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Effects of Maternal Diet During Pregnancy on the Risk of Childhood Acute Lymphoblastic Leukemia: A Systematic Review

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ABSTRACT

Acute lymphoblastic leukemia (ALL) is the most common type of leukemia in children that can be affected by maternal diet. The aim of this study was to evaluate maternal dietary risk factors of ALL. We searched MEDLINE, Cochrane Library, Springer Link, Wiley Online, Science Direct, Mosby, ISI Web of Science, OVID, ProQuest, and Scopus from database inception until February 2, 2016. Two reviewers scanned titles, abstracts, and keywords of articles after excluding duplicates. We included case–control studies evaluating the relationship between maternal diet during pregnancy and childhood ALL. The search resulted in 2,940 papers, of which 11 full-text articles met the criteria for inclusion in the review and were analyzed. The finding of these studies suggest that maternal diet composed largely of vegetables, fruits, and protein sources before and during pregnancy can reduce the risk of ALL in offspring. Maternal alcohol intake had no effect. Nevertheless, inherent limitations of case–control studies like measurement error, random error, recall bias, and selection bias preclude conclusive evidence. Persuading pregnant women to follow a healthy diet rich in fruits, vegetables, and protein may reduce the risk of childhood ALL. Avoiding alcohol intake seems prudent.

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Introduction

Almost one-third of all pediatric cancers (including benign brain tumors) are related to leukemia[1]. Acute lymphoblastic leukemia (ALL), a neoplasm of the immune system, is the most common form of leukemia which accounts for 80% of all leukemia diagnosed in children aged 0–14 years 1,2, with the peak age of incidence at 2–5 years (3). The incidence of ALL is higher in Caucasian children compared to Black kids, is most common among children who are of Hispanic ethnicity, and is slightly more diagnosed in males than in females (4). Although the etiology is poorly understood, several causes have been proposed for childhood leukemia such as genetic and epigenetic aberrations, exposure to infections, and other immune-related illnesses (5). Based on Greaves hypothesis, ALL happens as a result of an unusual response to infections. At first, a genetic alteration in B-cell precursors arises and then another mutation develops following antigenic challenge (6,7). Ionizing radiation, parental smoking, pesticide and household chemicals, traffic fumes, immunologic modifiers, and lower expression of interleukin-10 (IL-10) are suspected as risk factors of leukemia (8). However, growing body of evidence has suggested that the initiating genetic mutations of leukemia often occur in the prenatal period (9–12). In addition to genetic and immunologic causes, other factors including nutritional factors, for example, diet of the mother and child, are suggested to be important in etiology of this type of cancer (13). It is shown that maternal diet may have some effects on epigenetic processes including DNA methylation, histone modifications, and noncoding RNAs in fetus (14), but its role in the induction of childhood leukemia has been studied less extensively. Only few studies have been conducted on the relationship between maternal intake of dietary supplements and further incidence of leukemia (15,16). Accordingly, the balance among folate, vitamin B_6, and vitamin B_{12}, which are involved in methylation of DNA, might influence the risk of hematologic cancers. A meta-analysis including six investigations found a modest protective effect of taking vitamin supplements during pregnancy, such effect was attributed to folate (16). A population-based case–control study in Shanghai revealed an inverse association between ALL and

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maternal use of cod liver oil, containing vitamins A and D (17). However, it is necessary to conduct a review focusing on the role of maternal dietary intake in this regard. The objective of the present review was to evaluate and interpret all available research evidence relevant to maternal diet and the risk of ALL in her offspring.

Methods

Queries of literature were performed using the electronic databases MEDLINE, Cochrane Library, Springer Link, Wiley Online, Science Direct, Mosby, ISI Web of Science, OVID, ProQuest, and Scopus until February 2, 2016 with no restrictions to language and calendar date using the following search terms: ("leukemia" OR "acute lymphoblastic leukemia" OR "ALL") in combination with ("food" OR "diet" OR "dietary pattern" OR "eating habits" OR "maternal diet").

At first, 2,940 articles (excluding duplicates) were found. Obtained reviews and articles were manually searched for additional studies. The titles and abstracts of the obtained documents were initially reviewed and the reference lists of selected papers were searched to identify additional articles. Studies were included in the systematic review if they met all the following criteria: 1) case–control study design; 2) evaluation of the maternal dietary risk factors of ALL. We excluded studies in which maternal supplement use during pregnancy were reported. Two prior systematic review and meta-analysis were found on the association between maternal beverages consumption during pregnancy and childhood leukemia, including subgroup analysis in the mothers of ALL children. No study has been published since then, except for five case–control studies regarding maternal alcohol intake (18–22). Finally, we reviewed 11 ($n = 11$) studies (18–28) (Fig. 1). The following data were extracted from qualified articles and tabulated: first author, year of publication, country name, number of cases/controls, main results, and adjusted factors (Tables 1 and 2).

Results

In all studies, controls were matched to the cases on date of birth (4) (23–25) or age (2) (18–22,26,28). They were also matched to cases by sex (18,20,21,24,27), ethnicity (24,26–28), and residency (19–22) in different studies. Study population comprised children under the age of 15 in seven studies (18,20,21,24,26–28) and infants in four studies (19,22,23,25). Conditional (4) (23,24,26,27) and unconditional (2) (18–22,25,28) logistic regression were used in studies to obtain odds ratios and 95% confidence intervals. Maternal diet was assessed by Food Frequency Questionnaire (FFQ) or questionnaires for evaluating maternal drinking habits. Two studies had used short FFQs focused on topoisomerase II inhibitor-containing foods (23,25).

Differences in Food Group and Component Food Intake Between Mothers of Patients with ALL and Controls

The most common observation was that mothers of children with ALL were less likely to consume vegetables and protein sources in their pregnancy. Only one study demonstrated a significant higher intake of sugars and syrups in these mothers (26). Maternal fruits intake and ALL risk were significantly and inversely correlated in three studies (25–27), but two studies reported a marginally significant relationship (24,27) (Table 1).

Two papers using a comprehensive FFQ showed that maternal consumption of cantaloupe, carrots, green beans (string beans), beans, and beef may reduce the risk of childhood ALL (24,27). Moreover, fish consumption by mother was related to lower ALL risk in some studies (23,26). Other food items like peas (significantly) (24), oranges (significantly) (27), and butter and margarine (marginally significantly) (26) had some effects.

Differences in Maternal Intake of Micronutrients and DNA Topoisomerase II Inhibitors Containing Foods Between Mothers of Patients with ALL and Controls

Mothers of pediatrics with a diet poor in vitamin A and its precursors, provitamin A carotenoids, α-carotene, and vitamin B9 were more likely to have ALL (24,27,28). Similar marginally significant findings came up for selenium, β-carotene, total and reduced glutathione, lutein, and vitamin B_{12} (24,27,28). Albeit, higher intake of vitamin B_6 was related to increased risk of disease, the authors considered it as an accidental finding (28). There was no relationship between consumption of DNA topoisomerase II inhibitors containing foods and ALL incidences (23,25) (Table 1).

Differences in Maternal Intake of Alcoholic Beverages Between Mothers of Patients with ALL and Controls

Maternal alcohol consumption categories were different among studies. Three studies did not show any significant relationship between maternal alcohol intake during pregnancy and risk of ALL in offspring (18,21,22). Polymorphism of ethanol metabolizing gene, cytochrome *P*-450 2E1 (CYP2E1), had no interaction with maternal alcohol consumption (18). When evaluating subtypes of ALL, alcohol drinking by mother during pregnancy was associated with B-cell precursor ALL with moderate

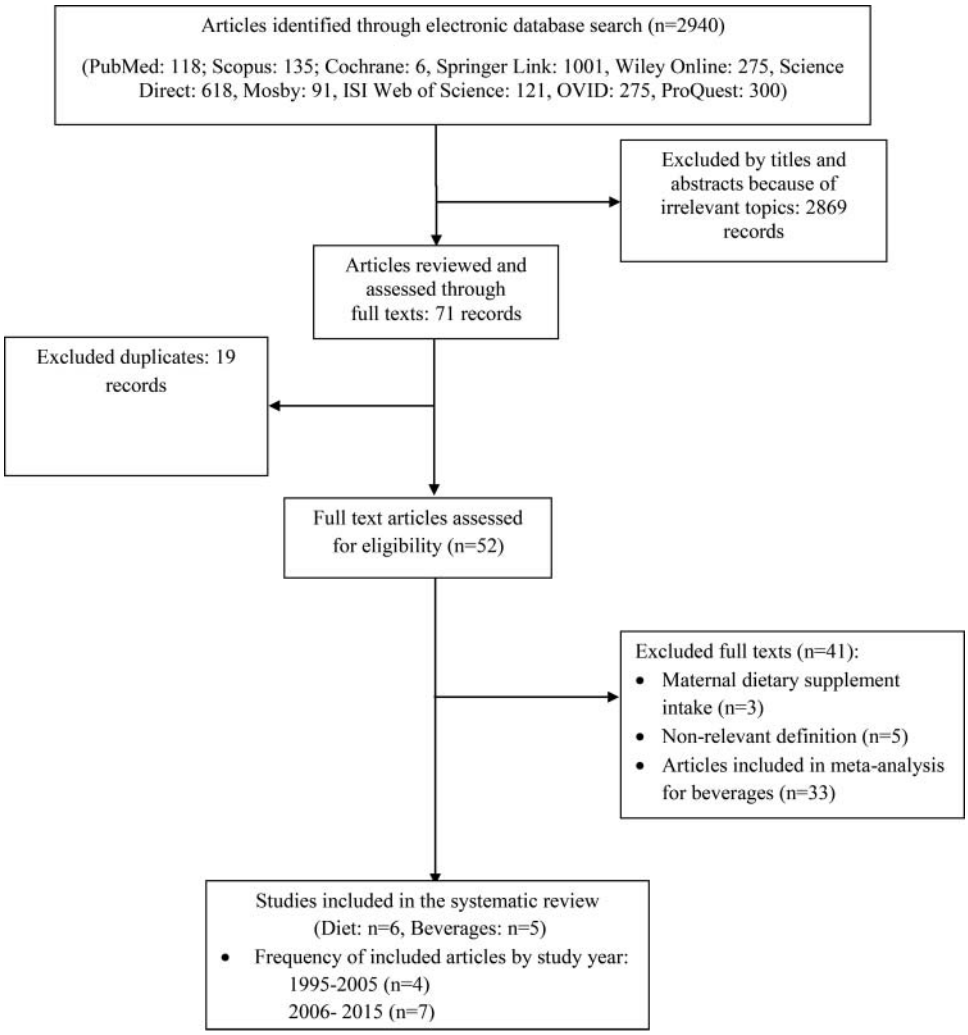

Figure 1. Flowchart of the search and selection process for articles included in the systematic review.

hyperdiploidy (21) and inversely related to mixed lineage leukemia rearrangements (MLL+) (22). Positive relationship was reported in one study (19), whereas another found a protective effect (20). Maternal drinking of all kinds of alcoholic beverages in different category of consumption during the year before pregnancy and gestational period was associated with significant reduced risk of ALL subtypes including pre-B-cell, T-cell, ETV6-RUNX1 (t12, 21), hyperdiploidy (47+), and trisomy 21 plus (20). Ferria's study which was conducted on children aged $\leq$2 years revealed that $<$1 per wk beer consumption preconception was significantly related to increased risk of childhood ALL (19). This finding disappeared after adjustment, but for weekly intake of beer a significant dose–response was seen (Table 2).

Discussion

The results of limited number of studies reviewed here, although not conclusive, suggest that following a healthy diet rich in fruits, vegetables, and protein sources before and during pregnancy may reduce the risk of ALL in offspring. We also did not observe any association between maternal alcohol drinking and risk of ALL in her child. The results of our review are somewhat in accordance with case–control study findings by Liu et al. in children between 2 and 20 years (29); however, some limitations should be considered when interpreting the results. As different factors that may influence maternal diet had been adjusted in reviewed studies, the results were heterogeneous. In general, all included studies had inherent limitations of case–control studies like measurement error, random error, recall bias, and selection bias. Different period of times had been selected to evaluate mothers' diet; two studies assessed maternal intake of foods 1 year before pregnancy, while maternal diet during pregnancy was evaluated in the other investigations. Intake of limited food items was assessed in some studies that could attenuate the possibility of finding a significant relationship (25,26,28). Age range was also different in studies.

Table 1. Characteristics of studies investigating maternal diet and childhood ALL risk.

Author	Year published	Country	Age of children (years)	Number of cases/ controls	Maternal diet component	OR/AOR (95% CI)*P* value	Adjustment factor
Ross et al. (23)	1996	USA	<1	54/54	Fish	1	Maternal education
					<1 m	0.3 (0.1–0.8)	
					1–3 wk	0.2 (0.1–0.6)	
					≥4 wk	0.01	
					P trend		
Jensen et al. (24)	2004	USA	<15	138/138	Vegetables	0.53 (0.33–0.85), 0.008	Energy intake, income, previous miscarriages or stillbirths, hours the child was exposed to other children at preschools, indoor insecticide exposure during pregnancy, and proportion of foods reported as large or extra-large portion size
					Protein sources	0.40 (0.18–0.90), 0.03	
					Fruits	0.71 (0.49–1.04), 0.08	
					Carrots	0.79 (0.67–0.94), 0.009	
					Cantaloupe	0.87 (0.75–1.02), 0.095	
					String beans or peas	0.84 (0.71–1.00), 0.048	
					Beans	0.83 (0.70–0.99), 0.03	
					Beef	0.80 (0.66–0.99), 0.04	
					Total vitamin A	0.58 (0.32–0.98), 0.04	
					Provitamin A carotenoids	0.65 (0.42–1.01), 0.05	
					α-Carotene	0.66 (0.49–0.90), 0.008	
					β-Carotene	0.70 (0.47–1.06), 0.09	
					Reduced glutathione	0.42 (0.16–1.10), 0.08	
Spector et al. (25)	2005	USA	<1	149/255	Vegetable and fruit plus (VF+)	1	Mother's age at birth of index child, income, and education, and infant's race and sex
					Q1	0.7 (0.4–1.2)	
					Q2	0.5 (0.3–0.9)	
					Q3	0.7 (0.4–1.2)	
					Q4	0.09	
					P trend		
Petridou et al. (26)	2005	Greece	1–4	131/131	Fruits	0.72 (0.57–0.91), 0.007	Maternal age at birth, birth weight, maternal smoking during pregnancy, maternal years of schooling, maternal occupation, and maternal daily energy intake during pregnancy
					Vegetables	0.76 (0.60–0.95), 0.01	
					Fish and seafood	0.72 (0.59–0.89), 0.003	
					Sugars and syrups	1.32 (1.05–1.67), 0.02	
					Meat and meat products	1.25 (1.00–1.57), 0.05	
					Milk and dairy products	0.82 (0.66–1.02), 0.08	
					Butter/margarine	1.41 (0.97–2.06), 0.07	
Kwan et al. (27)	2009	USA	<15	282/282	Vegetable	0.65 (0.50–0.84)	Total energy intake, household income, indoor insecticide exposure during pregnancy, and proportion of foods reported as large or extra-large portion size
					Fruits	0.81 (0.65–1.00)	
					Protein sources	0.55 (0.32–0.96)	
					Legume	0.75 (0.59–0.95)	
					Carrots	0.82 (0.71–0.96)	
					Cantaloupe	0.87 (0.76–0.98)	
					Oranges	0.87 (0.77–0.99)	
					Green beans	0.85 (0.74–0.98)	
					Other beans	0.86 (0.74–0.99)	
					Beef	0.82 (0.69–0.98)	
					Fiber from fruits and vegetables	0.52 (0.31–0.88)	
						0.77 (0.60–0.98)	
					Provitamin A carotenoids	0.78 (0.65–0.93)	
					α-Carotene	0.79 (0.62–1.01)	
					β-Carotene	0.82 (0.66–1.01)	
					Lutein	0.48 (0.25–0.90)	
					Total glutathione	0.49 (0.27-0.90)	
					Reduced glutathione		
Bailey et al. (28)	2012	Australia	<15	333/695	Dietary folate (μg)		
					≤395	Reference	Energy intake
					>395–454	0.68 (0.44–1.06)	
					>454–524	0.58 (0.37–0.91)	
					>524–624	0.44 (0.27–0.71)	
					>624	0.70 (0.44–1.12)	
					P trend	0.05	
					Dietary B6 (mg)		
					≤1.39	Reference	
					>1.39–1.54	1.04 (0.67–1.62)	
					>1.54–1.67	1.15 (0.74–1.81)	
					>1.67–1.85	1.28 (0.82–2.00)	
					>1.85	1.60 (1.02–2.51)	
					P trend	0.03	
					Dietary B12 (μg)		
					≤3.18	Reference	
					>3.18–3.75	0.72 (0.47, 1.10)	
					>3.75–4.27	0.79 (0.52, 1.21)	
					>4.27–5.34	0.85 (0.56, 1.31)	
					>5.34	0.49 (0.31, 0.77)	
					P trend	0.02	

m = month; Q = quartile; wk = week; ALL = acute lymphoblastic leukemia.

Table 2. Characteristics of studies investigating maternal alcohol intake and childhood ALL risk.

Author	Year published	Country	Age of children (years)	Number of cases/ controls	Alcoholic beverage type consumed by mother	OR/AOR (95% CI)*P* value	Adjustment factor
Slater et al. (22)	2011	USA	<1	264/156	**>1 alcoholic drink per week**		Maternal age, education, race/ ethnicity and alcohol use during pregnancy, household income and child's year of birth
					Year before pregnancy	0.85 (0.60, 1.20)	
					During pregnancy	0.75 (0.49, 1.17)	
Bonaventure et al.(18)	2013	France	<15	648/1681	**Any alcohol drinking (wine, beer or cider, spirits)**		Gender × age quota variable, birth order, breastfeeding, maternal education, parental socioprofessional category, and European ancestry
					<1 glass/week	1.8 (1.1–3.0)	
					1 or 2 glasses/week	1.1 (0.6–2.2)	
					>2 glasses/week	1.2 (0.5–2.8)	
Milne et al. (20)	2013	Australia	<15	388/1396	**12 months before pregnancy**		Matching variables (age, sex, and residency), year of birth group, maternal age group, ethnicity, household income, birth order, maternal smoking
					Any alcohol (light, mid-strength and full-strength beer, wine, premixed soda, and spirits)	0.50 (0.38, 0.66)	
					>0–2 days/week	0.51 (0.36, 0.72)	
					>2–4 days/week	0.66 (0.44, 0.97)	
					>4–7 days/week	0.51 (0.34, 0.78)	
					>7 days/week	0.38 (0.26, 0.55)	
					During pregnancy		
					Any	0.62 (0.48, 0.81)	
					>0–2 days/week	0.66 (0.49, 0.88)	
					>2 days/week	0.56 (0.37, 0.86)	
Ferreira et al. (19)	2015	Brazil	≤2	193/423	**Preconception**		Use of oral contraceptives during pregnancy, maternal age at child birth, maternal education, birth weight, and infant ethnicity
					Beer		
					≤1 glass/week	1.30 (0.71–2.36)	
					>1 glass/week	1.47 (0.88–2.46)	
					During pregnancy		
					≤1 glass/week	1.13 (0.50–2.52)	
					>1 glass/week	1.43 (0.74–2.77)	
					Preconception		
					Spirits		
					≤1 glass/week	0.79 (0.08–7.90)	
					>1 glass/week	0 (0.0)	
					During pregnancy		
					≤1 glass/week	0 (0.0)	
					>1 glass/week	0 (0.0)	
					Preconception		
					Other beverage		
					≤1 glass/week	1.93 (0.84–4.44)	
					>1 glass/week	0.93 (0.28–3.16)	
					During pregnancy		
					≤1 glass/week	0.99 (0.28–3.46)	
					>1 glass/week	1.19 (0.27–5.19)	
Orsi et al. (21)	2015	France	<15	636/1421	**Alcohol during pregnancy (glass/week)**		Sex, mother's age at child's birth, mother's education, and birth order
					<1	1.0 (0.7–1.3)	
					1-2	1.0 (0.6–1.5)	
					>2	0.7 (0.4–1.5)	
					Kind of alcohol		
					Wine	1.0 (0.7–1.3)	
					Beer/Cider	0.8 (0.6–1.2)	
					Spirits	1.0 (0.7–1.5)	
					Alcohol during first trimester of pregnancy (glass/week)		
					<1	0.8 (0.5–1.2)	
					1–2	0.9 (0.6–1.4)	
					>2	0.7 (0.4–1.5)	

ALL = acute lymphoblastic leukemia.

A recent meta-analysis showed that higher intake of fruits and vegetables was related to lower risk of mortality from all causes and cardiovascular diseases (30). A case–control study on pancreatic cancer patients also revealed that most of the nutrients present in fruits and vegetables including magnesium, potassium, β-carotene, lutein, zeazanthin, β-cryptoxanthin, vitamin C, thiamin, and vitamin B_6 were associated with decreased risk of the disease (31). Among them, carotenoids might be the most powerful protective groups of compounds. We found some evidence on the protective effects of maternal intake of carotenoid-rich foods like carrot and cantaloupe against childhood ALL. The mentioned nutrients are vitamin A precursors, which may affect immune

modulation, hormone and growth factor signaling, regulatory mechanisms of cell cycle progression, cell differentiation, and apoptosis (32). In 2007, the World Cancer Research Fund reported that (33) increased fruits and vegetables intake was associated with reduced risk of cancer. It is worth noting that this report had used "probable" or "limited-suggestive" for different types of cancer. A meta-analysis demonstrated that blood concentrations of carotenoids are more strongly associated with reduced breast cancer risk compared to dietary intake (34). As consumption of five to nine servings of fruits and vegetables is recommended in a healthy balanced diet (35), it seems prudent for cancer prevention. Mostly, high intake of red meat has been associated with increased cancer risk, while vegetable protein consumption might decrease it (36–38); unlikely, a few studies have shown that total intake of protein is associated with decreased risk of cancer (39). Our knowledge in this area relies on the diet of cancer patients. On the other hand, limited studies have been conducted on maternal diet during pregnancy and its association with offspring risk of malignancies. A recent study revealed that lower protein:carbohydrate ratios in maternal diet during pregnancy were related to increased offspring systolic blood pressure up to 4 years of age (40). Our review showed protective effects of maternal protein sources intake including beef and beans against pediatrics ALL. The only explanation for this finding can be related to glutathione (GSH) content of protein sources. GSH acts as an anticarcinogenic agent in two ways: by acting as an antioxidant and by binding to mutagens (41). Cured meat including bacon, sausage, ham, salami contain salt, nitrite, nitrosamines, polycyclic aromatic hydrocarbons (in smoked meats), or heterocyclic amines (in cooked foods) (42,43). All of these compounds are well known for their role in carcinogenesis as a result of N-nitroso compounds formation in the acidic stomach (44), but underlying mechanism in utero is unclear. Our review showed folate as a cytoprotective agent against cancer. Folate plays role in DNA methylation, its synthesis, and repair (45). Folate deficiency results in cellular *S*-adenosylmethione depletion, which induces DND hypomethylation and consequent proto-oncogene expression leading to cancer (46). Peroxisome proliferator-activator receptor γ (PPAR-γ) is a nuclear transcription factor, which controls gene expression. Folic acid supplementation during pregnancy decreases the methylation of PPAR-γ promoter in rats. Promoter methylation induces PPAR-γ expression (47). It has shown that macrophages and mylomonocytic leukemic cells express abundant PPAR-γ; however, its anticancer effects are controversial (48). Although one study demonstrated vitamin B_6 as a risk factor for ALL, it has been proven that vitamin B_6, vitamin B_{12}, and methionine protect cells against carcinogenesis. These nutrients are involved in one-carbon methylation, which is important for synthesis of DNA, its repair, and methylation (49). Their deficiency results in aberrant gene expression and DNA stability, and finally cancer development (50). Lower folate intake is accompanied by unhealthy behaviors, which may also affect cancer risk (51).

Data from recent case–control studies showed null effects of maternal alcohol consumption on the risk of childhood ALL. This is consistent with a meta-analysis on 21 case–control studies that showed drinking alcohol during pregnancy by mother was significantly related to childhood acute myeloid leukemia (AML), but not with ALL (52). Most commonly used alcoholic beverage by mothers was different among studies, which depend on socioeconomic status. This should be considered in future research. However, it is prudent to avoid drinking alcohol during pregnancy.

Conclusion

In summary, the results of this systematic review showed that mothers with a diet poor in protein, and fruits and vegetables are more likely to deliver a child with higher risk of developing ALL. Our findings confirmed the results of previous meta-analysis, implying neutral effect of maternal alcohol consumption during gestation on offspring ALL.

Limitations

To our knowledge, this is the first review that has attempted to evaluate the relationship between maternal diet and childhood ALL risk. However, our systematic review is limited by the small number of eligible studies included to make the evidence. This is partly due to the fact that some databases like "CINAHL plus, Academic Search Complete, ArticleFirst, and Taylor & Francis" were inaccessible for the authors. The studies reviewed here were heterogonous according to the adjusted factors, using different questionnaires for evaluating maternal diet, and the interval between childbirth and the study. As there were insufficient studies on the association between maternal diet during pregnancy and risk of ALL, we recommend that more research should be done to find a causal relationship. To overcome some of the methodological issues mentioned here as limitation, cohort studies may be more helpful.

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