

score (p = .02) than in control mothers (Table 5).

Table 4. Descriptive analysis (mean ± SD) of categorical variables of case mothers of children with CL/P-I, CP-I, and CL/P-I and CP-I and control mothers.

	Controls n =636	CL/P-I n =313	CP-I n= 98	CL/P-I, CP-I n = 411
Mother's ethnicity (%)				
• Caucasian	89.5	86.6	88.8	87.1
• Hispanic/Latino	5.4	8.0	4.1	7.1
• Other	5.1	5.4	7.1	5.8
Maternal education at 2 levels (%)				
• Some college to graduate degree	72.5	60.7	67.3	62.3
• No college	27.5	39.3	32.7	37.7
Mothers exposure to tobacco smoke (%)				
• Not exposed (periconception or 1st tri)	79.9	71.8	78.6	73.4
• Ever smoker or passive smoker	9.7	13.1	7.1	11.7
• Smoked (periconception or 1st tri)	10.4	15.1	14.3	14.9
Mothers exposure to alcohol (periconception period)				
• Never	85.7	83.7	83.7	83.7
• Former drinker	8.0	10.2	9.2	10.0
• Drank in periconceptional period	6.3	6.1	7.1	6.3
Multivitamin use during pregnancy				
• No vitamin use	9.3	9.6	8.2	9.2
• Some vitamin use	90.7	90.4	91.8	90.8

Table 5. Mean food group servings and DASH scores based on 1000 kcals per day of case mothers of children with CL/P-I, CP-I, and CL/P-I and CP-I compared to control mothers.

Food Group/ Scores (svgs/1000 kcals)	Controls n =636	CL/P-I n =313	CP-I n= 98	CL/P-I, CP-I n = 411
Fruits	1.0	0.98	0.99	0.98
Vegetables	1.5	1.4	1.3	1.3
Whole Grains	0.4	0.3*	0.3	0.3*
Low-Fat Dairy	0.8	0.7	0.8	0.8
Sweets	0.7	0.8*	0.8	0.8*
DASH Score	30.2	29.4	29.2	29.4*

*P-value <.05

Table 6. Odds ratio and 95% CI of CL/P-I and CP-I by level of whole grain intake.

Level of Intake of Whole Grains	Odds Ratio	95% Confidence interval
Low <20% (0-0.6 Svgs/1000 Kcal	1.0	(reference)
Middle 20-80% (0.6-0.59 Svgs/1000 Kcal	0.81	(0.65-1.20)
High >80% (0.59-3.05 Svgs/1000 Kcal	0.60	(0.47-0.95)

After adjusting for maternal age, education, smoking and alcohol, and multivitamin use during pregnancy, the ORs for developing isolated OFCs were calculated according to increasing tertiles of whole grain intake with the lowest tertile as the reference. The risk of having a child with an isolated OFCs declined in a strong dose response manner with increasing tertile of whole grain intake (tertile 1 = reference; tertile 2: OR = 0.81, 95% CI = 0.65-1.20; tertile 3: OR = 0.6, 95% CI = 0.47-0.95). This pattern was observed for the sub-groups of CL/P-I and CP-I combined (Table 6).

DISCUSSION

We found   that a lower whole grain intake of mothers was associated with a higher isolated OFC risk in their children. The strongest finding was that increased intake of whole grains were associated with a reduced risk of isolated OFCs in a strong dose response manner. Furthermore, higher intakes of sweets were weakly associated and more statistically significant among case mothers than that of control mothers in CL/P-I as well as the CL/P-I and CP-I combined group.   These findings indicate that increased intake of whole grains along with decreased consumption of sweets during pregnancy may reduce the risk of OFCs in the offspring.

Limitations of the study include the potential for recall bias due to retrospective data. However, using a prospective approach in collecting data before pregnancy would be extremely

difficult because of the large sample size required as well as the high cost of this type of study. In addition, the findings of this study in regards to dietary patterns may not be applicable to other populations. Dietary patterns are likely to vary according to socioeconomic status, ethnic group and culture; therefore, it is necessary to replicate the results in diverse populations. Another limitation is that whole grain intake may be positively correlated with other healthy dietary patterns or lifestyle patterns, thus the causal nature of this association is uncertain. Whole grain intake may also be negatively correlated with unhealthy dietary patterns such as sugary snacks and sweets that may have a role in oral clefts. Despite these limitations, the strengths of the study include the state-wide, populations-based ascertainment of cases via a birth defects registry. Controls were obtained using all Utah births that were free of OFCs from the same time period as the sampling frame. Furthermore, participation rates were reasonably high due to active recruitment of participants through multiple methods.

CONCLUSION

This study demonstrates differences in the dietary intake of food groups and lifestyle factors in mothers of isolated OFC children compared with controls. Of particular interest is the protective effect of a higher whole grain intake and lower sweet intake on isolated OFC risk. These data may suggest that periconceptional dietary intake of whole grains is inversely associated with risk of OFC birth defects in Utah including isolated cleft lip, with or without cleft palate and cleft palate alone.

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AUTHOR'S BIOGRAPHY

Tara Finnerty began her college education by completing a two-year Associate's degree from Salt Lake Community College. From the beginning of her education, Tara has always found a great interest in health and nutrition. As a Presidential Scholar, she transferred to Utah State University as a Nutrition and Food Science Major with an emphasis in Dietetics. During her 3-year education at USU, Tara served two years as an Ambassador for the College of Agriculture and spent one month as a Nutrition Study Abroad student in Lima, Peru. During this time, Tara has also conducted and taught a monthly kids cooking class at Hamilton's Steak and Seafood Restaurant where she instructed children between the ages of seven to eleven years old how to cook and have fun with food.

After graduation, Tara will complete a seven month internship for the USU Dietetic Internship Program, and from there on hopes to continue her education for a Master's of Science Degree.