Title

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Journal

Cancer Causes & Control, 27(7)

ISSN

0957-5243

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Publication Date

2016-07-01

DOI

10.1007/s10552-016-0773-y

Peer reviewed

HHS Public Access

Author manuscript

Cancer Causes Control. Author manuscript; available in PMC 2017 July 01.

Published in final edited form as:

Cancer Causes Control. 2016 July ; 27(7): 929–940. doi:10.1007/s10552-016-0773-y.

Maternal prenatal intake of one-carbon metabolism nutrients and risk of childhood leukemia

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Abstract

Purpose—Folate, vitamins B12 and B6, riboflavin, and methionine are critical nutrients for the one-carbon metabolism cycle involved in DNA synthesis and epigenetic processes. We examined the association between maternal intake of these nutrients before pregnancy and risk of childhood acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) in a matched case-control study.

Methods—Maternal dietary intake and vitamin supplement use in the year before pregnancy was assessed by food frequency questionnaire for 681 ALL cases, 103 AML cases, and 1,076 controls. Principal components analysis was used to construct a variable representing combined nutrient intake, and conditional logistic regression estimated the odds ratio (OR) and 95% confidence interval (CI) for the association of ALL and AML with the principal component and each nutrient.

Results—Higher maternal intake of one-carbon metabolism nutrients from food and supplements combined was associated with reduced risk of ALL (OR for one-unit change in the principal component=0.91, CI 0.84–0.99) and possibly AML (OR for the principal component=0.83, CI 0.66–1.04). When analyzed separately, intake of supplements high in these nutrients was associated with a reduced risk of ALL in children of Hispanic women only.

Conclusions—In conclusion, these data suggest that higher maternal intake of one-carbon metabolism nutrients may reduce risk of childhood leukemia.

Keywords

cancer risk; case/control; micronutrients; epidemiology; methyl donors

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Ethical Approval: All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Conflict of Interest: The authors declare that they have no conflict of interest.

INTRODUCTION

Acute leukemia, an aggressive malignancy originating from lymphoid and myeloid progenitor cells in the bone marrow, is the most common cancer in children, comprising around a third of all pediatric cases [1,2]. Approximately 80% of childhood leukemia cases are lymphocytic, with a distinctive peak in incidence from 2–6 years of age, while leukemias of myeloid lineage and other subtypes occur less frequently among children [2]. Observations of concordant leukemia in monozygotic twins and identification of leukemia-related chromosomal alterations in neonatal blood spots provide strong evidence that many of the genetic abnormalities involved in childhood leukemia are initiated *in utero* [3,4]. However, pre-leukemic chromosomal translocations occur around 100 times more frequently than the development of acute leukemia, indicating that in order for these initiating genetic abnormalities to result in disease, additional prenatal or postnatal oncogenic events are required [3,4].

Maternal nutrition during pregnancy may be related to both the occurrence of primary genetic abnormalities and to additional oncogenic events that lead to the development of childhood leukemia. One-carbon metabolism refers to three interrelated metabolic cycles in the cytosol of cells responsible for critical cellular processes, including the synthesis of nucleotides required for DNA and RNA, the conversion of homocysteine to methionine, and the generation of s-adenosylmethionine (SAM), the primary methyl donor for DNA, RNA, proteins and lipids [5,6]. One-carbon metabolism has been described as an “integrator of nutrient status” [5] due to its reliance on a variety of nutrients, including folate, vitamins B12 and B6, riboflavin, and amino acids methionine, serine, and glycine. In addition to the importance of these nutrients for DNA synthesis and repair and chromosomal integrity, they directly affect epigenetic processes that determine gene expression and influence cancer risk, including histone modification, levels of non-coding RNAs, and DNA methylation [7,8,5,9]. These types of epigenetic modifications may constitute additional oncogenic events required for the development of childhood leukemia [10,11].

Maternal nutritional factors are important to fetal development, as demonstrated by the ability of folic acid supplementation to prevent neural tube defects [12]. Observational studies of maternal folate intake through diet or supplements and risk of childhood leukemia have yielded mixed findings, with some studies demonstrating a protective effect for folic acid supplementation or food folate intake before or during pregnancy [13–15] and several others finding no association [16–21]. A recent Childhood Leukemia International Consortium study, the largest to date, found that folic acid taken before conception or during pregnancy was associated with a reduced risk of childhood acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) [22]. Only a small number of studies, however, have examined folate intake from food or the role of any other nutrients involved in the one-carbon metabolism cycle and risk of childhood leukemia. In addition, there has been limited consideration of the role of maternal diet on risk of AML [23].

The incidence of ALL differs among racial and ethnic groups, with the highest incidence observed among Hispanics and the lowest in African-Americans [24,25]. The associations

between various genetic and environmental exposures and ALL have also been found to differ by Hispanic ethnicity [26–31], including the effect of genetic variants in the folate pathway [21]. Nevertheless, despite ethnic differences in leukemia risk and distinct dietary patterns among ethnic groups [32], most previous studies have examined the relationship between maternal diet or vitamin supplement use and risk of childhood leukemia in populations with little ethnic diversity and have been unable to explore the influence of maternal ethnicity on these relationships.

The objective of this study is to examine the associations between maternal intake of folate and other one-carbon metabolism nutrients before pregnancy and risk of ALL and AML in children in an ethnically-diverse, population-based case-control study, the California Childhood Leukemia Study (CCLS).

METHODS

Study Population

The CCLS is a population-based case-control study that began in 1995. Phase I of the study (1995–1999) included 17 counties in the San Francisco Bay Area, and Phases II (1999–2002) and III (2002–2008) of the study expanded to include 18 additional counties in the California Central Valley [33]. Incident cases of newly diagnosed childhood leukemia in children 0–14 years old were ascertained from major pediatric clinical centers throughout Northern and Central California, usually within 72 hours after diagnosis. Controls were randomly selected from California birth certificates through the Office of Vital Records at the California Department of Public Health, as described in detail elsewhere [33,34]. Of 1,263 controls sampled and determined to be eligible, 1,089 (86%) were enrolled in the study [34]. Cases and controls were matched 1:1 or 1:2 on date of birth, gender, Hispanic ethnicity (based on a parent self-reporting as Hispanic), and maternal race (White, Black, or Other). Eligibility was restricted to incident cases and controls who 1) resided in the study area, 2) were under 15 years of age at time of diagnosis for cases and the corresponding date for controls, 3) had at least one parent or guardian who spoke English or Spanish, and 4) had no previous history of any malignancy. This analysis includes ALL and AML case and control participants recruited between 1995 and 2008 whose mothers reported dietary information. Previous CCLS studies examining maternal nutrient intake and childhood leukemia [19,20] were based only on Phase I and II respondents (less than half of the sample size in this analysis) and did not examine associations with AML or effect modification by maternal ethnicity. Approval for this study was obtained from the University of California, Berkeley Committee for the Protection of Human Subjects, the California Health and Human Services Agency Committee for the Protection of Human Subjects, and the Institutional Review Boards of the participating hospitals. Prior to the interview, written informed consent was obtained from the responding parent of each participating child, and assent was obtained for children seven years of age and older.

Data Collection

Data were collected by in-person interview in either English or Spanish and were abstracted from birth certificates. Details on dietary data collection have been described elsewhere

[20,19]. In brief, maternal dietary intake was assessed by in-person interview, using a modified version of the Block Food Frequency Questionnaire (FFQ). Dietary information in the year before pregnancy was provided by 98% of all study participants. All biological mothers were asked to report dietary intake and vitamin supplement use in the twelve months before the index pregnancy in order to examine nutritional adequacy at the time of conception and early pregnancy. Most children (67%) were diagnosed with leukemia under the age of six years; consequently, most women were asked to recall their diet before pregnancy less than seven years in the past. The FFQ included 76 foods items and questions about regular (at least weekly) use of vitamin or mineral supplements in the year before pregnancy, as well as type of supplement (multiple vitamins or select single vitamins: vitamins A, C, and E, beta-carotene, calcium, iron, zinc, and selenium) and frequency of use (no use, 1–3 days/week, 4–6 days/week, and every day). Spanish-speaking respondents were administered a Spanish version of the FFQ by bilingual interviewers. The Spanish FFQ included seven additional food items common in the diets of the Hispanic population (i.e., evaporated or condensed milk, cooked green peppers, avocado or guacamole, chile peppers or chile sauce, sauces such as mole or sofrito, corn tortillas, and flour tortillas). Dietary nutrients from food were calculated using the BlockSys and NutritionQuest computer programs (NutritionQuest, Berkeley, CA, USA) by multiplying the frequency of consumption of each food by its nutrient content and portion size and summing nutrient intake over all foods. Nutrient intake from vitamin supplements was calculated by multiplying the frequency of consumption of each type of supplement (multiple vitamins and single vitamins) by the amount of the nutrient typically found in compositions of each type; all supplemental B vitamin intake before pregnancy was based on use of multiple vitamins (i.e. “Regular Once-A-Day, Centrum, or Thera type”). Dietary folate intake was calculated in units of dietary folate equivalents (DFE) [35] and accounted for the different amounts of folic acid available from food before and after national fortification of grain products with folic acid in 1998. Following the publication of research suggesting that maternal vitamin supplement use during pregnancy may influence childhood leukemia risk, an additional questionnaire to assess vitamin supplement use *during* pregnancy (i.e. use of any vitamins or minerals and use of specific types of vitamins during pregnancy) was administered to Phase III respondents. Women were categorized as using vitamin supplements during pregnancy if they reported use of prenatal vitamins, one-a-day Centrum or Thera-type multiple vitamins, Stresstabs/B-complex vitamins, or folic acid supplements during pregnancy.

Statistical Analysis

Analyses were carried out separately for ALL and AML. Mothers of cases and controls with Down syndrome (N=36) were excluded due to the distinct genetic risk of leukemia among these children. We also excluded respondents reporting implausible daily energy consumption of <500 or >6000 calories (N=21). Cases and controls were compared by Pearson chi-square tests for categorical variables and Mann-Whitney rank sum tests for continuous variables. Nutrient intake was examined both as total combined intake from food and supplements and from food only. Principal components analysis (PCA) was used to create two variables summarizing intake of folate, vitamins B12 and B6, riboflavin, and methionine from 1) food and supplements and 2) food only. The first components accounted

for more than 80% of the variance. The principal component values ranged from −3.5 to 9.3 for food and supplements and from −3.5 to 9.9 for food only. In addition to models based on principal component variables, the association between each nutrient and case-control status was analyzed in separate models due to the high correlations among the nutrients ($r > 0.75$ for most pairs of one-carbon metabolism nutrients). Conditional logistic regression was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for nutrient intake and case-control status.

Analyses for all mothers included respondents of all races/ethnicities, while stratified analyses were restricted to the three major ethnic groups represented in this study (Hispanic, non-Hispanic white, and Asian). The potential modifying influence of maternal ethnicity (Hispanic, non-Hispanic white, or Asian) on nutrient associations with ALL was assessed through the addition of interaction terms to the statistical models; interaction terms with a p-value less than 0.2 were considered statistically significant to account for the low power of tests of homogeneity. Interaction by maternal ethnicity was not assessed for AML due to a small sample size. Because the Spanish version of the FFQ included seven additional foods, stratified analyses for nutrient intake from food and ALL were restricted to Hispanic mothers who responded in Spanish (N=83 Hispanic English respondents excluded), non-Hispanic white mothers who responded in English (N=35 non-Hispanic white Spanish respondents excluded), and Asian mothers who responded in English (N=1 Asian Spanish respondent excluded). Sensitivity analyses of stratified results among all members of the race/ethnicity categories (responding in both English and Spanish) were applied to determine the influence of this restriction on results.

Intake of B vitamins from supplements in the year before pregnancy was categorized into no intake, moderate intake, and high intake based on the distribution of intake in the data among controls (moderate intake: >0 and <600 μg folic acid, >0 and <5 μg vitamin B12, and >0 and <1.5 mg vitamin B6 and riboflavin; high intake: ≥600 μg folic acid, ≥5 μg vitamin B12 and ≥1.5 mg vitamin B6 and riboflavin). Results for the moderate intake category for Asian women are not shown due to the small number of respondents in this category. Stratified analyses included both English- and Spanish-speaking respondents of a given racial/ethnic group since the questions on vitamin supplement use did not differ by language. For Phase III respondents who reported supplement use during pregnancy, vitamin supplement use was also modeled as vitamin supplement intake during pregnancy only (reference group), intake both before and during pregnancy, and no intake before or during pregnancy for ALL and results were stratified by maternal ethnicity.

Covariates were determined a priori based on known or hypothesized associations with maternal diet and childhood leukemia [36,37,24,38]. All multivariable models included household income, mother's education, father's education, and maternal age at child's birth; models among all mothers also included mother's ethnicity. In order to examine the influence of the source of nutrients, models examining nutrient intake from food only also included a variable indicating intake of B vitamins from supplements (yes/no), and vitamin supplement models included the principal component for nutrient intake from food. All models examining nutrient intake from food and supplements or food only were also adjusted for total energy intake, a potential confounder [39,40]; this adjustment did not

substantially influence results for models examining risk of ALL but had a more pronounced influence on models examining risk of AML, with associations of larger magnitude observed between AML and the principal component and nutrients of interest after energy adjustment. Maternal body mass index (BMI) before pregnancy was available for only two-thirds of respondents and was not included as a covariate in final models because it did not improve the accuracy of the principal component or vitamin supplement models, as assessed through likelihood ratio tests. Although alcohol consumption is known to influence nutrient levels [41,42], 94.6% of respondents reported drinking much less or no alcohol at all during pregnancy; consequently, we did not consider alcohol consumption to be a likely confounder. All covariates were categorical variables with the exception of energy intake (Table 1). All statistical tests were two-sided and considered statistically significant if the 95% CI excluded 1.0. Statistical analyses were carried out using STATA version 12.

RESULTS

For ALL, there were significant differences between cases and controls by income ($p<0.01$), mother's education ($p<0.01$), father's education ($p=0.04$), maternal age ($p<0.01$), and vitamin supplement use in the year before pregnancy ($p=0.01$) (Table 1). For AML, cases and controls differed significantly by income ($p=0.03$) and maternal age ($p=0.01$). Thirty-five percent (N=650) of women reported taking any single or multiple vitamin supplements in the year before pregnancy. Only 14.7% of Hispanic mothers reported use of multiple vitamins in the year before pregnancy in contrast to 40.6% of white mothers and 29.5% of mothers of other ethnicities (31.5% of Asian mothers). Source of nutrients differed by maternal ethnicity: for example, Hispanic mothers had significantly higher folate intake from food than white mothers or mothers of other ethnicities ($p<0.001$), but significantly lower folic acid intake from vitamin supplements than non-Hispanic mothers ($p<0.001$) (Table 2).

Childhood ALL

Higher total intake of one-carbon metabolism nutrients from *food and supplements* before pregnancy as summarized in the principal component was associated with reduced risk of ALL among all mothers (OR =0.91, 95% CI 0.84–0.99 for a one-unit change) (Table 3). Higher total intake of each individual nutrient was also associated with reduced risk of ALL, although the ORs were less pronounced for folate and vitamin B12 and all 95% CIs included 1.0. Tests for interaction by maternal ethnicity were statistically significant in the models for the principal component and every nutrient (i.e., p-values for the interaction terms were all <0.2), with reduced risks observed for the principal component and each nutrient for Hispanic and non-Hispanic white women but not for Asian women.

For intake of one-carbon metabolism nutrients from *food only*, the OR for the principal component was less than 1.0 and similar across racial/ethnic groups, although the 95% CIs all included the null value (Table 3). The ORs for each individual nutrient were all less than 1.0 except for folate intake in white women and methionine intake in Asian mothers. Only the association between methionine and ALL was significantly modified by maternal

ethnicity (p=0.04 for interaction term), with the ORs less than 0.8 for Hispanic and white women and greater than 1.0 for Asian women.

The associations of B vitamin intake from supplements in the year before pregnancy and risk of ALL differed by maternal ethnicity (p<0.01 for the interaction term). Children of Hispanic women who reported high B vitamin intake from supplements in the year before pregnancy had substantially reduced risk of ALL (OR=0.36; 95% CI 0.17–0.74) (Table 4). Conversely, for children of non-Hispanic white women, the OR for high B vitamin intake from supplements was less pronounced and the 95% CI included 1.0 (OR = 0.76, 95% CI 0.50–1.16). The OR for high maternal B vitamin intake from supplements and risk of ALL among children of Asian women was 1.51 (95% CI 0.47–4.89).

Only 6% (N=62) of mothers interviewed in Phase III did not take vitamin supplements during pregnancy, and of the women who reported prenatal vitamin use, 93% began vitamin use during the first trimester. Measures of association are not presented for the category of no vitamin supplement use before or during pregnancy due to the small number of respondents. Children of Hispanic women who took supplements both before and during pregnancy had reduced risk of ALL (OR=0.34, 95% CI 0.14–0.79), compared to children of Hispanic women who took supplements during pregnancy only (Table 4). Among white women, the OR for taking supplements before and during pregnancy was 0.66 (95% CI 0.39–1.11). Results are not presented for Asian women due to the small number of Phase III matched sets.

Childhood AML

When examining combined intake of one-carbon metabolism nutrients among all mothers, all ORs for nutrient intake from food and supplements combined, and from food only, were less than 1.0. However, only the OR for intake of vitamin B6 from food had a 95% CI that excluded 1.0 (OR=0.47, 95% CI 0.23–0.98) (Table 5). The OR for vitamin supplement use in the year before pregnancy and risk of AML was 0.93 (95% CI 0.44–1.95, with 45 matched sets discordant on exposure).

DISCUSSION

Our findings provide some evidence that higher maternal intake of one-carbon metabolism nutrients from food and supplements before pregnancy is associated with reduced risk of ALL and possibly AML. This study also suggests that maternal intake of one-carbon metabolism nutrients other than folate may influence the risk of childhood leukemia. When examined by source of nutrients, ORs for intake of one-carbon metabolism nutrient intake from food and ALL were mostly consistent across categories of maternal race/ethnicity and almost all less than 1.0. In contrast, the associations between B vitamin intake from supplements in the year before pregnancy and risk of ALL appeared to differ by maternal ethnicity, with the greatest reduction in risk observed in children of Hispanic women.

Most research to date has examined the association between maternal vitamin supplement use and childhood leukemia, while fewer studies have investigated maternal intake of folate and other one-carbon metabolism nutrients from food [22]. One Australian case-control

study found that higher intakes of folate and vitamin B12 from food in the last six months of pregnancy were associated with a decreased risk of ALL, whereas higher dietary intakes of vitamin B6 were paradoxically associated with an increased risk for ALL [15]. The inverse associations of childhood leukemia with greater maternal micronutrient intakes are consistent with findings from other studies, including those from the CCLS, that have found maternal consumption of vegetables and fruits before or during pregnancy decreases risk of leukemia in children [43,20,19]. There are several plausible biological mechanisms by which maternal micronutrient intake may influence childhood leukemia risk, supported by a large body of literature examining the importance of one-carbon metabolism nutrients for genetic and epigenetic processes involved in fetal development and the importance of maternal nutritional status in the establishment of the child's immune system [44–46,9,47]. Although our analyses were based on an assessment of maternal diet in the year preceding pregnancy in order to capture nutritional status at conception and in early pregnancy, some research indicates that overall diet composition before pregnancy largely reflects diet composition during pregnancy, with the exception of specific dietary items (i.e. alcohol, caffeinated beverages) and increased micronutrient intake due to the use of vitamin supplements, which was accounted for in our analysis [48,49].

The effect of maternal vitamin supplement use on children's risk of ALL appeared to differ by maternal ethnicity. This finding is consistent with the modifying influence of Hispanic ethnicity on associations of other exposures with risk of ALL, including the effect of genetic variants in the folate pathway [21]. Nutrient levels in the body are influenced by dietary intake, genetic polymorphisms, behavioral factors, and nutrient-nutrient interactions [50–52]. These factors are often distributed unequally across ethnic groups. For example, the frequency of some polymorphisms that influence nutrient levels differs by race and ethnicity, with the prevalence of the MTHFR 677C→T polymorphism involved in folate metabolism significantly higher among Mexican-Americans compared to non-Hispanic whites or non-Hispanic blacks [53]. The distribution of nutrient intakes also differs between ethnic groups [54]. In this study, a smaller proportion of Hispanic women had nutrient intakes below the recommended daily allowance than non-Hispanic white women or Asian women, which is contradictory to some national data measuring dietary intake with 24-hour recalls [54,55]. The additional foods included in the Spanish FFQ may partially account for the higher intake of nutrients from food observed in Hispanic mothers, although other studies have found that Hispanics tend to have a healthier diet than non-Hispanic whites in the US [38]. Although it seems that our findings cannot be explained by lower micronutrient intakes among Hispanic women in our population, Hispanics may have higher nutrient requirements due to a higher frequency of particular single nucleotide polymorphisms that influence one-carbon metabolism nutrient levels [56,57].

There are important differences in socioeconomic status between these racial/ethnic groups, with Hispanic women comprising the majority of women with low household income and low education levels. In this study, Hispanic women had a much lower prevalence of vitamin supplement use than white women, which is consistent with data examining folic acid intake among women of childbearing age in the US [58,55,54]. Because most Hispanic women who used vitamin supplements had higher education and income, vitamin supplement use may reflect other exposures related to socioeconomic status. Finally, the findings for B

vitamin intake from supplements and ALL in Hispanic and Asian women are based on a smaller number of matched sets discordant on exposure, and bias away from the null value can occur in conditional logistic regression if there are too few discordant sets or adjustment for too many covariates [59]. Because the heterogeneity by maternal ethnicity observed in the vitamin supplement findings was not found for maternal nutrient intakes from food, this finding may be due to systematic error.

The strengths of this study include a large sample size and extensive dietary and vitamin supplement data collected through the FFQ and interview, which allowed for detailed exposure categorization. Furthermore, the study population is representative of the California population. Despite these strengths, there are potential limitations. There is substantial measurement error in the estimation of food and nutrient intakes by FFQs, and most mothers in this study were asked to recall their usual diet several years in the past. There is evidence that women are able to accurately recall their diets during past pregnancies [60] and that FFQs can be used to capture habitual diet reasonably well up to ten years in the past [61]. However, the large degree of random error associated with dietary assessment methods tends to result in null findings or small effect sizes [62,39]. Differences in the sensitivity and specificity of maternal recall or reporting may differ by case-control status and result in differential misclassification, biasing measures of association [63,64]. Recall bias may be less likely in this study because maternal diet is not an established or publicized risk factor for childhood leukemia [64]. Furthermore, a maternal diet reliability sub-study in the CCLS (N=85) found that the reliability of five select FFQ questions did not differ by case-control status (unpublished data). One-carbon metabolism nutrients are highly correlated with other nutrients that are important for fetal development, such as iron and calcium; some of these nutrients have been previously associated with childhood leukemia [65]. Thus, though it is difficult to attribute a reduction in risk specifically to the B vitamins, our findings are consistent with the importance of the one-carbon metabolism cycle in genetic and epigenetic processes that influence carcinogenesis. Finally, alcohol consumption during pregnancy was extremely rare among the participating mothers, preventing the assessment of its possible influence on the relationship between prenatal intake of B vitamins and childhood leukemia.

In conclusion, this study found that maternal intake of one-carbon metabolism nutrients from food and supplements was associated with a reduced risk of ALL, and suggests that nutrients other than folate may be important in reducing risk. This study is also the first to indicate that this relationship may differ by maternal ethnicity; it would be of interest to determine if the associations of vitamin supplement use with childhood leukemia are influenced by maternal race/ethnicity in other study populations. Additionally, this is one of few studies to examine the relationship between maternal consumption of one-carbon metabolism nutrients and risk of AML, and suggests higher maternal consumption of these nutrients may also reduce risk for this leukemia sub-type. Although childhood leukemia is an increasingly curable disease, the illness continues to result in substantial morbidity, and advances in understanding the role of modifiable risk factors such as diet are important in efforts to prevent the disease.

Acknowledgments

This research was supported by National Institute of Environmental Health Sciences grants R01ES009137 and P-42-ES-04705-18 (University of California, Berkeley). We thank Semira Gonseth Nusslé and Joe Wiemels for helpful feedback on this work, and the staff of the California Childhood Leukemia Study for their contributions to this research. We are grateful to the families who participated in this study and the clinical investigators and their teams at the collaborating hospitals for their role in recruiting patients to this study: University of California, Davis, Medical Center (J. Ducore), University of California, San Francisco (M. Loh and K. Matthay), Children's Hospital of Central California (V. Crouse), Lucile Packard Children's Hospital (G Dahl), Children's Hospital Oakland (J. Feusner), Kaiser Permanente Roseville (formerly Sacramento; K. Jolly and V. Kiley), Kaiser Permanente Santa Clara (C. Russo, A. Wong, and D. Taggar), Kaiser Permanente San Francisco (K. Leung), and Kaiser Permanente Oakland (D. Kronish and S. Month).

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Table 1

Select characteristics of matched case and control children, by leukemia subtype: the California Childhood Leukemia Study

	ALL		ALL	
	Cases N (%)	**Controls** N (%)	**Cases** N (%)	**Controls** N (%)
Total	681	931	103	145
Child sex				
Male	390 (57.3)	538 (57.8)	56 (54.4)	80 (55.2)
Female	291 (42.7)	393 (42.2)	47 (45.6)	65 (44.8)
Child's age at diagnosis/reference date (years)				
< 2	83 (12.2)	106 (11.4)	28 (27.2)	44 (30.3)
2–6	396 (58.2)	543 (58.3)	19 (18.5)	28 (19.3)
6–9	96 (14.1)	132 (14.2)	15 (14.6)	19 (13.1)
≥ 9	106 (15.6)	150 (16.1)	41 (39.8)	54 (37.2)
Child's ethnicity				
Hispanic	312 (45.9)	414 (44.5)	40 (38.8)	56 (38.6)
Non-Hispanic White	256 (37.7)	365 (39.2)	44 (42.7)	62 (42.8)
Non-Hispanic Other	112 (16.5)	152 (16.3)	19 (18.5)	27 (18.6)
Mother's ethnicity				
Hispanic	285 (41.9)	364 (39.1)	35 (34.0)	50 (34.5)
Non-Hispanic White	298 (43.8)	437 (46.9)	55 (53.4)	75 (51.7)
Non-Hispanic Other	98 (14.4)	130 (14.0)	13 (12.6)	20 (13.8)
Household annual income (USD)				
<15,000	105 (15.4)	93 (10.0)	21 (20.4)	12 (8.3)
15,000–29,999	119 (17.5)	116 (12.5)	20 (19.4)	22 (15.2)
30,000–44,999	106 (15.6)	116 (12.5)	13 (12.6)	15 (10.3)
45,000–59,999	104 (15.3)	126 (13.5)	9 (8.7)	20 (13.8)
60,000–74,999	51 (7.5)	103 (11.1)	11 (10.7)	14 (9.7)
75,000+	196 (28.8)	377 (40.5)	29 (28.2)	62 (42.8)
Mother's education				
None or elementary	84 (12.3)	71 (7.6)	12 (11.7)	14 (9.7)
High school or similar	211 (31.0)	251 (30.0)	34 (33.0)	38 (26.2)
Some college or similar	188 (27.6)	293 (31.5)	24 (23.3)	38 (26.2)
Bachelor's degree or higher	198 (29.1)	316 (33.9)	33 (32.0)	55 (37.9)
Father's education				
None or elementary	78 (11.8)	99 (11.1)	13 (13.0)	14 (9.9)
High school or similar	238 (36.1)	271 (30.3)	36 (36.0)	44 (31.0)
Some college or similar	137 (20.8)	231 (25.8)	17 (17.0)	35 (24.7)
Bachelor's degree or higher	207 (31.4)	295 (32.9)	34 (34.0)	49 (34.5)

	ALL		ALL	
Maternal age at child's birth (years)				
<25	231 (33.9)	237 (25.5)	34 (33.0)	25 (17.2)
25–35	342 (50.2)	516 (55.4)	55 (53.4)	89 (61.4)
>35	108 (15.9)	178 (19.1)	14 (13.6)	31 (21.4)
Vitamin supplement use before pregnancy[a]				
Yes	213 (31.5)	347 (37.5)	34 (33.3)	56 (38.9)
No	463 (68.5)	579 (62.5)	68 (66.7)	88 (61.1)
Dietary nutrient intake before pregnancy	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
Folate (DFE)[b]	506.90 (282.0)	508.08 (279.6)	471.70 (253.6)	482.23 (293.1)
Vitamin B12 (μg)	5.07 (3.0)	5.19 (3.3)	5.36 (3.2)	5.39 (3.3)
Vitamin B6 (mg)	2.14 (1.0)	2.13 (1.0)	2.19 (1.1)	2.15 (1.1)
Riboflavin (mg)	2.20 (1.0)	2.21 (1.0)	2.34 (1.3)	2.25 (1.1)
Methionine (g)	1.94 (0.9)	1.95 (1.0)	2.09 (1.0)	2.00 (1.1)

ALL cases and controls differed by income ($p<0.01$), mother's education ($p<0.01$), father's education ($p=0.04$), maternal age ($p<0.01$), and vitamin supplement use in the year before pregnancy ($p=0.01$). AML cases and controls differed by income ($p=0.03$) and maternal age ($p=0.01$).

[a] Any use of single or multiple vitamins

[b] Dietary folate equivalent (DFE)

Table 2

Nutrient intake and supplemental B vitamin intake before pregnancy among controls, stratified by maternal race/ethnicity

	Hispanic Mothers[a] N=365	Non-Hispanic White Mothers[a] N=499	Asian Mothers[a] N=99
Nutrient intake from food and supplements	**Median (25^{th}–75^{th} percentiles)**	**Median (25^{th}–75^{th} percentiles)**	**Median (25^{th}–75^{th} percentiles)**
Folate (DFE)	607.1 (398.1–921.3)	546.4 (341.2–976.1)	561.3 (298.0–1018.7)
Vitamin B12 (μg)	5.8 (3.9–9.1)	6.0 (3.6–9.3)	4.8 (2.9–8.6)
Vitamin B6 (mg) *	2.6 (1.9–3.5)	2.3 (1.6–3.5)	2.2 (1.4–3.2)
Riboflavin (mg) *	2.6 (1.9–3.6)	2.4 (1.6–3.4)	2.1 (1.3–2.9)
Nutrient intake from food			
Folate (DFE) *	552.4 (375.3–780.6)	390.4 (270.2–536.1)	447.3 (280.2–597.8)
Vitamin B12 (μg) *	5.2 (3.6–7.5)	4.0 (2.9–5.9)	3.9 (2.3–5.8)
Vitamin B6 (mg) *	2.3 (1.8–3.1)	1.7 (1.3–2.3)	1.7 (1.1–2.5)
Riboflavin (mg) *	2.4 (1.8–3.2)	1.8 (1.4–2.4)	1.6 (1.2–2.3)
Methionine (g) *	2.0 (1.5–2.7)	1.6 (1.2–2.1)	1.6 (1.1–2.1)
Any B vitamin intake from supplements	N (%)	N (%)	N (%)
Yes	62 (17.0)	207 (41.5)	29 (29.3)
No	303 (83.0)	292 (58.5)	70 (70.7)

* Kruskal-Wallis test $p<0.05$

[a] Because of differences in the Spanish and English FFQ, Hispanic mothers include those who responded to the Spanish FFQ and white and Asian mothers include those who responded to the English FFQ.

Table 3

Association of childhood ALL with intake of one-carbon metabolism nutrients before pregnancy from food and supplements and food only, by maternal race/ethnicity

	All mothers[a] 645 cases, 854 controls	Hispanic mothers[a] 185 cases, 226 controls	White mothers[a] 253 cases, 357 controls	Asian mothers[a] 68 cases, 79 controls
Nutrients from food and supplements (Unit-change for OR)	**Odds Ratio (95% CI)**	**Odds Ratio (95% CI)**	**Odds Ratio (95% CI)**	**Odds Ratio (95% CI)**
Principal component (one-unit change) *[b]	0.91 (0.84–0.99)	0.79 (0.64–0.97)	0.92 (0.81–1.03)	1.08 (0.81–1.44)
Folate (100 DFE/day) *	0.97 (0.94–1.01)	0.92 (0.84–1.01)	0.98 (0.93–1.03)	1.02 (0.89–1.17)
Vitamin B12 (1 μg/day) *	0.96 (0.93–1.00)	0.94 (0.87–1.02)	0.95 (0.90–1.01)	1.01 (0.89–1.14)
Vitamin B6 (1 mg/day) *	0.89 (0.79–1.00)	0.68 (0.50–0.92)	0.90 (0.75–1.08)	1.11 (0.74–1.65)
Riboflavin (1 mg/day) *	0.88 (0.77–1.00)	0.69 (0.49–0.97)	0.87 (0.72–1.07)	1.07 (0.66–1.73)
Nutrients from food only (Unit-change for OR)				
Principal component (one-unit change)[b]	0.93 (0.83–1.04)	0.86 (0.68–1.08)	0.89 (0.72–1.09)	0.75 (0.43–1.33)
Folate (100 DFE/day)	0.99 (0.93–1.06)	0.96 (0.85–1.09)	1.00 (0.90–1.12)	0.87 (0.66–1.13)
Vitamin B12 (1 μg/day)	0.97 (0.92–1.02)	0.98 (0.90–1.07)	0.91 (0.82–1.02)	0.85 (0.68–1.07)
Vitamin B6 (1 mg/day)	0.91 (0.74–1.12)	0.69 (0.45–1.08)	0.88 (0.59–1.29)	0.75 (0.34–1.63)
Riboflavin (1 mg/day)	0.91 (0.74–1.12)	0.78 (0.51–1.20)	0.85 (0.60–1.19)	0.59 (0.24–1.43)
Methionine(1 g/day) *[c]	0.90 (0.73–1.10)	0.75 (0.50–1.15)	0.78 (0.54–1.14)	1.39 (0.70–2.75)

Conditional logistic regression models adjusted for father's education, mother's education, household income, maternal age at child's birth, and energy intake. Models for all mothers also adjusted for mother's ethnicity. Models for nutrient intake from food only also adjusted for intake of B vitamin-containing supplements (yes/no).

*P-value <0.2 for tests of interaction by maternal ethnicity.

[a]All mothers includes mothers of all races/ethnicities who responded in English and Spanish. Hispanic mothers include those who responded to the Spanish FFQ and white and Asian mothers include those who responded to the English FFQ.

[b]The principal component represents the combined dietary intake of folate, vitamins B12 and B6, riboflavin and methionine from food and supplements and from food only.

[c]Methionine was measured from food only.

Table 4

Association of childhood ALL with intake of vitamin supplements containing B vitamins before and during pregnancy, by maternal race/ethnicity

Vitamin supplements before pregnancy	**Hispanic mothers**[a] 234 cases, 296 controls		**White mothers**[a] 265 cases, 374 controls		**Asian mothers**[a] 68 cases, 79 controls	
	Discordant sets (%)[b]	**Odds Ratio (95% CI)**	**Discordant sets (%)**[b]	**Odds Ratio (95% CI)**	**Discordant sets (%)**[b]	**Odds Ratio (95% CI)**
Level of B vitamin intake from multiple vitamins[c]	68 (29.1)		177 (66.8)		31 (45.6)	
None		(Ref)		(Ref)		(Ref)
Moderate intake		1.12 (0.44–2.84)		1.25 (0.75–2.07)		---
High intake		0.36 (0.17–0.74)		0.76 (0.50–1.16)		1.51 (0.47–4.89)
Vitamin supplements during pregnancy	194 cases, 229 controls		154 cases, 261 controls			
Pregnancy only	53 (41.7)	(Ref)	86 (71.1)	(Ref)		---
Before and during pregnancy[d]		0.34 (0.14–0.79)		0.66 (0.39–1.11)		---

Conditional logistic regression models adjusted for adjusted for father's education, mother's education, household income, and maternal age at child's birth and the principal component for nutrient intake from food.

[a] Race/ethnic categories for vitamin supplement use include both English and Spanish respondents because questions did not differ by language.

[b] Discordant sets are case-control pairs or triplets for which the mothers were discordant on exposure and contributed to estimation of the OR in the conditional logistic models.

[c] For folic acid, moderate intake is >0 & <600 μg and high intake is ≥600 μg. For vitamins B12, B6, and riboflavin, moderate intake is >0 & <5 μg B12 and <1.5 mg B6 and riboflavin, and high intake is ≥5 μg B12 and ≥1.5 mg B6 and riboflavin.

[d] Multiple vitamin use before pregnancy and use of prenatal vitamins, one-a-day Centrum or Thera-type multiple vitamins, Stresstabs/B-complex vitamins, or folic acid during pregnancy.

Table 5

Association of childhood AML with intake of one-carbon metabolism nutrients before pregnancy from food and supplements and food only

	All Mothers 98 cases, 128 controls
Nutrients from food and supplements	**Odds Ratio (95% CI)**
Principal component[a]	0.83 (0.66–1.04)
Folate (100 DFE/day)	0.93 (0.85–1.03)
Vitamin B12 (1 μg/day)	0.92 (0.84–1.02)
Vitamin B6 (1 mg/day)	0.72 (0.51–1.04)
Riboflavin (1 mg/day)	0.85 (0.60–1.20)
Nutrients from food only	
Principal component[a]	0.68 (0.46–1.02)
Folate (100 DFE/day)	0.90 (0.76–1.07)
Vitamin B12 (1 μg/day)	0.86 (0.73–1.02)
Vitamin B6 (1 mg/day)	0.47 (0.23–0.98)
Riboflavin (1 mg/day)	0.85 (0.49–1.50)
Methionine (1 g/day)[b]	0.68 (0.35–1.34)

Conditional logistic regression models adjusted for mother's ethnicity, father's education, mother's education, household income, maternal age at child's birth, and energy intake. Models for nutrients from food additionally adjusted for B vitamin intake from supplements (yes/no).

[a]The principal component represents the combined dietary intake of folate, vitamins B12 and B6, riboflavin and methionine from food and supplements and from food only.

[b]Methionine was measured from food only.