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Maternal Supplementation with Folic Acid and Other Vitamins and Risk of Leukemia in the Offspring: a Childhood Leukemia International Consortium Study

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Abstract

Background—Maternal prenatal supplementation with folic acid and other vitamins has been inconsistently associated with a reduced risk of childhood acute lymphoblastic leukemia (ALL). Little is known regarding the association with acute myeloid leukemia (AML), a rarer subtype.

Methods—We obtained original data on prenatal use of folic acid and vitamins from 12 case-control studies participating in the Childhood Leukemia International Consortium (enrollment period: 1980-2012), including 6,963 cases of ALL, 585 cases of AML, and 11,635 controls. Logistic regression was used to estimate pooled odds ratios (OR) and 95% confidence intervals (CI), adjusted for child's age, sex, ethnicity, parental education, and study center.

Results—Maternal supplements taken any time preconception and/or during pregnancy were associated with a reduced risk of childhood ALL; ORs for vitamin and folic acid use were 0.85 (95% CI: 0.78-0.92) and 0.80 (95% CI: 0.71-0.89) respectively. The reduced risk was more pronounced in children whose parents' education was below tertiary level. The analyses for AML led to somewhat unstable estimates; ORs= 0.92 (95% CI: 0.75-1.14) and 0.68 (95% CI: 0.48-0.96) for prenatal vitamins and folic acid, respectively. There was no strong evidence that risks of ALL or AML varied by period of supplementation (preconception, pregnancy, or trimester).

Conclusions—Our results, based on the largest number of childhood leukemia cases to date, suggest that maternal prenatal use of vitamins and folic acid reduces the risk of ALL and AML, and that the observed association with ALL varies by parental education, a surrogate for lifestyle and socio-demographic characteristics.

Introduction

Acute leukemias are the most common cancers in children under 15 years of age; 80% are acute lymphoblastic leukemia (ALL), 17% acute myeloid leukemia (AML), and 3% chronic myeloid leukemia.^{1,2} The incidence of ALL peaks in children 2-5 years old, while the incidence of AML is constant across ages.^{1,2} The early onset of leukemia is suggestive of genetic predisposition and critical exposures occurring before and during pregnancy. Prenatal supplementation with folic acid and other vitamins, known to maintain DNA integrity³ and reduce oxidative stress^{4,5} could play a role in the prevention of childhood leukemia. The risk of childhood ALL following maternal folic acid or vitamin intake before and during pregnancy has been studied before but results have been inconsistent.⁶⁻¹⁷ This may be due to different underlying genetic susceptibilities in the studied populations, temporal variations in folic acid and vitamin intake over study periods, but also to limited statistical power of individual studies. Meta-analyses of published results reported a non-statistically significant reduced risk of ALL associated with maternal use of vitamins during pregnancy, but not before conception.^{7,8,10} Little is known about the risk of AML in relation to maternal supplementation with folic acid or vitamins⁶⁻¹⁷

To overcome the limitations of previous studies, we pooled original data on prenatal intake of folic acid and vitamins from 12 case-control studies participating in the Childhood Leukemia International Consortium (CLIC)¹⁸, and examined the associations with childhood ALL (overall and by immunophenotype) and AML. We also evaluated the modifying effects of education level as a marker of nutritional status¹⁹⁻²³, and of alcohol consumption, which is known to modify folate metabolism.²⁴

Methods

Study Population

Twelve case-control studies conducted in 10 countries from 1980 to 2012 and participating in CLIC (clic.berkeley.edu) 18 contributed data to the current pooled analyses (Table 1); this included eight studies with published data from Australia,¹⁰ Canada,¹⁴ France,⁶ Germany,¹³ New Zealand,⁷ and the United States,^{9,16,17} and four studies from Brazil, Costa Rica, Egypt, and Greece with unpublished data at the time of this report. Study design and characteristics of participants in individual studies have been described previously.¹⁸ A total of 19,183 children were available for analysis (6,963 cases of ALL, 585 cases of AML, and 11,635 controls). Information on immunophenotype was available for 84% of ALL, including 5,193 children diagnosed with precursor B-cell ALL and 678 with T-cell ALL.

Data Collection and Standardization

The participating CLIC studies provided original data on self-reported maternal supplementation with folic acid and other vitamins up to one year before conception and during pregnancy. Information on the type and period of supplementation included (i) the use of dietary supplements, which may have contained folic acid or not, (ii) the use of specific vitamins such as folic acid, vitamin C, vitamin D, or others (iii) the supplementation taken at any time during the prenatal period (whether or not information on the periods of use preconception and/or during pregnancy was specified, referred to as “any time” in the text), and (iv) the supplementation taken in a specific time period (preconception or during pregnancy as a whole or by trimester). We also obtained data on leukemia subtypes, the child's race/ethnicity, gender, and age (at diagnosis for cases and corresponding age for controls participating in age-matched studies or age at enrollment/interview), birth weight, mother's age at delivery, maternal and paternal education level, and maternal alcohol consumption. The availability of data on maternal supplement use by type and period, for each participating study and overall is summarized in Table 1. Twelve studies provided data on vitamin supplementation any time before or during pregnancy (98% complete), whereas seven studies provided data specific to supplementation with folic acid during pregnancy, representing data for 47% of all study subjects (Table 1).

Data were checked in collaboration with the principal investigators of each study and were standardized across studies for the pooled analyses. In particular, the standardized variable for use of any vitamins included women who reported single or multivitamins that did or did not contain folic acid; the use of mineral supplements such as iron was not taken into consideration. Women who specifically reported taking folic acid were included in the group “folic acid”. Time-specific variables were created for maternal supplementation with any

vitamins any time prenatally, preconception, during pregnancy, and by trimesters. Identical time-specific variables were created for maternal intake of folic acid. Other variables with heterogeneous definitions across studies were classified into the following categories for ethnicity (White/Caucasian/European vs. other) and highest level of parental (father or mother) education (none or primary, secondary, and tertiary, generally meaning some university education). For each study, we obtained the approximate year when food fortification with folic acid was recommended and/or implemented. Information was either publicly available or provided by the investigators of the participating studies. Based on the year of birth, we assigned for each child a value for being born before or after folic acid fortification.

Statistical Analyses

Study-specific and pooled odds ratios (ORs) as well as approximate 95% confidence intervals (CIs) were estimated from unconditional logistic regression models, separately for ALL and AML, and by immunophenotype for ALL (B- and T-cell lineage). All variables, except mother's age at delivery, child's age at diagnosis (and corresponding age for controls) and birth weight, were categorical. Models were adjusted for child's age, sex, ethnicity, and parental education level as these variables were either matching factors in the individual matched studies or treated as confounders. We present models without and with adjustment for study center (Models 1 and 2, respectively) for the main analyses on use of vitamin/folic acid supplements any time, preconception and during pregnancy; only study-adjusted models (Model 2) are presented for additional analyses. Overall, adjusting for study center improved the fit of all models (p-values for log-likelihood ratio test [LRT] < 0.001). Other variables (child's birth weight, maternal age at delivery, maternal alcohol intake, and child born before/after folic acid food fortification) were not included in the final models as the ORs changed by less than 10%. We conducted stratified analyses by sex, age at diagnosis (infants 0-1 year old vs. older children), parental education (none/primary, secondary, and tertiary), maternal alcohol consumption (drinkers vs. non-drinkers), and folic acid food fortification (child born before vs. after). P-values for heterogeneity between strata were obtained from the LRT or Woolf's test.

In order to characterize the heterogeneity in vitamin and folic acid supplementation between participating CLIC studies and account for it in the analysis, we assessed the contribution of the between-study variability and within-study variability into the total variability. Total variability $N_p(1-p)$ was partitioned into between-study variability (which represents the deviation of study-specific prevalence from the mean prevalence for all studies combined, weighted by the number of subjects in individual studies, $V_B = \sum n_i(p_i - p)^2$) and within-study variability (which represents the deviation of individual subjects from the study-specific mean prevalence, weighted by the number of subjects in their corresponding study ($V_W = \sum n_i p_i(1 - p_i)$), where N is the total number of cases and controls across all studies, n is the total number of subjects in each study, p is the proportion of women taking vitamins across all studies, and p_i is the proportion of women taking vitamins in each study. For use of vitamin and folic acid any time and during pregnancy, V_B accounted for approximately 33% to 44% of the total variability, whereas for preconception vitamin and folic acid intake V_B accounted for about 16% of the total variability. Subsequently, we grouped the study

sites into those contributing to either the lowest between-study variability ($V_B < 30\%$ of total variability) or the highest between-study variability ($V_B \geq 30\%$ of total variability), and conducted stratified analyses for each group to assess the impact of study heterogeneity in Models 1 versus 2. The cut point for grouping studies with low versus high V_B was driven by the data. Lastly, we conducted sensitivity analyses by systematically excluding two studies (out of 12) at a time, which resulted in 66 sets of 10 studies. For each set, we then computed the ORs and 95% CI for each type and period of maternal supplementation. Out of a total of 66 ORs, we calculated the minimum, mean and maximum OR, and the corresponding 95% CIs.

Results

The distribution of socio-demographic characteristics among cases and controls in the pooled dataset is shown in Table 2. The percentages of mothers reporting vitamin supplementation before and during pregnancy varied considerably by country and by study period (Figure 1). Between 1% and 39% of mothers reported taking vitamins before pregnancy, while use during pregnancy ranged from 9% to 95% vitamin use during pregnancy was most common in North America, Costa Rica and Australia, and least common in Brazil, France, Germany and New Zealand. Between-study differences were also observed for maternal intake of folic acid in the subset of studies where this information was available (Figure 2). The Pearson correlation coefficients between maternal supplementation before conception and during pregnancy were 0.28 for vitamins and 0.23 for folate ($p < 0.001$).

Childhood ALL

The adjusted study-specific ORs for risk of ALL associated with maternal intake of vitamins any time prenatally ranged from 0.44 (95% CI: 0.26-0.77) in Costa-Rica to 1.18 (95% CI: 0.65-2.14) in Brazil (Table 3). The study-specific ORs for vitamin supplementation preconception and during pregnancy also varied across studies (eTable 1, <http://links.lww.com/EDE/A806>).

Table 4 shows the results of the pooled analyses for type and period of maternal supplementation for ALL. The ORs for maternal intake of vitamins and folic acid any time prenatally, with no adjustment for study center, were 1.21 (95% CI: 1.13-1.28) and 1.09 (95% CI: 0.99-1.19), respectively (Table 4, Models 1). In contrast, the analyses with adjustment for study center showed that maternal intake of vitamins and folic acid at any time was associated with a reduced risk of ALL in the offspring, with pooled ORs of 0.85 (95% CI: 0.78-0.92) and 0.80 (95% CI: 0.71-0.89), respectively (Table 4, Models 2). There was no evidence that the magnitude of the association between prenatal vitamin and folic acid supplementation and ALL varied by period of use, i.e., preconception and pregnancy (Table 4), or by trimester (Table 5). The impact of adjustment for study on the pooled ORs for supplementation at any time and during pregnancy was stronger in the group of studies contributing to high between-study variability compared with those contributing to low between-study variability. Sensitivity analyses removing two studies at a time showed that the minimum, mean, and maximum study-adjusted ORs for ALL remained below one for

each type and period of supplementation (eFigure 1). The findings for vitamins use and risk of childhood ALL using data from the 7 studies with folic acid data were very similar to those using the full set of 12 studies presented in Table 4 (data not shown).

The magnitude of the associations with vitamin and folic acid intake was similar for B- and T-cell precursor ALL (Table 6). The reduction in ALL risk associated with folic acid intake any time prenatally was stronger for children whose parents had no formal or primary education (OR=0.47, 95% CI: 0.33-0.68), compared to those with secondary education (OR=0.73, 95% CI: 0.59-0.90) and tertiary education (OR=0.96, 95% CI: 0.82-1.12; p-value for interaction =0.01) (Table 6). A similar trend across education levels was observed for vitamin intake (p-value for interaction 0.14). Also, a reduction in risk was somewhat stronger for children whose mothers reported not drinking alcohol compared to those drinking alcohol; the 95% CIs, however, overlapped between strata (Table 6). Mothers drinking alcohol were more likely to have tertiary education (54%), than none/primary (12%) or secondary (34%) education (results not shown).

Stratified analyses for children born before or after folic acid food fortification did not reveal substantial differences in ORs (all 95% CIs overlapped) (Table 6). All stratified analyses were also conducted separately for supplement use preconception and during pregnancy (eTable 2, <http://links.lww.com/EDE/A806>). The results were similar for the period of the pregnancy while those for the preconception period were less consistent; for example, there was a tendency for lower risk estimates associated with vitamin and folate supplementation for children born after folic acid food fortification (eTable 2). The reductions in risk following folate acid supplementation appeared stronger in infants and boys, although these observations were consistent with chance variation (data not shown).

Childhood AML

The study-specific ORs estimating the risk of childhood AML associated with maternal intake of vitamins any time ranged from 0.26 (95% CI: 0.09-0.79) in Costa Rica to 1.13 (95% CI: 0.75-1.70) in Brazil (Table 3). The study-specific ORs associated with supplementation preconception and during pregnancy also varied across studies (eTable 3).

Table 7 shows the results of the pooled analyses for type and period of maternal supplementation, without and with adjustment for study center (Models 1 and Models 2, respectively). Just as in the analyses for ALL, the impact of adjustment for study center on the pooled ORs for AML was stronger in the group of studies with high between-study variability compared with those with low between-study variability. The study-adjusted pooled ORs associated with vitamin and folic acid supplementation at any time were 0.92 (95% CI: 0.75- 1.14) and 0.68 (95% CI: 0.48-0.96), respectively (Table 7, Models 2). The reduction in risk appeared stronger for maternal intake of folic acid during pregnancy (OR=0.52; 95% CI: 0.31- 0.89) vs. preconception (OR=0.88; 95% CI: 0.59-1.32), although the 95% CI intervals overlapped; there was no evidence that the risk of AML associated with vitamin intake varied by period of use (Table 7, Models 2). Sensitivity analyses for supplementation with folic acid showed that the mean ORs for AML remained below one; however, maximum ORs and most upper limits of the 95% CIs were above one, indicating that the results may be unstable (eFigure 2). Also, the ORs_{model 2} using data from the 7

studies with folic acid data were 0.74 (95% CI (0.53-1.05) and 0.65 (95% CI (0.43, 1.00) for vitamin use anytime and during pregnancy, respectively (not shown in tables); these were lower than the ORs from the analysis using the full set of 12 studies (Table 7). Note that the same 7 studies provided data for vitamins and folate preconception. The sample size was insufficient for meaningful stratified analyses.

Discussion

Although acute leukemia is the most common cancer in children, it is a relatively rare disease, therefore bringing challenges to the investigation of possible risk factors. This large international collaborative CLIC study, which includes over 7,000 children diagnosed with acute leukemia and 11,000 controls, found moderate reductions in risk of ALL following maternal intake of vitamin and folic acid supplements before or during pregnancy. Similarly, a reduced risk of AML was observed with folic acid use before or during pregnancy, whereas results for vitamins were inconclusive. There was no strong evidence that the risks of ALL and AML varied by period of supplementation (preconception, pregnancy, and trimester). Stratified analyses revealed possible differences in risk by parental education, a crude indicator of dietary quality.

Previous individual case-control studies have reported inverse^{6,15} or null^{7,10,14} associations between maternal folic acid supplementation during pregnancy and childhood ALL, as well as inverse,^{6,7,13,16} null,^{10,14} or positive¹¹ associations with any or multi-vitamins. Regarding supplementation during the preconception period, reduced risks have been associated with folic acid,^{9,10} while results were inconsistent for any vitamins or multi-vitamin intake.^{9-12,16} These studies were generally limited by small number of leukemia cases. Also, some of them were conducted in affluent populations with high intakes of folate from dietary and supplemental sources, leading to low exposure variation and limited power to uncover the alternative hypothesis. Three meta-analyses including small numbers of published studies (two to five) on childhood ALL suggested a protective effect for prenatal vitamins,^{8,10} but not for folic acid.^{7,10} As for childhood AML, only a few studies have been conducted to date: null results or moderately decreased risks were reported for maternal supplementation with vitamins ‘before and during pregnancy,’^{6,11,13} and with folic acid use.⁶

To address the limitations of previous studies on childhood acute leukemias, we pooled original data from eight published series from Northern America, Europe, and Oceania^{6,7,9,10,13,14,16,17} and four unpublished studies mostly from developing countries. Most participating studies provided detailed information on type and period of prenatal supplementation, alcohol consumption, and disease classification. Data from two studies in the United States, one including 56 children with ALL¹² and the other limited to children with Down's syndrome diagnosed with ALL and AML¹¹ were not included in our analyses; however, this likely had a no tangible impact on our results. Moreover, consistent with our findings, both studies reported decreased risks of childhood ALL associated with prenatal maternal vitamin intake.^{11,12} While standardizing data across studies may introduce non-differential misclassification of exposure (and possibly underestimate the risk), pooling data from countries with different socioeconomic backgrounds provides substantial variation in vitamin use, therefore probably increasing the opportunity to detect associations overall.

Previous analyses pooling original data from observational studies or clinical trials have adjusted for study center to account for measured and unmeasured (or unidentifiable) differences in designs and backgrounds,²⁵ or have conducted meta-analyses with published results using fixed or random effect models.²⁵⁻²⁷ In our pooled analyses, the inclusion of study center as a variable in the logistic regression models had a substantial impact on all risk estimates. This was especially true for studies exhibiting the largest heterogeneity in vitamin/folic acid use; however, other study characteristics could not be identified as possible sources of heterogeneity. Also, adjusting for study center substantially improved the goodness of fit of the models. The sensitivity analyses excluding studies indicated that the results for childhood ALL were robust for supplementation at any time and during pregnancy, and to a lesser extent before conception. Results for AML were less precise overall because of small numbers. Results from meta-analyses were consistent with the study-adjusted pooled analyses for all types and periods of interest, except the preconception period for which we have the least data (data not shown). Therefore, we chose to present only the results of pooled analyses of individual data, as this method allows for a transparent evaluation of the possible impact of study heterogeneity on the risk estimates, and more flexibility to assess subgroup and modifying effects, as well as goodness of fit of the models.

In the 1990s, folic acid supplementation was recommended before conception and during early pregnancy because of its role in preventing neural tube defects.⁸ Multi-vitamins containing folic acid were later recommended for the additional benefit of preventing a larger spectrum of birth defects and perinatal conditions.⁸ Folic acid is the synthetic form of folate, which is involved in DNA synthesis, repair, and methylation³, while vitamins such as C and D are known to prevent oxidative stress,^{4,5} thus playing a critical role against carcinogenesis. Low folate levels have been associated with increased risk of colorectal cancer and possibly other solid cancers in adults; however, the association between high-dose folic acid supplementation and increased cancer incidence is still controversial.²⁸⁻³²

The approximate calendar periods during which the use of folic acid was recommended spanned from 1992 to 2002 in the countries that we studied (Table 1). Further, the recommendations varied over time and by country, including dosage (0.36 mg to 0.8 mg per day), time windows (peri-conception/early pregnancy or throughout pregnancy), schedule (daily or weekly), and the composition of multivitamins.⁸ Similarly, fortification of grain products with folic acid was introduced at different calendar periods across countries.³³ Detailed information on dietary and supplementary sources of folate was not available in most participating studies, and therefore could not be directly accounted for in our analyses; however, adjusting for study center likely accounted for some geographical, temporal and social differences.

In our study, supplementation with any vitamins and folic acid any time prenatally was associated with a 15% and 21% reduction in childhood ALL risk, respectively, suggesting that vitamins other than folic acid are unlikely to contribute to additional risk reduction. The interpretation of these findings should take into consideration that folic acid intake is likely to be more specific compared to vitamins, which is a more heterogeneous exposure variable. In contrast for childhood AML, folic acid intake was associated with a 32% reduction in risk, whereas no significant decreased risk was seen with vitamin intake. The observed

difference in AML risk by type of supplementation may be due to chance. Information on doses of folic acid and other vitamins was not available for most studies; however, taking vitamins or folic acid throughout the pregnancy seems to be important in preventing childhood ALL, rather than supplementation targeted in early pregnancy, as originally indicated for preventing neural tube defects.

We found that the reduced risk of childhood ALL and AML associated with prenatal supplementation, especially with folic acid, was more pronounced in families with lower education levels. In our study, the lower prevalence of alcohol consumption (a known folate antagonist) observed among mothers with lower education levels may have contributed to these observations. Overall, mothers of children with low education were less likely to use prenatal supplementation, and to have given birth after food fortification with folic acid; and this was true for both cases and controls (data not shown). Also, parental education may have been a surrogate for other unmeasured lifestyles and sociodemographic determinants. Alternatively, differential maternal recall or genetic background among individual study populations may have contributed to differential leukemia risks by education. While the distribution of education levels by case-control status varied among participating studies (i.e., lower education in cases vs. controls in 8 studies, lower education in controls vs. cases in 2 studies, and no difference between cases and controls in 3 studies), it is difficult to anticipate the impact on the overall pooled risk estimates.

The majority of infants with leukemia present rearrangements of the MLL gene located at chromosome 11q23, which may result from targeted insults by specific dietary and environmental agents.^{34,35} Our stratified analyses by age at diagnosis were inconclusive. Null findings were previously reported between prenatal vitamin and intake and infant leukemia risk, with the possible exception of those with the MLL+ gene fusion.³⁶ Also, a reduced frequency of the low-function variant of the 5,10-methylenetetrahydrofolate reductase (MTHFR) gene (C677T) was reported in ALL/MLL+ infants compared to cord blood samples.³⁷ CLIC is working toward obtaining and validating data on cytogenetic and molecular characterization of leukemia cases across studies in order to perform these subtype-specific analyses previously.

In conclusion, taking into consideration both strengths (inclusion of published and unpublished data, large sample size for main and subgroup analyses, diversity in exposures, and ability to conduct sensitivity analyses) and limitations (lack of specificity in type and dose of vitamins and other minerals, possible recall and selection biases in individual studies), the results of our pooled analysis indicate that maternal prenatal supplementation with vitamins and/or folic acid reduced the risk of childhood ALL, and that education, as a crude surrogate for lifestyle and socio-demographic characteristics, may modify the magnitude of the associations. Limited data for childhood AML also suggest that maternal supplementation with folic acid, but not vitamins, reduces the risk of this rarer subtype.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
CLIC	Childhood Leukemia International Consortium
MTHFR	Methylene tetrahydrofolate reductase

Figure 1. Maternal vitamin supplementation preconception and during pregnancy, by study. For data from Germany, data for vitamin use were collected for preconception and/or pregnancy period. CCG indicates Children's Cancer Group; NCCLS, Northern California Childhood Leukemia Study.

Figure 2. Maternal folic acid supplementation preconception and during pregnancy, by study. NCCLS indicates Northern California Childhood Leukemia Study.

Table 1
Study Characteristics and Data Availability for Acute Lymphoblastic Leukemia, Acute Myeloid Leukemia, and Controls

Studies	Study Characteristics					Data Availability						
	Enrollment Period	Year of Folic Acid Recommendation	No. controls	No. Cases		Vitamin Use			Folic Acid Use			
				ALL	AML	Total No.	Any Time ^a	Preconception ^b	Pregnancy	Any Time ^a	Preconception ^b	Pregnancy
Canada ¹⁴	1980–2000	1998	790	790	—	1580	99	87	97	88	87	87
US CCG ¹⁶	1989–1993	1992	1986	1842	—	3828	99	100	100	—	—	—
New Zealand ⁷	1989–1994	1995	303	97	22	422	96	95	96	96	96	96
Germany ¹³	1992–1997	1995	2458	751	130	3339	98	—	—	—	—	—
Costa Rica	1995–2000	1998	579	251	33	863	98	—	98	97	—	97
US NCCLS ^{9,17}	1995–2002	1992	492	406	74	972	97	97	—	99	99	—
Brazil	1999–2002	2002	413	141	47	601	98	99	98	98	100	98
Greece	1996–2011	n/a	1026	920	108	2054	100	—	100	—	—	—
France ⁶	2003–2005	2004	1681	647	100	2428	97	93	95	95	95	95
Australia ^{10,15}	2003–2006	1992	822	385	—	1207	100	100	100	100	100	100
US NCCLS ^{9,17}	2003–2008	1992	734	434	71	1239	99	97	98	97	98	98
Egypt	2009–2012	1997	351	299	—	650	98	—	98	—	—	—
Total no. studies			12	12	8	12	12	8	10	8	7	7
Total no. subjects			11635	6963	585	19183	18873	11794	14625	8921	8070	7943
B-cell				5193			5117	3289	4083	2192	2184	1817
T-cell				678			658	481	561	322	320	287
Not specified				1092			1070	796	1060	488	252	485

ALL indicates acute Lymphoblastic Leukemia; AML, Acute Myeloid Leukemia; CCG, Children's Cancer Group; NCCLS, Northern California Childhood Leukemia Study

^aAny time is defined as any point before or during pregnancy

^bPreconception is defined by studies as between 3 months to 1 year before conception, or time is not specified

Table 2
Sociodemographic Characteristics for Acute Lymphoblastic Leukemia Cases, Acute Myeloid Leukemia Cases, and Controls: Childhood Leukemia International Consortium

	Cases		
	ALL (n=6963 No. (%))	AML (n=585) No. (%)	Controls (n=11635) No. (%)
Child's age (year)^a			
0–1	871 (13)	204 (35)	2036 (17)
2–5	3782 (54)	122 (21)	5068 (44)
6–10	1582 (22)	148 (25)	2853 (25)
11–14	728 (11)	111 (19)	1678 (14)
Child's sex			
Male	3932 (56)	316 (54)	6457 (55)
Female	5178 (44)	269 (46)	5178 (45)
Child's ethnicity			
White/European/Caucasian	5565 (80)	453 (77)	9719 (84)
Other	1389 (20)	127 (22)	1875 (16)
Missing	9 (0)	5 (1)	41 (0)
Parental education^b			
None/Primary	1049 (15)	147 (25)	2145 (18)
Secondary	2826 (41)	188 (32)	4174 (36)
Tertiary	3043 (44)	236 (40)	5190 (45)
Missing	45 (1)	14 (2)	126 (1)
Birth weight (grams)			
<2499	373 (5)	28 (5)	676 (6)
2500–3999	5475 (79)	471 (81)	9363 (80)
>4000	881 (13)	71 (12)	1256 (11)
Missing	234 (3)	15 (3)	340 (3)
Mother's age at delivery (years)			
<26	2488 (36)	217 (37)	3735 (32)
26–30	2328 (33)	182 (31)	4249 (37)
31–35	1558 (22)	129 (22)	2605 (22)
36–40	502 (7)	41 (7)	871 (7)
>40	79 (1)	14 (2)	163 (1)
Missing	9 (1)	2 (0)	12 (0)

^a Child's age defined as recruitment/interview for controls, and diagnosis for cases

^b Parental education defined as highest education level between the mother and father

Table 3
Risk of Acute Lymphoblastic Leukemia and Acute Myeloid Leukemia Associated with Maternal Vitamin Supplementation Any Time Preconception or During Pregnancy, by Study

Studies	Total No.	No. Exposed			OR (95% CI) ^a		
		Controls	ALL	AML	ALL	AML	AML
Canada	1580	622	608	—	0.89 (0.70–1.13)	—	—
US CCG	3828	1827	1622	—	0.73 (0.59–0.91)	—	—
New Zealand	422	29	8	0	0.97 (0.42–2.23)	—	—
Germany	3339	1046	290	53	0.87 (0.73–1.04)	1.00 (0.69–1.47)	—
Costa Rica	863	508	203	23	0.44 (0.26–0.77)	0.26 (0.09–0.79)	—
US NCCLS (1995–2002)	972	155	127	22	1.08 (0.80–1.47)	1.10 (0.61–1.97)	—
Brazil	601	46	21	5	1.18 (0.65–2.14)	1.11 (0.39–3.11)	—
Greece	2054	586	494	65	0.87 (0.72–1.04)	1.13 (0.75–1.70)	—
France	2428	331	89	14	0.65 (0.50–0.84)	0.72 (0.40–1.29)	—
Australia	1207	612	279	—	1.03 (0.77–1.37)	—	—
US NCCLS (2003–2008)	1239	689	409	63	1.02 (0.58–1.79)	0.73 (0.27–1.99)	—
Egypt	650	228	198	—	0.87 (0.61–1.24)	—	—

^a Study-specific results adjusted for age, sex, ethnicity, and parental education

Table 4
Risk of Acute Lymphoblastic Leukemia Associated with Maternal Vitamin and Folic Acid Supplementation, Stratified by Study with Low or High Between-Study Variability^a

Supplement, Period	Data Availability			All Studies						Low Between-study Variability ^b						High Between-study Variability ^c									
	No. Studies	No. Controls	No. Cases	Model 1 ^d			Model 2 ^e			No. Controls	No. Cases	Model 1 ^d			Model 2 ^e			No. Controls	No. Cases	Model 1 ^d			Model 2 ^e		
				OR	(95% CI)	OR	(95% CI)	OR	(95% CI)			OR	(95% CI)	OR	(95% CI)	OR	(95% CI)			OR	(95% CI)	OR	(95% CI)		
Vitamins																									
Any time	12	11466	6845																						
no ^f				4787	2497	1.00		1.00		1312	1108	1.00		1.00		3475	1389	1.00		1.00					
Yes				6679	4348	1.21 (1.13–1.28)	0.85 (0.78–0.92)			2711	1909	0.84 (0.76–0.93)	0.89 (0.80–0.99)		3968	2439	1.46 (1.34–1.59)	0.80 (0.71–0.90)							
Preconception	8	6931	4566																						
no ^f				5749	3834	1.00		1.00		—	—				—	—									
Yes				1182	732	0.93 (0.84–1.03)	0.88 (0.79–0.99)																		
Pregnancy	10	8554	5704																						
no ^f				3161	1844	1.00		1.00		1051	873	1.00		1.00		2110	971	1.00		1.00					
Yes				5393	3860	1.17 (1.09–1.26)	0.81 (0.74–0.88)			3200	2160	0.79 (0.71–0.88)	0.88 (0.78–0.98)		2193	1700	1.57 (1.41–1.74)	0.68 (0.58–0.80)							
Folic acid																									
Any time	8	5588	3002																						
no ^f				3416	1769	1.00		1.00		1460	794	1.00		1.00		1956	975	1.00		1.00					
Yes				2172	1233	1.09 (0.99–1.19)	0.80 (0.71–0.89)			439	261	1.08 (0.90–1.30)	0.92 (0.76–1.12)		1733	972	1.06 (0.95–1.19)	0.72 (0.62–0.84)							
Preconception	7	5011	2756																						
no ^f				4313	2404	1.00		1.00		—	—				—	—									
Yes				698	352	0.89 (0.77–1.02)	0.82 (0.70–0.96)																		
Pregnancy	7	5094	2589																						
no ^f				3294	1585	1.00		1.00		1317	597	1.00		1.00		1977	988	1.00		1.00					
Yes				1800	1004	1.13 (1.02–1.25)	0.77 (0.67–0.88)			106	57	1.15 (0.82–1.62)	1.10 (0.78–1.55)		1694	947	1.06 (0.94–1.18)	0.72 (0.62–0.83)							

^aStudies were separated into low- and high-high-variability groups, based on proportions of women taking vitamins or folic acid across each of the studies, when between-study variability contributed to more than 30% of the overall variability. Based on this criteria, studies were not stratified for the preconception time period.

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^b Low-variability studies: *Vitamins, any time*: canada, Costa Rica, US NCCLS (1995–2002), greece, australia, egypt; *Vitamins, pregnancy*: canada, Costa Rica, Greece, Australia, US NCCLS (2003–2008), egypt; *Folic acid, pregnancy*: New Zealand, Brazil, US NCCLS (2003–2008)

^c High-variability studies: *Vitamins, any time*: US CCG, New Zealand, Germany, Brazil, France, US NCCLS (2003–2008); *Vitamins, pregnancy*: US CCG, New Zealand, Canada, Costa Rica, France, Australia; *Folic acid, pregnancy*: Canada, Costa Rica, France, Australia

^d Pooled OR adjusted for age, sex, ethnicity, and parental education

^e Pooled OR adjusted for age, sex, ethnicity, parental education, and study

^f Reference category

Risk of Acute Lymphoblastic Leukemia Associated with Use of Vitamin and Folic Acid Supplementation Before and by Trimester During Pregnancy: Subsets of Childhood Leukemia International Consortium Studies

Table 5

Use Before and During Pregnancy	Vitamins (7 Studies) ^a				Folic Acid (5 Studies) ^b			
	No. Controls (n=6098)	No. Cases (n=4020)	OR	(95% CI) ^c	No. Controls (n=3608)	No. Cases (n=1898)	OR	(95% CI) ^c
No ^d	2235	1183	1.00		2326	1096	1.00	
Yes	3863	2837	0.78	(0.69–0.88)	1282	802	0.78	(0.67–0.91)
Preconception only	41	29	0.85	(0.51–1.39)	21	12	1.05	(0.51–2.18)
Trimester 1 ^e	288	151	0.79	(0.63–0.99)	268	132	0.80	(0.63–1.03)
Trimester 2/3 ^e	445	330	0.86	(0.72–1.03)	270	145	0.66	(0.52–0.84)
Trimester 1/2/3 ^e	3089	2327	0.75	(0.66–0.85)	723	513	0.82	(0.69–0.98)

^aStudies include: Australia, Brazil, Canada, Egypt, France, US CCG, US NCCLS (2003–2008)

^bStudies include: Australia, Brazil, Canada, France, US NCCLS (2003–2008)

^cPooled OR adjusted for age, sex, ethnicity, parental education, and study

^dReference category

^eMay or may not include preconception use

Table 6

Risk Of Acute Lymphoblastic Leukemia Associated With Maternal Vitamin And Folic Acid Supplementation Any Time Before Or During Pregnancy: Stratified Analyses In Subsets Of Childhood Leukemia International Consortium Studies

	Vitamins (Any Time)						Folic Acid (Any Time)					
	No. Studies	No. Exposed	OR		(95% CI) ^a	Test for Interaction	No. Studies	No. Exposed	OR		(95% CI) ^a	Test for Interaction
			Controls	Cases					Controls	Cases		
Immunophenotype												
Overall ^b	10	6125	3585	0.87	(0.80–0.94)		6	1661	1001	0.86	(0.76–0.97)	
B-cell	10	6125	3222	0.87	(0.80–0.95)	<i>P</i> = 0.45 ^c	6	1661	905	0.86	(0.75–0.97)	<i>P</i> = 0.59 ^c
T-cell	9	5897	363	0.81	(0.65–0.99)		6	1661	96	0.84	(0.62–1.14)	
Maternal consumption of alcohol (any time)												
Overall ^b	12	5989	3742	0.83	(0.76–0.91)		8	2168	1232	0.80	(0.71–0.90)	
No	12	3274	2133	0.79	(0.71–0.89)	<i>P</i> = 0.66 ^d	8	1059	595	0.75	(0.64–0.90)	<i>P</i> = 0.14 ^d
Yes	12	2715	1609	0.89	(0.78–1.01)		8	1109	637	0.87	(0.74–1.02)	
Parental education												
Overall ^b	12	6640	4336	0.85	(0.78–0.92)		8	2164	1228	0.80	(0.71–0.89)	
None/Primary	12	873	447	0.72	(0.60–0.88)	<i>P</i> = 0.14 ^d	8	352	132	0.47	(0.33–0.68)	<i>P</i> = 0.01 ^d
Secondary	12	2649	1879	0.78	(0.68–0.88)		8	660	410	0.73	(0.59–0.90)	
Tertiary	12	3118	2010	0.97	(0.86–1.09)		8	1152	686	0.96	(0.82–1.12)	
Child born before/after fortification												
Overall ^b	12	6679	4348	0.85	(0.78–0.92)		8	2172	1233	0.80	(0.71–0.89)	
Before fortification	12	6046	3971	0.86	(0.79–0.93)	<i>P</i> = 0.15 ^d	8	1892	1075	0.78	(0.69–0.89)	<i>P</i> = 0.96 ^d
After fortification	12	633	377	0.66	(0.45–0.97)		8	280	158	0.84	(0.64–1.11)	

^a Adjusted for age, sex, ethnicity, parental education, and study. Or for parental education is adjusted for age, sex, ethnicity, and study

^b Overall OR is given on the entire subset for which data are available for a specific stratified analysis

^c Woolf test

^d Log ratio test

Parental education defined as the highest education level between the mother and father

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Table 7
Risk of Acute Myeloid Leukemia Associated with Maternal Vitamin and Folic Acid Supplementation, Stratified by Study with Low or High Between-Study Variability^a

Supplement, Period	Data Availability				All Studies						Low Between-study Variability ^b						High Between-study Variability ^c													
				No. Cases	Model 1 ^d			Model 2 ^e						No. Controls	No. Cases	Model 1 ^d			Model 2 ^e			No. Controls	No. Cases	Model 1 ^d			Model 2 ^e			
	No. Studies	No. Controls			No.	OR	(95% CI)	OR	(95% CI)	No.	OR	(95% CI)	OR			(95% CI)	No.	OR	(95% CI)	OR	(95% CI)			No.	OR	(95% CI)	OR	(95% CI)		
Vitamins																														
Any time	8	7534	562																											
No ^f				4144	317	1.00		1.00						2448	192	1.00		1.00					1696	125	1.00		1.00			
Yes				3390	245	0.95	(0.80–1.14)	0.92	(0.75–1.14)					2324	163	1.01	(0.80–1.26)	1.00	(0.79–1.28)				1066	82	1.06	(0.77–1.46)	0.75	(0.47–1.18)		
Preconception	5	3448	297																											
no ^f				2959	247	1.00		1.00						—	—								—	—						
Yes				489	50	1.28	(0.92–1.79)	0.96	(0.66–1.39)																					
Pregnancy	6	4638	367																											
no ^f				2477	198	1.00		1.00						811	78	1.00		1.00					1666	120	1.00		1.00			
Yes				2161	169	1.02	(0.82–1.26)	0.85	(0.64–1.14)					1804	151	0.84	(0.63–1.13)	0.88	(0.63–1.25)				357	18	0.69	(0.41–1.16)	0.75	(0.44–1.25)		
Folic acid																														
Any time	6	4078	331																											
no ^f				2964	264	1.00		1.00						1460	167	1.00		1.00					1504	97	1.00		1.00			
Yes				1114	67	0.73	(0.55–0.97)	0.68	(0.48–0.96)					439	41	0.86	(0.59–1.26)	0.86	(0.58–1.27)				675	26	0.67	(0.42–1.07)	0.35	(0.18–0.68)		
Preconception	5	3510	303																											
no ^f				3131	266	1.00		1.00						—	—								—	—						
Yes				379	37	1.19	(0.82–1.73)	0.88	(0.59–1.32)																					
Pregnancy	5	3593	260																											
no ^f				2825	226	1.00		1.00						1317	129	1.00		1.00					1508	97	1.00		1.00			
Yes				768	34	0.61	(0.41–0.90)	0.52	(0.31–0.89)					106	8	0.81	(0.38–1.71)	0.85	(0.40–1.80)				662	26	0.67	(0.42–1.08)	0.36	(0.18–0.71)		

^aStudies were separated into low- and high-variability groups, based on proportions of women taking vitamins or folic acid across each of the studies, when between-study variability contributed to more than 30% of the overall variability. Based on this criteria, studies were not stratified for the preconception time period.

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^bLow-variability studies: *Vitamins, any time*: canada, Costa Rica, US NCCLS (1995–2002), greece, australia, egypt; *Vitamins, pregnancy*: canada, Costa Rica, Greece, Australia, US NCCLS (2003–2008), egypt; *Folic acid, pregnancy*: New Zealand, Brazil, US NCCLS (2003–2008)

^cHigh-variability studies: *Vitamins, any time*: Brazil, France, US NCLS (2003–2008); *Vitamins, pregnancy*: Brazil, France; *Folic acid, any time*: Costa Rica, France; *Folic acid, pregnancy*: Costa Rica, France

^dPooled OR adjusted for age, sex, ethnicity, and parental education

^ePooled OR adjusted for age, sex, ethnicity, parental education, and study

^fReference category