*Review*

# Role of Maternal Diet in the Risk of Childhood Acute Leukemia: A Systematic Review and Meta-Analysis

Jessica Blanco-Lopez [1],[*],[†], Isabel Iguacel [2],[†], Silvia Pisanu [3], Claudia Choma Bettega Almeida [4], Eva Steliarova-Foucher [1], Ciska Sierens [5], Marc J. Gunter [6], Elena J. Ladas [7], Ronald D. Barr [8], Koen Van Herck [5] and Inge Huybrechts [1]

1   International Agency for Research on Cancer, 69007 Lyon, France
2   Faculty of Health Sciences, University of Zaragoza, 50009 Zaragoza, Spain
3   Department of Biomedical Sciences, Section of Microbiology and Virology, University of Cagliari, 09124 Cagliari, Italy
4   Department of Nutrition, Federal University of Paraná, Curitiba 1299, Brazil
5   Department of Public Health and Primary Care, Ghent University, 9000 Ghent, Belgium
6   Faculty of Medicine, School of Public Health, Imperial College London, London SW7 2AZ, UK
7   Division of Hematology, Oncology, and Stem Cell Transplantation, Department of Pediatrics, Columbia University Irving Medical Center, New York, NY 10032, USA
8   Departments of Pediatrics, Pathology and Medicine, McMaster University, Hamilton, ON L8S 4L7, Canada
*   Correspondence: blancoj@iarc.who.int; Fax: +33-(0)4-72-73-85-75
†   These authors contributed equally to this work.

**Abstract:** Many studies have investigated the etiology of acute leukemia, one of the most common types of cancer in children; however, there is a lack of clarity regarding preventable risk factors. This systematic review and meta-analysis aimed to summarize the current evidence regarding the role of maternal dietary factors in the development of childhood leukemia. All epidemiological studies published until July 2022 that evaluated maternal dietary risk factors for childhood acute leukemia were identified in two electronic databases (PubMed and Web of Science) without limits of publication year or language. A total of 38 studies (1 prospective cohort study, 34 case-control studies and 3 studies with pooled analysis) were included. The published risk estimates were combined into a meta-analysis, using the Generic Inverse Variance method. The maternal consumption of fruits (two or more daily servings vs. less) was inversely associated with acute lymphoblastic leukemia (odds ratio = 0.71; 95% CI, 0.59–0.86), whereas maternal coffee intake (higher than two cups per day vs. no consumption) was associated with an increased risk of acute lymphoblastic leukemia (odds ratio = 1.45; 95% CI, 1.12–1.89). Despite these findings, more high-quality research from cohort studies and the identification of causal factors are needed to develop evidence-based and cost-effective prevention strategies applicable at the population level. Review Registration: PROSPERO registration no. CRD42019128937.

**Keywords:** acute lymphoblastic leukemia; acute myeloid leukemia; maternal diet; prevention; risk factor

## 1. Introduction

Acute leukemia is one of the most frequently diagnosed cancers among children and adolescents. Its worldwide incidence is approximately 46 cases per million per year in children aged 0–14 years and approximately 29 cases per million in adolescents aged 15–19 years [1]. In many populations of children aged 0–14 years, almost 80% of cases have acute lymphoblastic leukemia (ALL), while 15% have acute myeloid leukemia (AML) [2].

The etiology of childhood acute leukemia is linked to X-ray radiation exposure, specific forms of chemotherapy and some genetic syndromes [3]. However, all these risk factors together may explain only 10% of cases [4]. Although acute leukemia is the most common cancer in children and adolescents, it is a rare disease; therefore, studying its etiology

remains challenging. Nonetheless, a causal mechanism for the most common variant (ALL) has been proposed, which incorporates both antenatal and postnatal factors [5].

Considering the differential incidence of acute leukemia by geographic region worldwide, the potential roles of lifestyle and environmental factors in its etiology have been proposed [1]. A peak incidence occurs at approximately two-five years of age, and it is reasonable to assume that factors in the prenatal or perinatal period affect the pathogenesis of childhood leukemia [3,6]. Indeed, several studies have demonstrated an increased risk of leukemia due to maternal smoking and alcohol consumption during pregnancy [7,8]. However, little is known about the impact of other lifestyle factors such as the mother's overall diet during pregnancy on the risk of childhood leukemia.

The current systematic review and meta-analysis focused on the role of maternal diet in the risk of childhood acute leukemia. It provides an overview of existing data linking the influence of maternal diet, supplementation and the consumption of non-alcoholic beverages to the development of acute leukemia in children. We used combined evidence to assess the potential impact of maternal diet on the risk of childhood acute leukemia.

## 2. Materials and Methods

### 2.1. Definition of the Outcome

The main outcome of our systematic review is acute leukemia (AL) incidence in children aged 0–14 years and adolescents aged 15–19 years. The leukemia types considered included acute lymphoblastic leukemia (ALL) and acute non-lymphoblastic leukemia (ANLL), mainly acute myeloid leukemia (AML).

### 2.2. Definition of the Risk Factors

The exposures included maternal dietary and non-alcoholic drink intake and supplements consumed during the peri-pregnancy period.

### 2.3. Systematic Review Registration

Details of the protocol for this systematic review were registered on PROSPERO, registration number CRD42019128937.

### 2.4. Search Strategy

To identify the maternal dietary factors that have been studied in relation to childhood leukemia risk, we performed a multi-tiered electronic search of PubMed and Web of Science. First, an explorative search for studies on leukemia in infants, children and adolescents was conducted in December 2017; this was not restricted by language or publication date. A total of 66 studies were identified in this search. Based on the results of this first search, we were able to narrow down the keywords further and perform a more targeted search in July 2022, which focused on some identified maternal exposures such as dietary intake (food groups and micronutrients), consumption of non-alcoholic beverages (coffee, tea and soft drinks) and supplements used during pregnancy, and no limit of publication year or language restriction was used. For all constructs, database-specific thesauri were used to identify the relevant synonyms. The search strategy is illustrated in Figure 1.

### 2.5. Selection of the Studies and Quality Assessment

Studies were eligible for inclusion if they reported effect estimates (relative risk (RR), odds ratio (OR) or hazard ratio (HR) and 95% confidence intervals (CI)) or if they provided sufficient data to calculate the estimates for different levels of exposure.

Table 1 lists the inclusion and exclusion criteria used in the review. The PRISMA guidelines were followed [9] (Supplementary Table S1). All references found through the search questions (Figure 1) were imported into the Endnote software program (Version x8, Clarivate Analytics, Philadelphia, PA, USA). Two authors independently searched each database (Pubmed and Web of Science) for publications. Any uncertainty regarding the selection of a given article was resolved after screening by a third reviewer (IH) and

discussed in the working group, if needed. The final eligibility criteria for the included studies are listed according to the PICOS (Table 2), and the selected studies included for each extracted factor are summarized in Table 3.
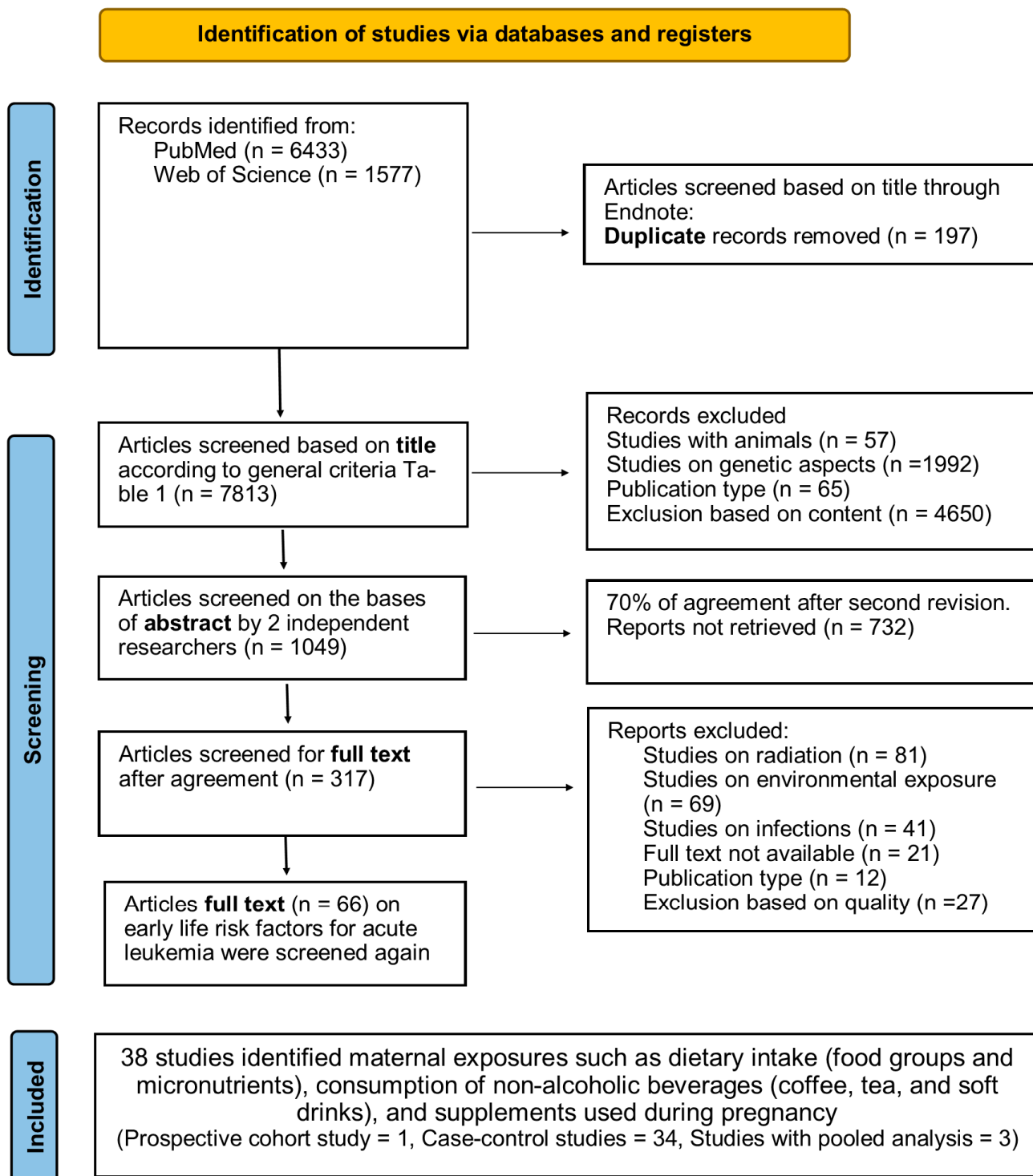
**Identification of studies via databases and registers**

**Identification**

Records identified from:
    PubMed (n = 6433)
    Web of Science (n = 1577)

Articles screened based on title through Endnote:
**Duplicate** records removed (n = 197)

**Screening**

Articles screened based on **title** according to general criteria Table 1 (n = 7813)

Records excluded
Studies with animals (n = 57)
Studies on genetic aspects (n =1992)
Publication type (n = 65)
Exclusion based on content (n = 4650)

Articles screened on the bases of **abstract** by 2 independent researchers (n = 1049)

70% of agreement after second revision.
Reports not retrieved (n = 732)

Articles screened for **full text** after agreement (n = 317)

Reports excluded:
    Studies on radiation (n = 81)
    Studies on environmental exposure (n = 69)
    Studies on infections (n = 41)
    Full text not available (n = 21)
    Publication type (n = 12)
    Exclusion based on quality (n =27)

Articles **full text** (n = 66) on early life risk factors for acute leukemia were screened again

**Included**

38 studies identified maternal exposures such as dietary intake (food groups and micronutrients), consumption of non-alcoholic beverages (coffee, tea, and soft drinks), and supplements used during pregnancy
(Prospective cohort study = 1, Case-control studies = 34, Studies with pooled analysis = 3)

**Figure 1.** Search Strategy.

**Table 1.** Inclusion and exclusion criteria.

| General inclusion criteria |
| --- |
|     All studies describing the maternal dietary factors and their influence on the incidence of acute leukemia in children and adolescents were included in the systematic review. The risk factors considered were maternal nutrition (food and beverages) and supplement use during pregnancy. Pooled analysis including new data was also included in the review. |

| General exclusion criteria |
| --- |
| • Studies on animals<br>• Studies on the genetic aspects<br>• Full text not available<br>• Studies without original data (editorial, review, reports, guidelines) |

| Exclusion criteria based on content |
| --- |
| • Studies of leukemia in children who already have other concomitant disorders (e.g., Down syndrome, congenital malformations)<br>• Studies of the association between radiation and leukemia (e.g., prenatal boot setting for X-rays during pregnancy; living near a nuclear power station)<br>• Studies of the association between environmental exposure and leukemia (e.g., air pollution, exhaust fumes, pesticides)<br>• Studies on the association between infectious diseases and leukemia (maternal infections during pregnancy, illness of the child in the early years of life, presence in the nursery) |

| Exclusion criteria based on study scope and data quality |
| --- |
| • Small studies (e.g., fewer than 50 cases)<br>• Insufficient quality based on the checklist of Fowkes et al. |

**Table 2.** PICOS criteria for inclusion and exclusion of studies.

| Parameter | Criterion |
| --- | --- |
| Participants | Children and adolescents diagnosed with acute leukemia |
| Interventions | Maternal dietary intake (including food groups and caffeinated beverages) and supplements |
| Control/comparator group | Healthy children and adolescents |
| Outcomes | Childhood acute leukemia |
| Study design | Observational studies with a comparison group (cohort studies, case-control studies) |

    Subsequently, quality control of the selected articles was performed using the checklist by Fowkes et al. to ensure the inclusion of high-quality studies [10]. This checklist includes questions on the study design and sample, control group characteristics, quality of measurements and outcomes, completeness and influences of distortions. A major flaw identified for a given criterion is flagged by the sign ++. The + sign was applied to a criterion with a minor flaw. In case of no flaws, nil (0) was applied. If a study scored ++ on more than one criterion of this checklist, it was excluded (Figure 1). The quality control results of the selected articles are shown in Supplementary Table S2.

**Table 3.** Overview of the included studies.

| Extracted Factors<br>(Maternal Factors during Pregnancy) | Number of Included Articles [1] | References |
| --- | :---: | :---: |
| Food group intake (vegetables, fruits, cereals and grains, meats, diary) | 7 | [11–17] |
| Coffee intake | 11 | [15,18–27] |
| Tea intake | 7 | [15,18,19,21–24] |
| Soft drink intake (cola drinks) | 3 | [15,16,22] |

*Int. J. Environ. Res. Public Health* **2023**, *20*, 5428

5 of 28

**Table 3.** *Cont.*

| Extracted Factors (Maternal Factors during Pregnancy) | Number of Included Articles [1] | References |
|---|---|---|
| Micronutrient intake (glutathione, carotenoids, folates, etc.) | 4 | [11,14,28,29] |
| Supplements of vitamins and minerals (folic acid, iron, etc.) | 21 | [11,14,28–46] |

[1] A total of 38 studies were included in total (1 prospective cohort study, 3 pooled analysis studies and 34 case-control studies).

### 2.6. Data Extraction

Table 4 summarizes the included studies by name, design, sample size, age at diagnosis and country of study population. The extracted key data from all included studies, effect estimates (RR, OR, or HR, 95% CI) and tested confounding variables are presented in Tables 5–10. The results from the pooled studies were also included, as reported in the summary tables.

### 2.7. Quantitative Meta-Analysis

A quantitative analysis of the risk of AL, ALL, or AML in children was performed to determine the risk factors that met the eligibility criteria for the meta-analysis. For each included factor, the choice of performing an additional quantitative analysis was based on the number (at least two studies) and homogeneity of the included studies (e.g., results from studies restricted to infants or from univariate analysis with no adjustments were not pooled with the rest of the results) and overlapping study data were also excluded. We used the adjusted odds ratio (OR) reported in case-control studies and the relative risk (RR) reported in cohort studies to calculate the overall effect. The analyses were conducted using the Generic Inverse Variance method, in which the weight of each study was equivalent to the inverse of the variance of the effect estimate [47]. A random-effects model was used if there was evidence of heterogeneity. Some exposures were reported at different levels; consequently, we calculated an estimate for binary exposure status (exposed vs. not exposed) by pooling exposed cases and controls across all levels of exposure. I2 statistics were used to assess heterogeneity, where 0% indicated perfect homogeneity and 100% complete heterogeneity [48]. Data were analyzed using Review Manager (RevMan) V.5.4.1, Cochrane, London, UK [49]. The results are summarized in Table 11.

*Int. J. Environ. Res. Public Health* **2023**, *20*, 5428

6 of 28

**Table 4.** Characteristics of the included studies.

| Study/Reference | Location and Study Period | Leukemia Type | Age Range (Years) | Cases/Controls | Control Source | Maternal Exposure Variable(s) | Source(s)/Assessment Tool |
|---|---|---|---|---|---|---|---|
| Cohort | | | | | | | |
| Madsen et al. [27] | Denmark, 1996–2002 | Acute leukemia | 0–14 | 96/Cohort 141, 216 | | Coffee and tea consumption | Health registries |
| Case control | | | | | | | |
| Abudaowd et al. [31] | Saudi Arabia, 2008–2019 | ALL, AML | 1–19 | 74/148 | Community controls matched on age and gender | Use of supplements | Structured telephone interview |
| Ajrouche et al. [40] (ESTELLE [a]) | France, 2010–2011 | ALL, AML | 0–14 | 747/1421 | Population controls matched on age and gender | Use of supplements | Structured telephone questionnaires |
| Amigou et al. [41] (ESCALE [a]) | France, 2003–2004 | ALL, AML | 0–14 | 764/1681 | Randomly selected from French households with a landline telephone | Use of supplements | Standardized telephone interview |
| Bailey et al. [28] (Aus-ALL [b]) | Australia, 2003–2007 | ALL | 0–14 | 333/695 | Prospectively recruited by random digit dialing and matched on age, sex and residence | Micronutrients and supplements | Mailed, self-administered questionnaires and Food Frequency Questionaries |
| Bonaventure et al. [22] 2013 (ESCALE [a]) | France, 2003–2004 | ALL, AML | 0–14 | 764/1681 | Randomly selected with a landline telephone | Coffee, tea and cola drink consumption | Interviewed with standardized questionnaires |
| Bonaventure et al. [30] 2015 (UKCCS [c]) | UK, 1991–1996 | ALL, AML | 0–14 | 864/2524 | Community controls matched on sex, month and year of birth and region of residence | Use of supplements | Primary care (general practice) records |
| Clavel et al. [26] (ADELE [a]) | France, 1995–1999 | ALL, AML | 0–14 | 247/288 | Hospitalized controls (for diseases other than cancer or birth defects) matched on age, gender and center | Coffee consumption | Interviewer-administered questionnaire |

**Table 4.** *Cont.*

| Study/Reference | Location and Study Period | Leukemia Type | Age Range (Years) | Cases/Controls | Control Source | Maternal Exposure Variable(s) | Source(s)/Assessment Tool |
|---|---|---|---|---|---|---|---|
| Dockerty et al. [42] | New Zealand, 1990–1993 | ALL | 0–14 | 97/303 | Randomly from birth records, on age and sex | Use of supplements | Interviewer-administered questionnaire |
| Jensen et al. [11] (NCCLS [d]) | Northern California, 1995–1999 | ALL | 0–14 | 138/138 | Community controls matched on age, sex, Hispanic ethnicity and maternal race | Dietary intake, micronutrient and supplement use | Interviewer-administered questionnaire |
| Kwan et al. [35] (NCCLS [d]) | California, 1995–2002 | Acute leukemia | 0–14 | 311/398 | Community controls matched on age, sex, Hispanic ethnicity and maternal race | Use of supplements | Interviewer-administered questionnaire |
| Kwan et al. [14] (NCCLS [d]) | California, 1995–2002 | ALL | 0–14 | 282/359 | Community controls matched on age, sex, Hispanic ethnicity and maternal race | Dietary intake and micronutrients | Interviewer-administered questionnaire |
| Linabery et al. [36] (COG [e]) | USA, Canada, 1996–2006 | ALL, AML | <1 year | 443/324 | Community controls matched on birth year and location of residence | Use of supplements | Telephone interviews |
| McKinney et al. [32] | Scotland, 1976–1994 | Acute leukemia | 0–14 | 144/716 | Community controls matched on age, sex, region (for four studies) | Use of supplements | Interviewer-administered questionnaire |
| Menegaux et al. [20] (ELECTRE [a]) | France, 1995–1998 | ALL, AML | 0–14 | 534/567 | Community controls matched on age, sex, region | Coffee consumption | Self-administered standardized questionnaire |
| Menegaux et al. [21] (ADELE [a]) | France, 1995–1999 | ALL, AML | 0–14 | 280/288 | Hospitalized controls (for diseases other than cancer or birth defects) matched on age, gender and center | Coffee and tea consumption | Interviewer-administered questionnaire |
| Milne et al. [43] (Aus-ALL [b]) | Australia, 2003–2007 | ALL | 0–14 | 416/1361 | Prospectively recruited by random digit dialing and matched on age, sex and residence | Use of supplements | Mailed, self-administered questionnaires and Food Frequency Questionaries |

*Int. J. Environ. Res. Public Health* **2023**, 20, 5428

8 of 28

**Table 4.** *Cont.*

| Study/Reference | Location and Study Period | Leukemia Type | Age Range (Years) | Cases/Controls | Control Source | Maternal Exposure Variable(s) | Source(s)/Assessment Tool |
|---|---|---|---|---|---|---|---|
| Milne et al. [23] (Aus-ALL [b]) | Australia, 2003–2007 | ALL | 0–14 | 393/1249 | Prospectively recruited by random digit dialing and matched on age, sex and residence | Coffee and tea consumption | Mailed, self-administered questionnaires and Food Frequency Questionaries |
| Ognjanovic et al. [44] (COG [e]) | USA, Canada, 1996–2006 | ALL, AML | <1 year | 434/323 | Community controls matched on birth year and location of residence | Use of supplements | Telephone interview |
| Orsi et al. [24] (ESTELLE [a]) | France, 2010–2011 | ALL, AML | 0–14 | 747/1421 | Community controls matched on age and gender | Coffee and tea consumption | Structured telephone questionnaires |
| Peters et al. [16] | California, USA, 1980–1987 | Acute leukemia | 0–10 | 232/288 | Community controls matched on age, ethnicity and sex by random digit dialing | Dietary intake and cola drink consumption | Interviewer-administered questionnaire |
| Petridou et al. [25] | Greece, 1993–1994 | Acute leukemia | 0–14 | 153/300 | Hospitalized controls matched on age and sex, contemporaneously hospitalized for minor conditions | Coffee consumption | Interviewer-administered questionnaire |
| Petridou et al. [13] | Greece, 1999–2003 | ALL | 0–4 | 131/131 | Hospitalized controls matched on age and sex, contemporaneously hospitalized for minor conditions | Dietary intake | Interviewer-administered questionnaire |
| Robison et al. [33] (CCG [f]) | USA, 1980–1984 | AML | 0–14 | 204/203 | Controls were chosen with random digit dialing and matched on age, race and location | Use of supplements | Interview |
| Ross et al. [15] (CCG [f]) | USA, 1983–1988 | AML | <18 months | 84/97 | Controls were chosen with random digit dialing and matched on age, race and location | Dietary intake, coffee, tea and cola drink consumption and use of supplements | Medical records and interview |

*Int. J. Environ. Res. Public Health* **2023**, *20*, 5428

9 of 28

**Table 4.** *Cont.*

| Study/Reference | Location and Study Period | Leukemia Type | Age Range (Years) | Cases/Controls | Control Source | Maternal Exposure Variable(s) | Source(s)/Assessment Tool |
|---|---|---|---|---|---|---|---|
| Sarasua et al. [12] | USA, 1973–1986 | ALL | 0–14 | 56/206 | Community controls matched by age, sex and telephone exchange area. By random digit dialing | Dietary intake | Medical records and interview |
| Schuz et al. [37] | Germany, 1992–1997 | ALL, AML | 0–14 | 755/2057 | Community controls matched on age, sex and residence | Use of supplements | Self-administered questionnaire and telephone interview |
| Shaw et al. [38] | Canada, 1980–2000 | Acute leukemia | 0–14 | 789/789 | Community controls matched on age and sex | Use of supplements | Telephone interview |
| Singer et al. [17] (NCCLS [d]) | California, 1995–2008 | ALL, AML | 0–14 | 784/1,076 | Community controls matched on age, sex, Hispanic ethnicity and maternal race | Dietary intake | Interviewer-administered questionnaire |
| Singer et al. [29] (NCCLS [d]) | California, 1995–2008 | ALL, AML | 0–14 | 784/1,076 | Community controls matched on age, sex, Hispanic ethnicity and maternal race | Micronutrient intake and maternal supplement use | Interviewer-administered questionnaire |
| Thompson et al. [45] | Australia, 1984–1992 | ALL | 0–14 | 98/166 | Controls matched for age and sex randomly selected from the state electoral roll | Use of supplements | Self-administered questionnaire, interview and medical records |
| Van Steensel-Moll et al. [34] | Netherlands, 1973–2010 | ALL | 0–14 | 519/507 | Community controls matched on age, sex and residence | Use of supplements | Mailed questionnaires |
| Wen et al. [39] (CCG [f]) | USA, Canada, Australia, 1989–1993 | ALL | 0–14 | 1842/1986 | Controls were chosen with random digit dialing and matched on age, race and location | Use of supplements | Telephone interview |

*Int. J. Environ. Res. Public Health* **2023**, *20*, 5428

10 of 28

**Table 4.** *Cont.*

| Study/Reference | Location and Study Period | Leukemia Type | Age Range (Years) | Cases/Controls | Control Source | Maternal Exposure Variable(s) | Source(s)/Assessment Tool |
|---|---|---|---|---|---|---|---|
| Pooled analysis | | | | | | | |
| Karalexi et al. [18] (CLIC [g]) | France, Germany, Greece, USA, 1999–2003 | AML | 0–14 | 444/1255 | Community controls matched on age and sex | Coffee and tea consumption | Self-administered questionnaire and telephone interview |
| Metayer et al. [46] (CLIC [g]) | Australia, Canada, France, Germany, New Zealand and the United States (from CLIC) and Brazil, Costa Rica, Egypt and Greece, 1980–2012 | ALL, AML | 0–14 | 7548/11,635 | Controls participating in age-matched studies | Use of supplements | Self-administered questionnaire and telephone interview |
| Milne et al. [19] (CLIC [g]) | France, Australia, Greece, USA, 1995–2016 | ALL | 0–14 | 2552/4876 | Community controls (matched by study variables) | Coffee and tea consumption | Food frequency questionnaires and general questionnaires |

[a] ADELE, ELECTRE, ESCALE and ESTELLE studies are part of Etude Sur les Cancers et les Leucémies de l'Enfant, Study on Environmental and Genetic Risk Factors of Childhood Cancers and Leukemia, ADELE and ELECTRE, which studied leukemias from 1995 to 1998; ESCALE (2002–2003) and ESTELLE (2010–2011) studied cancer and leukemia. [b] Aus-ALL: Australian Study of Causes of Acute Lymphoblastic Leukemia in Children. [c] UKCCS: United Kingdom Childhood Cancer Study. [d] NCCLS: Northern California Childhood Leukemia Study. [e] COG: Children's Oncology Group. [f] CCG: Children's Cancer Group. [g] CLIC: Childhood Leukemia International Consortium.

**Table 5.** Overview of the association between maternal food group intake during pregnancy (if not specified) and the risk of acute leukemia in children.

| Reference | Type of Leukemia | Food Group | OR | 95% CI | Adjustments |
|---|---|---|---|---|---|
| Jensen et al. [11] [&] | ALL | Vegetables | 0.53 | 0.33–0.85 * | Total energy intake, income, history of miscarriage or stillbirth, hours of exposure to other children in day care, indoor exposure to insecticide during pregnancy and the proportion of foods reported as great or very large |
| | | Fruits | 0.71 | 0.49–1.04 | |
| | | Grain products | 1.6 | 0.37–1.98 | |
| | | Dairy products | 1.16 | 0.78–1.72 | |
| | | Protein sources | 0.4 | 0.18–0.90 * | |
| | | Cured meat | 0.71 | 0.44–1.15 | |
| | | Fat, sweets and snacks | 1.18 | 0.67–2.06 | |
| Kwan et al. [14] [&] | ALL | Vegetables (excludes salad, potatoes, soup and stew) | 0.65 | 0.50–0.84 * | Adjusted for total energy intake, household income, indoor insecticide exposure during pregnancy and proportion of foods reported as large or extra-large portion size |
| | | Fruit (excludes fruit juice) | 0.81 | 0.65–1.00 * | |
| | | Grain products | 1.2 | 0.70–2.05 | |
| | | Dairy products | 1.06 | 0.83–1.35 | |
| | | Legumes | 0.75 | 0.59–0.95 * | |
| | | Protein sources | 0.55 | 0.32–0.96 * | |
| | | Cured meat | 0.91 | 0.78–1.05 | |
| Peters et al. [16] | Acute leukemia | ≥12 servings/month: Ham, bacon and sausage | 1 | 0.50–2.00 | Self-reported use of indoor pesticides, hair dryers, black-and-white televisions and fathers' occupational exposure to spray paint during pregnancy and to other chemical exposures post-pregnancy |
| | | Hot dogs | 2.4 | 0.70–8.10 | |
| | | Bologna, pastrami, corned beef and lunch meat | 1.3 | 0.80–2.40 | |
| | | Hamburgers | 1.2 | 0.50–2.50 | |
| | | Charbroiled meats | 0.9 | 0.50–1.80 | |
| | | ≥30 servings/month: Oranges or orange juice | 0.8 | 0.50–1.40 | |
| | | Grapefruit or grapefruit juice | 1.1 | 0.50–2.70 | |
| | | Apple or apple juice | 0.9 | 0.50–1.40 | |
| Petridou et al. [13] | ALL | per quintile increase: Vegetables | 0.76 | 0.60–0.95 * | Sex and age, maternal age at birth, birth weight, maternal smoking during pregnancy, maternal education level, job occupation and total daily energy intake during pregnancy |
| | | Fruits | 0.72 | 0.57–0.91 * | |
| | | Grain products | 1.23 | 0.94–1.60 | |
| | | Milk and dairy products | 0.82 | 0.66–1.02 | |
| | | Meat and meat products | 1.25 | 1.00–1.57 * | |
| | | Butter and margarine | 1.41 | 0.97–2.06 | |
| | | Sugar and syrup | 1.32 | 1.05–1.67 * | |
| | | Pulses and nuts | 0.96 | 0.77–1.20 | |
| | | Fish and seafood | 0.72 | 0.59–0.89 * | |
| Ross et al. [15] | Acute leukemia | Vegetables [#] (daily) | 2.8 | 1.20–6.40 * | Adjusted for maternal education |
| | | Fruits [#] (daily) | 1.6 | 0.70–3.30 | |
| | | Beans [#] (≥1/week) | 1.2 | 0.50–3.10 | |
| | | Butter (≥1/week) | 1.4 | 0.70–3.00 | |
| | | Cured meats (≥4/week) | 1 | 0.50–2.20 | |
| | | Fish (≥4/week) | 0.5 | 0.20–1.10 | |

*Int. J. Environ. Res. Public Health* **2023**, 20, 5428

12 of 28

**Table 5.** *Cont.*

| Reference | Type of Leukemia | Food Group | OR | 95% CI | | Adjustments |
|---|---|---|---|---|---|---|
| Sarasua et al. [12] | ALL | ≥1 serving/week:<br>Ham, bacon and sausage | 1.5 | 0.70–3.00 | | Adjusted for other types of meat (dichotomized), age at diagnosis and per capita income |
| | | Hot dogs | 0.9 | 0.40–1.80 | | |
| | | Hamburgers | 1.2 | 0.50–2.70 | | |
| | | Charcoal-broiled foods | 1 | 0.50–1.90 | | |
| Singer et al. [17] & | ALL | 1 serving/4184 kJ (1000 kcal) | | | | Maternal Hispanic ethnicity, household income, mother's education, father's education, maternal age category and vitamin supplement use |
| | | Vegetables | 0.97 | 0.86–1.10 | | |
| | | Fruits | 0.7 | 0.52–0.94 * | | |
| | | Dairy products | 1.01 | 0.84–1.22 | | |
| | | Dietary fiber from beans (1 g) | 0.95 | 0.88–1.02 | | |
| | | Protein (10 g) | 0.91 | 0.79–1.05 | | |
| | | Fatty acid ratio | 1.07 | 0.78–1.45 | | |
| | | Trans fat (1 g) | 1.07 | 0.99–1.16 | | |
| | | Percentage of energy content from sweets (10%) | 1.09 | 0.94–1.26 | | |
| | AML | 1 serving/4184 kJ (1000 kcal): | | | | |
| | | Vegetables | 0.84 | 0.54–1.30 | | |
| | | Fruits | 0.23 | 0.08–0.70* | | |
| | | Dairy products | 0.87 | 0.48–1.57 | | |
| | | Dietary fiber from beans (1 g) | 1.03 | 0.80–1.34 | | |
| | | Protein (10 g) | 1 | 0.63–1.59 | | |
| | | Fatty acid ratio | 1.08 | 0.42–2.77 | | |
| | | Trans fat (1 g) | 1.11 | 0.85–1.44 | | |
| | | Percentage of energy content from sweets (10%) | 1.4 | 0.84–2.34 | | |

* = Statistically significant results. # Food that is an a priori topoisomerase II inhibitor. & These studies evaluated the intake during the year prior to the index pregnancy to represent the probable nutritional status at the beginning of the pregnancy.

**Table 6.** Overview of the association between maternal coffee consumption during pregnancy and risk of acute leukemia in children.

| Reference | Type of Leukemia | Consumption (Cups per Day) Never as Reference | OR | 95% CI | Adjustments |
|---|---|---|---|---|---|
| Cohort study | | | | | |
| Madsen et al. [27] | Acute leukemia | 0.5–3 | 0.89 | 0.48–1.65 | Adjusted for cohort (Danish National Birth/Aarhus Birth), smoking, maternal age at birth and parity |
| | | >3 | 1.37 | 0.56–3.32 | |
| Case-control study | | | | | |
| Bonaventure et al. [22] | Acute leukemia | <1 | 1.00 | 0.80–1.30 | Gender, age, birth order, breastfeeding, maternal education and parental socio-professional category |
| | | 1–2 | 1.30 | 1.00–1.70 * | |
| | | >2 | 1.60 | 1.20–2.10 * | |
| | ALL | <1 | 1.30 | 0.70–2.10 | |
| | | 1–2 | 1.80 | 1.00–3.30 * | |
| | | >2 | 2.40 | 1.30–4.30 * | |
| | AML | <1 | 1.00 | 0.80–1.30 | |
| | | 1–2 | 1.30 | 1.00–1.70 * | |
| | | >2 | 1.50 | 1.10–2.00 * | |

*Int. J. Environ. Res. Public Health* **2023**, 20, 5428

13 of 28

**Table 6.** *Cont.*

| Reference | Type of Leukemia | Consumption (Cups per Day) Never as Reference | OR | 95% CI | Adjustments |
|---|---|---|---|---|---|
| Clavel et al. [26] | Acute leukemia | <3 | 1.60 | 0.90–2.90 | Age, gender, center, origin and parental socio-professional category |
| | | ≥3 | 4.10 | 1.60–10.10 * | |
| Menegaux et al. [21] | ALL | ≤3 | 1.10 | 0.70–1.80 | Child's age, sex, center, origin |
| | | 4–8 | 2.40 | 1.30–4.70 * | |
| | | >8 | 3.10 | 1.00–9.50 * | |
| | ANLL | ≤3 | 1.60 | 0.60–4.30 | |
| | | 4–8 | 2.80 | 0.70–10.40 | |
| | | >8 | 3.00 | 0.30–35.10 | |
| Menegaux et al. [20] | ALL | ≤3 | 1.10 | 0.80–1.40 | Adjusted for age, gender, region, socio-professional category and birth order |
| | | >3 | 1.40 | 0.90–2.40 | |
| | AML | ≤3 | 1.60 | 0.80–3.00 | |
| | | >3 | 1.40 | 0.50–4.40 | |
| Milne et al. [23] | ALL | 0–1 | 0.77 | 0.51–1.16 | Age, sex, state of residence, maternal age, mother's country of birth and parent education |
| | | >1 | 1.12 | 0.72–1.74 | |
| Orsi et al. [24] | Acute leukemia | ≤1 | 0.80 | 0.70–1.00 | Age, sex, mother's age at child's birth, mother's education and birth order |
| | | >1–2 | 1.00 | 0.70–1.30 | |
| | | >2 | 1.10 | 0.90–1.50 | |
| | ALL | ≤1 | 0.80 | 0.60–1.10 | |
| | | >1–2 | 1.00 | 0.70–1.30 | |
| | | >2 | 1.30 | 1.00–1.70 * | |
| | AML | ≤1 | 0.90 | 0.60–1.50 | |
| | | >1–2 | 1.10 | 0.60–1.90 | |
| | | >2 | 0.50 | 0.20–1.10 | |
| Petridou et al. [25] | Acute leukemia | >2 | 0.89 | 0.55–1.46 | Gender, age and place of residence |
| Ross et al. [15] | Acute leukemia | ≤3/week | 1.50 | 0.70–3.30 | Adjusted for maternal education |
| | | ≥4/week | 2.50 | 1.00–6.20 * | |
| | ALL | ≤3/week | 1.10 | 0.40–3.00 | |
| | | ≥4/week | 2.30 | 0.70–8.20 | |
| | AML | ≤3/week | 2.40 | 0.60–9.20 | |
| | | ≥4/week | 2.60 | 0.70–10.00 | |
| **Pooled analysis** | | | | | |
| Karalexi et al. [18] | AML | 1 | 1.03 | 0.74–1.43 | Child's age, sex, ethnicity, maternal age, household socioeconomic status, maternal smoking, birth weight |
| | | >1 | 1.40 | 1.03–1.92 * | |
| | | 1 cup per day increment | 1.18 | 1.01–1.39 * | |
| Milne et al. [19] | ALL | Any | 1.04 | 0.94–1.19 | Child's age, sex and ethnicity, study of origin, birth order, birth year, maternal age and education, household socioeconomic status, maternal smoking during pregnancy and breastfeeding |
| | | >0–1 | 0.95 | 0.84–1.07 | |
| | | >1–2 | 1.07 | 0.92–1.25 | |
| | | >2 | 1.27 | 1.09–1.48 * | |

\* = Statistically significant results.

*Int. J. Environ. Res. Public Health* **2023**, 20, 5428

14 of 28

**Table 7.** Overview of the association between maternal tea consumption during pregnancy and risk of acute leukemia in children.

| Reference | Type of Leukemia | Consumption (Cups per Day) Never as Reference | OR | 95% CI | Adjustments |
|---|---|---|---|---|---|
| Case control study | | | | | |
| Bonaventure et al. [22] | Acute leukemia | <1 | 1.10 | 0.80–1.50 | Gender, age, birth order, breastfeeding, maternal education and parental socio-professional category |
| | | 1 | 0.80 | 0.70–1.10 | |
| | | >1 | 0.90 | 0.70–1.20 | |
| | ALL | <1 | 1.50 | 0.80–2.70 | |
| | | 1 | 0.90 | 0.50–1.60 | |
| | | >1 | 0.50 | 0.20–1.10 | |
| | AML | <1 | 1.10 | 0.80–1.50 | |
| | | 1 | 0.80 | 0.60–1.10 | |
| | | >1 | 1.00 | 0.70–1.30 | |
| Menegaux et al. [21] | ALL | ≤3 | 1.20 | 0.80–1.90 | Child's age, sex, center, origin |
| | | >3 | 1.20 | 0.60–2.60 | |
| | ANLL | ≤3 | 0.60 | 0.30–1.40 | |
| | | >3 | – | – | |
| Milne et al. [23] | ALL | Any | 0.82 | 0.56–1.18 | Age, sex, state of residence, maternal age, mother's country of birth and parent education |
| | | 0–1 | 0.81 | 0.54–1.22 | |
| | | >1 | 0.82 | 0.54–1.23 | |
| Orsi et al. [24] | Acute leukemia | ≤1 | 0.90 | 0.60–1.20 | Age, sex, mother's age at child's birth, mother's education and birth order. |
| | | 1 | 0.80 | 0.70–1.10 | |
| | | >1 | 1.10 | 0.80–1.40 | |
| | ALL | ≤1 | 0.90 | 0.60–1.20 | |
| | | 1 | 0.80 | 0.60–1.10 | |
| | | >1 | 1.00 | 0.80–1.40 | |
| | AML | ≤1 | 0.90 | 0.40–1.90 | |
| | | 1 | 1.20 | 0.70–2.10 | |
| | | >1 | 1.00 | 0.50.–1.80 | |
| Ross et al. [15] | AML | ≤3/week | 0.50 | 0.10–2.30 | Adjusted for maternal education |
| | | ≥4/week | 0.30 | 0.10–1.70 | |
| Pooled analysis | | | | | |
| Karalexi et al. [18] | AML | 1 | 0.95 | 0.68–1.33 | Child's age, sex, ethnicity, maternal age, household socioeconomic status, maternal smoking, birth weight |
| | | >1 | 0.70 | 0.42–1.15 | |
| | | 1 cup per day increment | 0.87 | 0.70–1.08 | |
| Milne et al. [19] | ALL | Any | 0.94 | 0.85–1.03 | Child's age, sex and ethnicity, study of origin, birth order, birth year, maternal age and education, household socioeconomic status, maternal smoking during pregnancy and breastfeeding |
| | | >0–1 | 0.95 | 0.83–1.08 | |
| | | >1–2 | 0.93 | 0.76–1.15 | |
| | | >2 | 1.02 | 0.83–1.25 | |

**Table 8.** Overview of the association between maternal soft drink consumption during pregnancy and risk of acute leukemia in children.

| Reference | Type of Leukemia | Consumption Never as Reference | OR | 95% CI | Adjustments |
|---|---|---|---|---|---|
| Bonaventure et al. [22] | Acute leukemia | 1 glass/day | 1.10 | 0.80–1.50 | Gender, age, birth order, breastfeeding, maternal education and parental socio-professional category |
| | | >1 glass/week | 1.30 | 1.00–1.60 * | |
| | | >1 glass/day | 1.30 | 1.00–1.80 * | |
| | ALL | 1 glass/day | 0.80 | 0.40–1.80 | |
| | | >1 glass/week | 1.30 | 0.80–2.20 | |
| | | >1 glass/day | 1.10 | 0.50–2.10 | |

**Table 8.** *Cont.*

| Reference | Type of Leukemia | Consumption Never as Reference | OR | 95% CI | Adjustments |
|---|---|---|---|---|---|
|  | AML | 1 glass/day | 1.20 | 0.80–1.60 |  |
|  |  | >1 glass/week | 1.20 | 1.00–1.60 * |  |
|  |  | >1 glass/day | 1.30 | 1.00–1.80 * |  |
| Peters et al. [16] | Acute leukemia | ≥30 glasses/month | 1.00 | 0.60–1.60 | Adjustments for all factors thought to be potential confounders did not affect these associations |
| Ross et al. [15] | Acute leukemia | ≤3 glasses/week | 1.60 | 0.70–3.60 | Adjusted for maternal education |
|  |  | ≥4 glasses/week | 0.90 | 0.40–2.00 |  |
|  | ALL | ≤3 glasses/week | 2.60 | 0.90–7.50 |  |
|  |  | ≥4 glasses/week | 1.00 | 0.30–2.80 |  |
|  | AML | ≤3 glasses/week | 0.70 | 0.10–3.00 |  |
|  |  | ≥4 glasses/week | 0.60 | 0.10–2.30 |  |

\* = Statistically significant results.

**Table 9.** Overview of the association between maternal micronutrient intake during pregnancy (or period specified) and risk of acute leukemia in children.

| Reference | Type of Leukemia | Micronutrient Intake | OR | 95% CI | Adjustments |
|---|---|---|---|---|---|
| Folate |  |  |  |  |  |
| Bailey et al. [28] | ALL | Energy-adjusted dietary folate (mcg) |  |  | Age, sex and state of residence in Australia |
|  |  | <395 | 1.00 |  |  |
|  |  | >395 to 454 | 0.68 | 0.44–1.06 |  |
|  |  | >454 to 524 | 0.58 | 0.37–0.91 * |  |
|  |  | >524 to 624 | 0.44 | 0.27–0.71 * |  |
|  |  | >624 | 0.70 | 0.44–1.12 |  |
|  |  | Energy-adjusted dietary B6 (mg) |  |  |  |
|  |  | <1.39 | 1.00 |  |  |
|  |  | >1.39 to 1.54 | 1.04 | 0.67–1.62 |  |
|  |  | >1.54 to 1.67 | 1.15 | 0.74–1.81 |  |
|  |  | >1.67 to 1.85 | 1.28 | 0.82–2.00 |  |
|  |  | > 1.85 | 1.60 | 1.02–2.51 * |  |
|  |  | Energy-adjusted dietary B12 (mcg) |  |  |  |
|  |  | <3.18 | 1.00 |  |  |
|  |  | >3.18 to 3.75 | 0.72 | 0.47–1.10 |  |
|  |  | >3.75 to 4.27 | 0.79 | 0.52–1.21 |  |
|  |  | >4.27 to 5.34 | 0.85 | 0.56–1.31 |  |
|  |  | >5.34 | 0.49 | 0.31–0.77 * |  |
| Jensen et al. [11] & | ALL | Non-users of vitamin supplements (continuous) |  |  | Energy intake, income, miscarriages or stillbirths, exposure to other children at preschools, indoor exposure to insecticide during pregnancy and the proportions of the food |
|  |  | Folate (dietary folate equivalents) | – | – |  |
|  |  | Vitamin B6 (mg) | – | – |  |
|  |  | Vitamin B12 (mcg) | – | – |  |
|  |  | Alpha carotene (mcg) | 0.66 | 0.42–1.05 |  |
|  |  | Total glutathione (mg) | 0.15 | 0.02–0.96 * |  |
|  |  | Reduced glutathione (mg) | 0.19 | 0.03–1.07 |  |

**Table 9.** *Cont.*

| Reference | Type of Leukemia | Micronutrient Intake | OR | 95% CI | Adjustments |
|---|---|---|---|---|---|
| Kwan et al. [14] [&] | ALL | Median daily intake (continuous) Folate (dietary folate equivalents) Vitamin B6 (mg) Vitamin B12 (mcg) Provitamin A carotenoids (mcg) Alpha-carotene (mcg) Total glutathione (mg) Reduced glutathione (mg) | 1.02 1.12 1.10 0.77 0.78 0.48 0.49 | 0.71–1.47 0.73–1.72 0.82–1.48 0.60–0.98 * 0.65–0.93 * 0.25–0.90 * 0.27–0.90 * | Energy intake, household income, indoor insecticide exposure during pregnancy and proportion of foods reported as large or extra-large portion size |
| Singer et al. [29] [&] | ALL | From food only (continuous, one unit change) Folate (100 dietary folate equivalent/day) Vitamin B6 (1 mg/day) Vitamin B12 (1 mcg/day) | 0.99 0.91 0.97 | 0.93–1.06 0.74–1.12 0.92–1.02 | Adjusted for parents' 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 |
|  | AML | From food only (continuous, one unit change) Folate (100 dietary folate equivalent/day) Vitamin B6 (1 mg/day) Vitamin B12 (1 mcg/day) | 0.90 0.47 0.86 | 0.76–1.07 0.23–0.98 * 0.73–1.02 |  |

* = Statistically significant result. [&] These studies evaluated the intake from the year before to the index pregnancy to represent the probable nutritional status at the beginning of pregnancy.

**Table 10.** Overview of the association between maternal supplement use during pregnancy (or period specified) and the risk of acute leukemia in children.

| Reference | Type of Leukemia | Type of Supplementation (vs. No-Use in the Index Period) | OR | 95% CI | Adjustments |
|---|---|---|---|---|---|
| Case control study | | | | | |
| Abudaowd et al. [31] | Acute leukemia | Folate | 0.181 | 0.076–0.43 * | Univariate analysis |
| Ajrouche et al. [40] | Acute leukemia | Folic acid (before) Folic acid | 0.70 0.80 | 0.50–1.00 * 0.50–1.20 | Age, gender, birth order, maternal educational and maternal age at child's birth |
|  | ALL | Folic acid (before) Folic acid (first trimester) Folic acid (second trimester) Folic acid (third trimester) | 0.70 1.10 1.10 1.20 | 0.50–1.10 0.90–1.50 0.90–1.50 0.90–1.60 |  |
|  | AML | Folic acid (three months before) Folic acid (first trimester) Folic acid (second trimester) Folic acid (third trimester) | 0.40 1.00 1.10 1.20 | 0.10–1.20 0.50–1.70 0.60–2.00 0.70–2.20 |  |
| Amigou et al. [41] | Acute leukemia | Folic acid (pre-conception or first trimester) Folic acid (second trimester) Folic acid (third trimester) Folic acid Folic acid or multivitamin | 0.30 0.60 0.30 0.40 0.60 | 0.20–0.60 * 0.30–1.00 * 0.10–0.70 * 0.30–0.60 * 0.50–0.80 | Age, gender and socioeconomic status |
|  | ALL | Folic acid (pre-conception or first trimester) Folic acid (second trimester) Folic acid (third trimester) Folic acid Folic acid or multivitamin | 0.30 0.60 0.20 0.40 0.70 | 0.20–0.70 * 0.30–1.10 0.10–0.80 * 0.30–0.60 * 0.50–0.90 * |  |

*Int. J. Environ. Res. Public Health* **2023**, 20, 5428

17 of 28

**Table 10.** *Cont.*

| Reference | Type of Leukemia | Type of Supplementation (vs. No-Use in the Index Period) | OR | 95% CI | Adjustments |
|---|---|---|---|---|---|
| | ANLL | Folic acid (pre-conception or first trimester) | 0.20 | 0.00–1.40 | |
| | | Folic acid (second trimester) | 0.50 | 0.10–2.00 | |
| | | Folic acid (third trimester) | 0.40 | 0.10–2.80 | |
| | | Folic acid | 0.30 | 0.10–0.90 * | |
| | | Folic acid or multivitamin | 0.60 | 0.30–1.10 | |
| Bailey et al. [28] | ALL | Any folate supplement use | 1.05 | 0.75–1.48 | Age, sex and state of residence |
| | | Any B6 or B12 supplement use | 1.22 | 0.87–1.71 | |
| Bonaventure et al. [30] | ALL | Iron | 1.36 | 1.14–1.63 * | Year of birth |
| | AML | | 1.26 | 0.86–1.85 | |
| Dockerty et al. [42] | ALL | Folic acid (with or without iron) | 1.10 | 0.50–2.70 | Age, sex, marital status and mother's education |
| | | Multivitamins | 0.80 | 0.20–3.10 | |
| | | Other vitamin or mineral supplements | 1.50 | 0.70–3.10 | |
| | | Iron (with or without folic acid) | 1.20 | 0.70–2.10 | |
| | | Iron without folic acid | 1.30 | 0.80–2.30 | |
| Jensen et al. [11] [&] | ALL | Average daily intake, continuous (before pregnancy) | | | Total energy intake, income, history of miscarriage or stillbirth, hours of exposure to other children in day care, indoor exposure to insecticide during pregnancy and the proportions of food as great or very large |
| | | Vitamin A | 0.58 | 0.32–0.98 * | |
| | | Folic acid | 0.78 | 0.33–1.81 | |
| | | Vitamin B6 | 0.84 | 0.41–1.75 | |
| | | Vitamin B12 | 0.86 | 0.45–1.45 | |
| | | Iron | 0.89 | 0.51–1.53 | |
| Kwan et al. [35] | Acute leukemia | Iron (3 months before pregnancy and during breastfeeding) | 0.70 | 0.51–0.97 * | Household income, maternal education, maternal age at birth |
| | | Iron (3 months before and during pregnancy) | 0.76 | 0.52–1.11 | |
| | ALL | Iron (3 months before pregnancy and during breastfeeding) | 0.67 | 0.47–0.94 * | |
| | | Iron (3 months before and during pregnancy) | 0.72 | 0.47–1.09 | |
| Kwan et al. [14] [&] | ALL | Median daily intake, continuous (before pregnancy) | | | Adjusted for total energy intake, household income, indoor insecticide exposure during pregnancy and proportion of foods reported as large or extra-large portion size |
| | | Vitamin A | 0.82 | 0.62–1.08 | |
| | | Folate | 1.02 | 0.71–1.47 | |
| | | Vitamin B6 | 1.12 | 0.73–1.72 | |
| | | Vitamin B12 | 1.10 | 0.82–1.48 | |
| | | Iron | 1.05 | 0.77–1.44 | |
| Linabery et al. [36] | ALL | Any prenatal vitamins | 0.63 | 0.34–1.18 | Race/ethnicity, household income |
| | | Vitamins (periconceptional) | 0.77 | 0.54–1.11 | |
| | | Vitamins | 0.66 | 0.39–1.11 | |
| | | Vitamins (the year before and during pregnancy) | 0.77 | 0.55–1.09 | |
| | | Iron (before pregnancy) | 1.22 | 0.82–1.80 | |
| | | Iron (periconceptional) | 1.30 | 0.62–2.72 | |
| | | Iron | 1.22 | 0.81–1.84 | |
| | | Iron (the year before and during pregnancy) | 3.04 | 0.77–12.03 | |
| | AML | Any prenatal vitamins | 1.20 | 0.53–2.73 | Race/ethnicity, household income |
| | | Vitamins (periconceptional) | 1.05 | 0.68–1.61 | |
| | | Vitamins | 1.05 | 0.55–2.04 | |
| | | Vitamins (the year before and during pregnancy) | 0.88 | 0.60–1.31 | |
| | | Iron (before pregnancy) | 0.82 | 0.51–1.33 | |
| | | Iron (periconceptional) | 1.26 | 0.55–2.88 | |
| | | Iron | 0.77 | 0.46–1.27 | |
| | | Iron (the year before and during pregnancy) | 1.72 | 0.33–9.06 | |

*Int. J. Environ. Res. Public Health* **2023**, *20*, 5428

18 of 28

**Table 10.** *Cont.*

| Reference | Type of Leukemia | Type of Supplementation (vs. No-Use in the Index Period) | OR | 95% CI | Adjustments |
|---|---|---|---|---|---|
| McKinney et al. [32] | Acute leukemia | Iron supplements | 0.95 | 0.62–1.45 | Maternal age |
| | ALL | Iron supplements | 0.80 | 0.51–1.25 | |
| Milne et al. [43] | ALL | Folate (first trimester) | 1.19 | 0.91–1.56 | Age, sex, residence, ethnicity, education, birth order and maternal age |
| | | Folate (second and third trimester) | 0.83 | 0.65–1.06 | |
| | | Iron (first trimester) | 1.08 | 0.43–2.75 | |
| | | Iron (second and third trimester) | 1.04 | 0.57–1.89 | |
| Ognjanovic et al. [44] | ALL | Multivitamin | 0.71 | 0.51–1.00 * | Child's year of birth |
| | AML | | 0.79 | 0.53–1.17 | |
| Robison et al. [33] | ALL | Vitamins/Iron | 1.00 | 0.51–1.96 | Adjusted for potential confounding factors |
| Schuz et al. [37] | ALL | Vitamins, folate and/or iron | 0.84 | 0.69–1.01 | Sex, age, year of birth, degree of urbanization and socioeconomic status |
| | AML | | 1.13 | 0.74–1.72 | |
| Shaw et al. [38] | ALL | Vitamins with folic acid | 1.00 | 0.80–1.20 | Maternal education and maternal age at birth |
| | | Other vitamins | 1.00 | 0.70–1.30 | |
| Singer et al. [29] & | ALL | Continuous, unite change (before pregnancy) Folate (100 dietary folate equivalent/day) | 0.97 | 0.94–1.01 | Father's and 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) |
| | | Vitamin B12 (1 mg/day) | 0.96 | 0.93–1.00 * | |
| | | Vitamin B6 (1 mg/day) | 0.89 | 0.79–1.00 * | |
| | AML | Continuous, unite change (before pregnancy) Folate 100 dietary folate equivalent/day | 0.93 | 0.85–1.03 | |
| | | Vitamin B6 1 mg/day | 0.72 | 0.51–1.04 | |
| | | Vitamin B12 1 mg/day | 0.92 | 0.84–1.02 | |
| Thompson et al. [45] | ALL | Folate with or without iron | 0.40 | 0.21–0.73 * | Univariate analysis |
| | | Iron or folate | 0.37 | 0.21–0.65 * | |
| | | Iron and folate | 0.41 | 0.22–0.75 * | |
| | | Iron alone | 0.75 | 0.37–1.51 | |
| Van Steensel-Moll et al. [34] | Acute leukemia | Iron preparations | 1.30 | 0.90–2.00 | Age and sex |
| Wen et al. [39] | ALL | Vitamins | 0.70 | 0.50–1.00 *† | Immuno-phenotype, sex, age, household income, maternal and paternal race, education, smoking and drinking before or during pregnancy |
| | | Iron supplements | 0.90 | 0.70–1.00 * | |
| Pooled analysis | | | | | |
| Metayer et al. [46] | ALL | Folic acid (any time) | 0.80 | 0.71–0.89 * | Age, sex, ethnicity, parental education and study |
| | | Folic acid (pre-conception) | 0.82 | 0.70–0.96 * | |
| | | Folic acid | 0.77 | 0.67–0.88 * | |
| | | Folic acid (before and during pregnancy) | 0.78 | 0.78–0.91 * | |
| | | Vitamins (any time) | 0.85 | 0.78–0.92 * | |
| | | Vitamins (pre-conception) | 0.82 | 0.79–0.99 * | |
| | | Vitamins | 0.81 | 0.74–0.88 * | |
| | | Vitamins (before and during pregnancy) | 0.78 | 0.69–0.88 * | |
| | AML | Folic acid (any time) | 0.68 | 0.48–0.96 * | |
| | | Folic acid (pre-conception) | 0.88 | 0.59–1.32 | |
| | | Folic acid | 0.52 | 0.31–0.89 * | |
| | | Vitamins (any time) | 0.92 | 0.75–1.14 | |
| | | Vitamins (pre-conception) | 0.96 | 0.66–1.39 | |
| | | Vitamins | 0.85 | 0.64–1.14 | |

* = Statistically significant results; † = 99% CI; & These studies evaluated the intake during the year before the index pregnancy to represent the probable nutritional status at the beginning of pregnancy.

*Int. J. Environ. Res. Public Health* **2023**, 20, 5428

19 of 28

**Table 11.** Summary Odds Ratios (ORs) and 95% Confidence Intervals (CIs) obtained in meta-analysis of data from referenced published studies of association of childhood leukemia with maternal dietary intake.

| | Leukemia Type | No. of Studies | References | OR (95% CI) | Heterogeneity I2, *p* |
|---|---|---|---|---|---|
| **Food group** | | | | | |
| Fruits | Acute leukemia | – | | – | – |
| | ALL | 2 | [13,17] | 0.71 (0.59–0.86) | 0%, 0.0003 |
| | AML | – | | – | – |
| Vegetables | Acute leukemia | – | | – | – |
| | ALL | 2 | [13,17] | 0.88 (0.69–1.11) | 69%, 0.28 |
| | AML | – | | – | – |
| Grains | Acute leukemia | – | | – | – |
| | ALL | 2 | [13,17] | 1.22 (0.96–1.56) | 0%, 0.10 |
| | AML | – | | – | – |
| Dairy products | Acute leukemia | – | | – | – |
| | ALL | 2 | [13,17] | 0.92 (0.75–1.12) | 51%, 0.41 |
| | AML | – | | – | – |
| Processed meat (cured meat) | Acute leukemia | – | | – | – |
| | ALL | 2 | [13,17] | 1.01 (0.68–1.51) | 37%, 0.96 |
| | AML | – | | – | – |
| **Non-alcoholic drinks** | | | | | |
| Coffee | Acute leukemia | 5 | [22,24–27] | 1.36 (0.97–1.91) | 68%, 0.08 |
| | ALL | 5 | [20–24] | 1.45 (1.12–1.89) | 35%, 0.005 |
| | AML | 4 | [20–22,24] | 1.18 (0.66–2.13) | 45%, 0.56 |
| Tea | Acute leukemia | 2 | [22,24] | 0.97 (0.80–1.51) | 0%, 0.78 |
| | ALL | 4 | [22–24] | 0.95 (0.79–1.14) | 0%, 0.56 |
| | AML | 2 | [22,24] | 1.00 (0.73–1.37) | 0%, 1.00 |
| Soft drinks | Acute leukemia | 2 | [16,22] | 1.23 (0.97–1.55) | 0%, 0.08 |
| | ALL | – | | – | – |
| | AML | – | | – | – |
| **Supplements** | | | | | |
| Folic Acid | Acute leukemia | 2 | [40,41] | 0.55 (0.28–1.09) | 84%, 0.08 |
| | ALL | 6 | [28,29,40,41,43,45] | 0.77 (0.59–1.01) | 89%, 0.06 |
| | AML | 3 | [29,40,41] | 0.87 (0.56–1.36) | 59%, 0.54 |
| Iron | Acute leukemia | 3 | [32,34,35] | 0.94 (0.65–1.38) | 68%, 0.30 |
| | ALL | 7 | [30,32,35,39,42–44] | 0.96 (0.76–1.21) | 73%, 0.35 |
| | AML | – | | – | – |

For each included factor, quantitative analysis was performed with at least two studies; results from studies restricted to infants, univariate analysis with no adjustments and overlapping data were excluded.

## 3. Results

### 3.1. Selected Studies

The results of the search strategy and process of selecting studies for review are illustrated in Figure 1. The preliminary search returned 7813 studies, which were screened based on the title. Following the assessment of titles and abstracts, 317 articles met the criteria for full-text review. The subsequent screening of the full reports of the 317 selected publications resulted in the selection of 38 eligible studies.

### 3.2. Study Characteristics

Table 3 provides an overview of the number of studies included in each extracted exposure. The detailed characteristics (authorship, year of publication, study design,

Int. J. Environ. Res. Public Health **2023**, 20, 5428

20 of 28

period and place of the study, number and age of participants, control source and extracted exposure variables) of each included study are shown in Table 4.

### 3.3. Quality Assessment

The quality assessment [10] for the included studies is shown in Supplementary Table S2. The most common weakness of many studies was the lack of adjustment for possible confounding factors such as maternal smoking status, maternal alcohol consumption and perinatal factors. The confounding factors used in the analysis for each included study are shown in Tables 5–10.

### 3.4. Maternal Intake

#### 3.4.1. Food Group Intakes

Seven case-control studies [11–17] investigated the association between maternal dietary intake and the risk of AL in children. The results are summarized in Table 5.

Two studies reported results for AL, one focused on cured meats but their results did not achieve statistical significance [16] and the other reported a statistically significant increased risk of leukemia in infants with the maternal daily consumption of fresh vegetables identified a priori as containing DNA topoisomerase II inhibitors [15].

Regarding ALL, three consecutive studies [11,14,17] conducted by the Northern California Childhood Leukemia Study (NCCLS) reported a statistically significant inverse association with a higher daily consumption of vegetables, fruits and proteins. Further analysis determined that these associations were statistically significant for carrots, cantaloupe, oranges, green beans, beans and beef. A case-control study [13] reported statistically significant inverse associations between the consumption of fruits, vegetables and fish during pregnancy and the risk of ALL in children. Conversely, a higher intake of sugar and syrup and meat and meat products had a statistically significantly increased risk of ALL. Two other studies [12,15] did not report statistically significant associations between the consumption of cured meats and ALL. A meta-analysis of two studies [13,17] was performed, in which a statistically significant inverse estimate for ALL was found for higher maternal consumption of fruits (OR = 0.71, 95% CI: 0.59–0.86), but not for vegetables (OR = 0.88, 95% CI: 0.69–1.11), and of two [12,14] studies for cured meats, which was not significant (OR = 1.01, 95% CI: 0.68–1.51) (Table 11).

A statistically significant increased risk for AML was reported in one case-control study related to the intake of certain fresh vegetables (e.g., vegetables such as onions, broccoli and asparagus that are rich in Quercetin, which induces human DNA topoisomerase II) [15], and another study reported an inverse association with fruit consumption [17].

#### 3.4.2. Non-Alcoholic Drinks

A. Coffee

Two pooled studies [18,19], eight case-control studies [15,20–26] and one cohort study [27] evaluated the association between the maternal consumption of coffee during pregnancy and the risk of AL (Table 6).

A cohort study [27] (N = 141,216/AL cases = 96) reported no statistically significant association between coffee intake during pregnancy and the risk of AL. In the present meta-analysis, including five studies [22,24–27] that compared the highest vs. the lowest consumption reported for coffee intake during pregnancy, we did not observe a statistically significant association for AL (OR = 1.36, 95% CI: 0.97–1.91).

In a pooled study [19] of eight case-control studies (from published [20–24] and unpublished data), an increased risk of ALL in children whose mother's coffee intake was more than two cups per day in comparison with no consumption (OR = 1.27, 95% CI: 1.09–1.43, p = 0.005) was reported. A meta-analysis of five studies [20–24] comparing the highest vs. the lowest consumption reported a similar result (OR = 1.45, 95% CI: 1.12–1.89).

Another pooled study [18] of eight case-control studies reported an increased risk of AML for children whose mothers consumed more than one cup per day (OR = 1.40,

95% CI: 1.03–1.92), and the risk increased with increments of one cup per day (OR = 1.18, 95% CI: 1.01–1.39). A meta-analysis of four studies comparing the highest versus the lowest consumption for AML [20,22–24] reported that the association was not statistically significant (OR = 1.18, 95% CI: 0.66–2.13) (Table 11, Figure 2a–c).
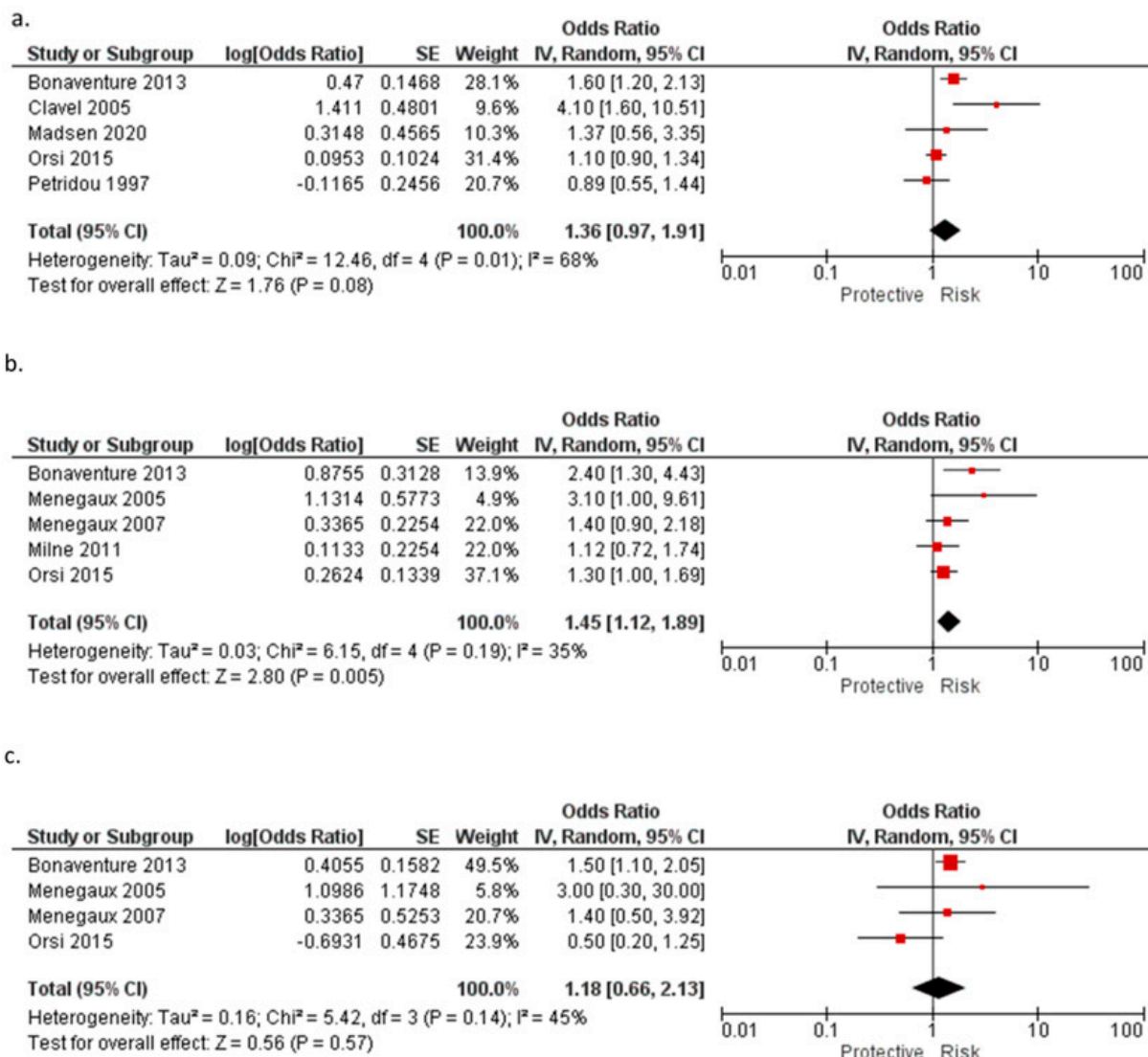


**Figure 2.** Meta-analysis of the association between the consumption of coffee during pregnancy and (**a**) acute leukemia [22,24–27], (**b**) acute lymphoblastic leukemia [20–24] and (**c**) acute myeloid leukemia [20–22,24]. Note: the individual estimate (OR) from the studies are represented by the red box, and the black diamond represents the estimate of the meta-analysis.

B.  Tea

Two pooled analyses [18,19] and five case-control studies [15,20–24] evaluated the association between maternal tea consumption during pregnancy and the risk of AL (Table 7).

Overall, the case control studies [15,20–24] did not report any statistically significant associations between maternal tea intake during pregnancy and the risk of childhood AL. Both pooled analyses looked for dose responses and interactions, but the findings were null [18,19]. A recent cohort study also added tea intake to their model and found no association (data not reported) [27]. A meta-analysis of two [22,24] studies found no statistically significant association estimate for AL with the highest vs. the lowest consumption of tea (OR = 0.97, 95% CI: 0.80–1.51) (Table 11).

    C.    Soft drinks

Three case-control studies [15,16,22] evaluated the association between maternal intake of soft drinks (mostly cola beverages) and AL risk (Table 8). Only one case-control study [22] reported an increased risk with the maternal intake of cola beverages and AL, especially for AML. A meta-analysis of the three studies found marginal association estimates for AL with the highest vs. the lowest consumption of cola beverages (OR = 1.23, 95% CI: 0.97–1.55) (Table 11).

### 3.5. Nutrients

#### 3.5.1. Micronutrient Intake

Four case-control studies [11,14,28,29] evaluated the association between maternal micronutrient intake and the risk of childhood AL (Table 9). Two of these studies from the NCCLS reported estimations with micronutrients from food only. One [11] found that the total glutathione level was inversely associated with ALL. Another study reported an inverse association between the daily vitamin B6 intake dose and the risk of AML [29].

#### 3.5.2. Supplements of Vitamins and Minerals

Twenty case-control studies [11,14,28–45] and one pooled study [46] evaluated the association between vitamin and mineral supplementation during pregnancy and the risk of AL in children. The results are compared in Table 10.

Folic acid supplementation and the risk of AL have been widely studied [11,14,28,29,31, 40–43,45]. A pooled study [46], which included published [11,14,41–43,45] and unpublished data, reported an inverse association between maternal folic acid for ALL (OR = 0.77, 95% CI: 0.67–0.88) and AML (OR = 0.52, 95% CI: 0.31–0.89) with supplementation during pregnancy versus no supplementation. A meta-analysis performed on two studies [40,41] (OR = 0.55, 95% CI: 0.28–1.09) for AL and on six studies [28,29,40,41,43,45] (OR = 0.77, 95% CI: 0.59–1.01) for ALL did not yield statistically significant results (Table 11, Figure 3a–c).
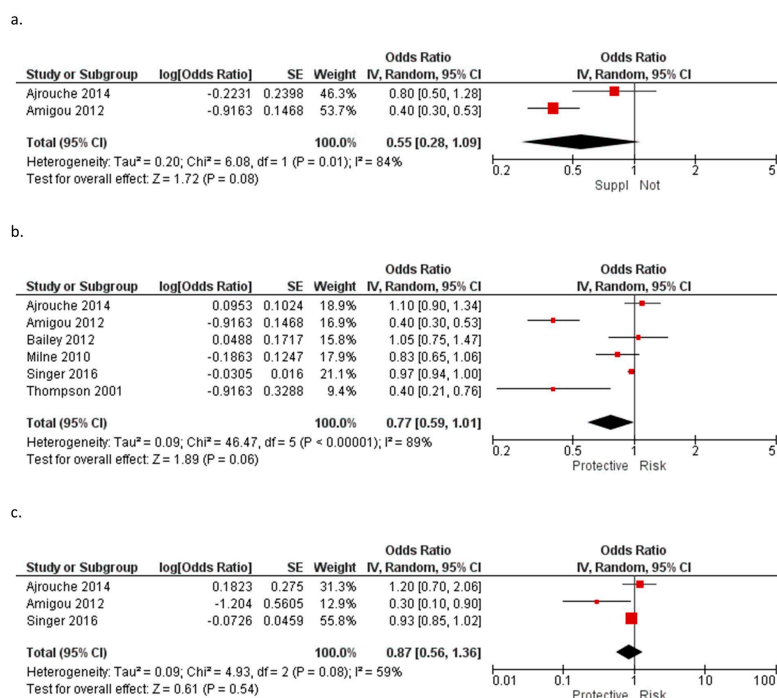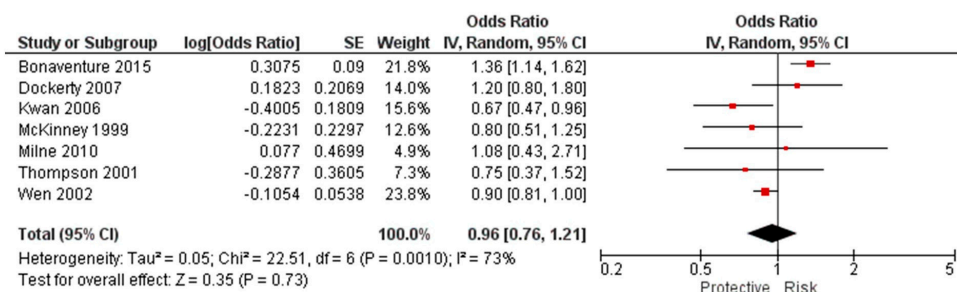


**Figure 3.** Meta-analysis of the association between the supplementation with folic acid during pregnancy and (**a**) acute leukemia [40,41], (**b**) acute lymphoblastic leukemia [28,29,40,41,43,45] and (**c**) acute myeloid leukemia [29,40,41]. Note: the individual estimate (OR) from the studies are represented by the red box, and the black diamond represent the estimate of the meta-analysis.

Supplementation with iron during pregnancy and the risk of childhood leukemia in offspring have also been studied [11,14,30,32,34–37,39,43,45]. Most studies have reported non-statistically significant associations with AL, ALL, or AML. A meta-analysis of iron supplementation during pregnancy in three studies [32,34,35] for AL (OR = 0.94, 95% CI: 0.65–1.38) and seven studies [30,32,35,39,42,43,45] for ALL (OR = 0.96, 95% CI: 0.76–1.21) found no statistically significant results (Table 11, Figure 4a,b).

a.

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI |
|---|---|---|---|---|
| Kwan 2006 | -0.3567 | 0.1616 | 36.4% | 0.70 [0.51, 0.96] |
| McKinney 1999 | -0.0513 | 0.2177 | 30.1% | 0.95 [0.62, 1.46] |
| Van Steensel-Moll 1985 | 0.2624 | 0.1876 | 33.4% | 1.30 [0.90, 1.88] |
| **Total (95% CI)** | | | **100.0%** | **0.94 [0.65, 1.38]** |

Heterogeneity: Tau² = 0.08; Chi² = 6.28, df = 2 (P = 0.04); I² = 68%
Test for overall effect: Z = 0.30 (P = 0.76)

b.

| Study or Subgroup | log[Odds Ratio] | SE | Weight | Odds Ratio IV, Random, 95% CI |
|---|---|---|---|---|
| Bonaventure 2015 | 0.3075 | 0.09 | 21.8% | 1.36 [1.14, 1.62] |
| Dockerty 2007 | 0.1823 | 0.2069 | 14.0% | 1.20 [0.80, 1.80] |
| Kwan 2006 | -0.4005 | 0.1809 | 15.6% | 0.67 [0.47, 0.96] |
| McKinney 1999 | -0.2231 | 0.2297 | 12.6% | 0.80 [0.51, 1.25] |
| Milne 2010 | 0.077 | 0.4699 | 4.9% | 1.08 [0.43, 2.71] |
| Thompson 2001 | -0.2877 | 0.3605 | 7.3% | 0.75 [0.37, 1.52] |
| Wen 2002 | -0.1054 | 0.0538 | 23.8% | 0.90 [0.81, 1.00] |
| **Total (95% CI)** | | | **100.0%** | **0.96 [0.76, 1.21]** |

Heterogeneity: Tau² = 0.05; Chi² = 22.51, df = 6 (P = 0.0010); I² = 73%
Test for overall effect: Z = 0.35 (P = 0.73)

**Figure 4.** Meta-analysis of the association between the supplementation with iron during pregnancy and (**a**) acute leukemia [32,34,35] and (**b**) acute lymphoblastic leukemia [30,32,35,39,42,43,45]. Note: the individual estimate (OR) from the studies are represented by the red box, and the black diamond represent the estimate of the meta-analysis.

Supplementation with multivitamins during pregnancy has been reported [33,36–38,42–44]. A pooled analysis [46] that included published [37,38,42,43] and unpublished data reported an inverse association for ALL (OR = 0.81, 95% CI: 0.74–0.88) with supplementation during pregnancy. A meta-analysis was not performed for this supplementation owing to the heterogeneity of the data.

## 4. Discussion

### 4.1. Summary of the Main Findings

The main findings of the systematic review suggest that maternal dietary intake rich in vegetables, fruits and protein sources (beans and beef) and supplementation with folic acid and multivitamins during pregnancy could have a protective effect against childhood acute leukemia. The increased intake of cured meats, coffee and/or caffeinated beverages could increase the risk of childhood acute leukemia. Some of these findings were confirmed by our meta-analysis; a higher maternal consumption of fruits was significantly inversely associated with ALL (OR = 0.71, 95% CI: 0.59–0.86). This association was recently found in a previous meta-analysis [50] in which fruit (OR = 0.81, 95% CI: 0.67–0.99), vegetables (OR: 0.51, 95% CI: 0.28,0.94) and legumes (OR = 0.76, 95% CI: 0.62–0.94) were inversely associated with ALL.

Our meta-analysis also confirmed that regular maternal coffee intake higher than two cups per day was associated with an increased risk of ALL (OR = 1.45; 95% CI, 1.12–1.89). Similarly, in a meta-analysis published in 2014 [51] maternal coffee consumption (high drinkers vs. non/lowest drinkers) was associated with an increased risk of ALL (OR = 1.65, 95% CI: 1.28–2.12) and childhood AML (OR = 1.58, 95% CI: 1.20–2.08). The results of other meta-analyses published in 2015 [52] on maternal coffee consumption (high

*Int. J. Environ. Res. Public Health* **2023**, 20, 5428

24 of 28

drinkers vs. non/lowest drinkers) were associated with an increased risk of AL ( OR = 1.57, 95% CI: 1.14–2.11) and ALL (OR = 1.43, 95% CI: 1.22–1.68) but not AML (OR = 1.81, 95% CI: 0.93–3.53). The results of a meta-analysis published in 2016 [53] found an increased risk of ALL associated with coffee drinking during pregnancy (adjusted OR = 1.44, 95% CI: 1.07–1.92).

Regarding maternal tea consumption during pregnancy, our analysis did not find a statistically significant association. These findings are consistent with those of a previous meta-analysis [52].

Regarding soft drink intake during pregnancy, the analysis suggested a possible increased risk for AL, but this finding was not significant. A previous meta-analysis [52] reported an increased risk between low and moderate consumption for AL (OR = 1.21, 95% CI: 1.03–1.44) and ALL (OR = 1.31, 95% CI: 1.09–1.59).

Folic acid supplementation during pregnancy suggested a modest inverse association with ALL (OR = 0.77; 95% CI: 0.59–1.01). A recent systematic review reported that the use of maternal folic acid supplementation before pregnancy was associated with a 30% decreased risk of ALL (OR = 0.69, 95% CI: 0.50–0.95) and the use of vitamin supplements before pregnancy was associated with a 20% decreased risk of ALL (OR = 0.81, 95% CI: 0.74–0.88) [50]. A more recent meta-analysis reported an inverse association between folic acid supplementation and ALL (OR = 0.75, 95% CI: 0.66–0.86) [54].

### 4.2. Potential Mechanisms

The inverse association between maternal fruit and vegetable intake and the risk of AL could be explained mainly by the high content of protective bioactive components such as micronutrients and fiber. Some fruits and vegetables that were found to be protective in some studies [11,14] are rich in carotenoids, flavonoids and vitamins A and C, which are important for DNA repair [55,56]. Also, the presence of the antioxidant tripeptide glutathione, present in meat and vegetables, plays a critical role in many cellular processes such as cell differentiation, proliferation and apoptosis [57].

Some studies suggest the association between the maternal intake of cured meats and the risk of childhood AL. This is because of the presence of N-nitroso precursors in these meats that can be converted to carcinogenic components [58] by acids in the stomach and then transported through the placenta to the developing child. This might increase the risk of malignancy as a result [59].

The decreased risk of ALL associated with the maternal use of vitamin formulations as supplements can be explained by the capacities of the components, including folate and iron, to protect against oxidative damage to lipids, lipoproteins and DNA [56]. On the other hand, folic acid and its derivatives, known as folates, are chemo-protective micronutrients with an essential role in the maintenance of health and genomic integrity [60].

The increased risk of AL associated with the maternal consumption of coffee and other caffeinated drinks could potentially be explained by the effects of their components (caffeine and chlorogenic acid) in inhibiting Topoisomerase I and Topoisomerase II [61,62], which are nuclear enzymes that solve the topological problems associated with DNA replication, transcription, recombination and chromatin remodeling [63]. Tea contains lower levels of caffeine, folate and polyphenols, which might explain the divergent results of coffee consumption.

### 4.3. Strengths and Limitations

The present systematic review and meta-analysis integrated the available published information regarding maternal dietary intake and the risk of childhood AL. Unfortunately, most of the evidence comes from case-control studies (which are prone to recall bias) that were conducted more than a decade ago and restricted to high-income countries. It is also important to note that the accurate evaluation of dietary intake is challenging. We also noticed that some studies restricted their search to specific food items [18] and, given the

*Int. J. Environ. Res. Public Health* **2023**, *20*, 5428

25 of 28

heterogeneity of how results were reported (above all the studies), this makes it difficult to compare results.

However, there are new generation studies (biomarker-based, which are not the focus of this review) that can support some of these findings. Studies have been conducted to assess the presence of carcinogens (such as acrylamide, nitrosamines and others) in the maternal diet, which can be found in the placenta, linked to fetal hemoglobin, and can also be found in newborn lymphocytes. Since these biomarkers were also found in healthy children, further studies focusing on genetic variants found some polymorphisms that could affect the expression of enzymes such as folate hydrolase 1. With lower detoxifying activity, DNA damage or the higher activity of carcinogens may occur [64].

Regardless of the limitations of these studies, professionals dedicated to treating childhood cancer have demonstrated a great capacity to collaborate and collect high-quality data and biospecimens. This could lead to improvements in the quantity and quality of future research, for more prospective cohort studies and a more comprehensive and accurate assessment of the role of nutrition in carcinogenesis are needed.

## 5. Conclusions

This systematic review of the available literature indicates that a maternal diet rich in vegetables, fruits and supplementation with folic acid and multivitamins during pregnancy could be inversely associated with the risk of childhood AL, while a higher intake of coffee and/or caffeinated beverages could increase the risk. Only the results regarding maternal diet rich in fruits and the consumption of coffee in relation with childhood AL were confirmed by the meta-analysis performed on the available published data. Although this review sheds light on the risk factors related to maternal diets and the prevention of cancers in children and adolescents, more studies are needed to confirm causality and the potential mechanisms involved.

## References

1. Steliarova-Foucher, E.; Colombet, M.; Ries, L.A.G.; Moreno, F.; Dolya, A.; Bray, F.; Hesseling, P.; Shin, H.Y.; Stiller, C.A.; Bouzbid, S.; et al. International incidence of childhood cancer, 2001–10: A population-based registry study. *Lancet. Oncol.* **2017**, *18*, 719–731. [CrossRef] [PubMed]
2. Coebergh, J.W.; Reedijk, A.M.; de Vries, E.; Martos, C.; Jakab, Z.; Steliarova-Foucher, E.; Kamps, W.A. Leukaemia incidence and survival in children and adolescents in Europe during 1978-1997. Report from the Automated Childhood Cancer Information System project. *Eur. J. Cancer* **2006**, *42*, 2019–2036. [CrossRef] [PubMed]
3. Belson, M.; Kingsley, B.; Holmes, A. Risk factors for acute leukemia in children: A review. *Environ. Health Persp.* **2007**, *115*, 138–145. [CrossRef] [PubMed]

4.  Wiemels, J. Perspectives on the causes of childhood leukemia. *Chem. Biol. Interact.* **2012**, *196*, 59–67. [CrossRef]
5.  Greaves, M. A causal mechanism for childhood acute lymphoblastic leukaemia. *Nat. Rev. Cancer.* **2018**, *18*, 471–484. [CrossRef]
6.  dos Santos Silva, I. *Cancer Epidemiology: Principles and Methods*; IARC Press: Lyon, France, 1999; pp. 1–34.
7.  Cao, Y.; Lu, J. Paternal Smoking Before Conception and During Pregnancy Is Associated With an Increased Risk of Childhood Acute Lymphoblastic Leukemia: A Systematic Review and Meta-Analysis of 17 Case-Control Studies. *J. Pediatr. Hematol. Oncol.* **2020**, *42*, 32–40.
8.  Karalexi, M.A.; Dessypris, N.; Thomopoulos, T.P.; Ntouvelis, E.; Kantzanou, M.; Diamantaras, A.A.; Moschovi, M.; Baka, M.; Hatzipantelis, E.; Kourti, M.; et al. Parental alcohol consumption and risk of leukemia in the offspring: A systematic review and meta-analysis. *Eur. J. Cancer Prev.* **2017**, *26*, 433–441. [CrossRef]
9.  Moher, D.; Liberati, A.; Tetzlaff, J.; Altman, D.G.; Group, P. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Med.* **2009**, *6*, e1000097. [CrossRef]
10. Fowkes, F.; Fulton, P. Critical appraisal of published research: Introductory guidelines. *Brit. Med. J.* **1991**, *302*, 1136–1140. [CrossRef]
11. Jensen, C.D.; Block, G.; Buffler, P.; Ma, X.; Selvin, S.; Month, S. Maternal dietary risk factors in childhood acute lymphoblastic leukemia (United States). *Cancer Causes Control* **2004**, *15*, 559–570. [CrossRef]
12. Sarasua, S.; Savitz, D.A. Cured and broiled meat consumption in relation to childhood cancer: Denver, Colorado (United States). *Cancer Causes Control* **1994**, *5*, 141–148. [CrossRef] [PubMed]
13. Petridou, E.; Ntouvelis, E.; Dessypris, N.; Terzidis, A.; Trichopoulos, D. Maternal Diet and Acute Lymphoblastic Leukemia in Young Children. *Cancer Epidem. Biomar.* **2005**, *14*, 1935–1939. [CrossRef]
14. Kwan, M.L.; Block, G.; Hudes, M.L.; Chu, L.W.; Buffler, P.A. Maternal diet and risk of childhood acute lymphoblastic leukemia. *Public Health Rep.* **2009**, *124*, 503–514. [CrossRef] [PubMed]
15. Ross, J.A.; Potter, J.D.; Reaman, G.H.; Pendergrass, T.W.; Robison, L.L. Maternal exposure to potential inhibitors of DNA topoisomerase II and infant leukemia (United States): A report from the Children's Cancer Group. *Cancer Causes Control* **1996**, *7*, 581–590. [CrossRef]
16. Peters, J.M.; Preston-Martin, S.; London, S.J.; Bowthan, J.D.; Buckley, J.D.; Thomas, D.C. Processed meats and risk of childhood leukemia (California, USA). *Am. J. Epidemiol.* **1994**, *5*, 195–202. [CrossRef]
17. Singer, A.W.; Carmichael, S.L.; Selvin, S.; Fu, C.; Block, G.; Metayer, C. Maternal diet quality before pregnancy and risk of childhood leukaemia. *Br. J. Nutr.* **2016**, *116*, 1469–1478. [CrossRef]
18. Karalexi, M.A.; Dessypris, N.; Clavel, J.; Metayer, C.; Erdmann, F.; Orsi, L.; Kang, A.Y.; Schuz, J.; Bonaventure, A.; Greenop, K.R.; et al. Coffee and tea consumption during pregnancy and risk of childhood acute myeloid leukemia: A Childhood Leukemia International Consortium (CLIC) study. *Cancer Epidemiol.* **2019**, *62*, 101581. [CrossRef]
19. Milne, E.; Greenop, K.R.; Petridou, E.; Bailey, H.D.; Orsi, L.; Kang, A.Y.; Baka, M.; Bonaventure, A.; Kourti, M.; Metayer, C.; et al. Maternal consumption of coffee and tea during pregnancy and risk of childhood ALL: A pooled analysis from the childhood Leukemia International Consortium. *Cancer Causes Control* **2018**, *29*, 539–550. [CrossRef]
20. Menegaux, F.; Ripert, M.; Hemon, D.; Clavel, J. Maternal alcohol and coffee drinking, parental smoking and childhood leukaemia: A French population-based case-control study. *Paediatr. Perinat. Epidemiol.* **2007**, *21*, 293–299. [CrossRef]
21. Menegaux, F.; Steffen, C.; Bellec, S.; Baruchel, A.; Lescoeur, B.; Leverger, G.; Nelken, B.; Philippe, N.; Sommelet, D.; Hemon, D.; et al. Maternal coffee and alcohol consumption during pregnancy, parental smoking and risk of childhood acute leukaemia. *Cancer Detect Prev.* **2005**, *29*, 487–493. [CrossRef]
22. Bonaventure, A.; Rudant, J.; Goujon-Bellec, S.; Orsi, L.; Leverger, G.; Baruchel, A.; Bertrand, Y.; Nelken, B.; Pasquet, M.; Michel, G.; et al. Childhood acute leukemia, maternal beverage intake during pregnancy, and metabolic polymorphisms. *Cancer Causes Control* **2013**, *24*, 783–793. [CrossRef] [PubMed]
23. Milne, E.; Royle, J.A.; Bennett, L.C.; de Klerk, N.H.; Bailey, H.D.; Bower, C.; Miller, M.; Attia, J.; Scott, R.J.; Kirby, M.; et al. Maternal consumption of coffee and tea during pregnancy and risk of childhood ALL: Results from an Australian case-control study. *Cancer Causes Control* **2011**, *22*, 207–218. [CrossRef] [PubMed]
24. Orsi, L.; Rudant, J.; Ajrouche, R.; Leverger, G.; Baruchel, A.; Nelken, B.; Pasquet, M.; Michel, G.; Bertrand, Y.; Ducassou, S.; et al. Parental smoking, maternal alcohol, coffee and tea consumption during pregnancy, and childhood acute leukemia: The ESTELLE study. *Cancer Causes Control* **2015**, *26*, 1003–1017. [CrossRef]
25. Petridou, E.; Trichopoulos, D.; Kalapothaki, V.; Pourtsidis, A.; Kogevinas, M.; Kalmanti, M.; Koliouskas, D.; Kosmidis, H.; Panagiotou, J.P.; Piperopoulou, F.; et al. The risk profile of childhood leukaemia in Greece: A nationwide case-control study. *Br. J. Cancer.* **1997**, *76*, 1241–1247. [CrossRef]
26. Clavel, J.; Bellec, S.; Rebouissou, S.; Menegaux, F.; Feunteun, J.; Bonaiti-Pellie, C.; Baruchel, A.; Kebaili, K.; Lambilliotte, A.; Leverger, G.; et al. Childhood leukaemia, polymorphisms of metabolism enzyme genes, and interactions with maternal tobacco, coffee and alcohol consumption during pregnancy. *Eur. J. Cancer. Prev* **2005**, *14*, 531–540. [PubMed]
27. Madsen, C.N.; Henriksen, T.B.; Ramlau-Hansen, C.H.; Parner, E.T.; Olsen, J.; Bech, B.H. Coffee intake during pregnancy and childhood acute leukemia-A cohort study. *Cancer Epidemiol.* **2020**, *67*, 101747. [CrossRef]
28. Bailey, H.D.; Miller, M.; Langridge, A.; de Klerk, N.H.; van Bockxmeer, F.M.; Attia, J.; Scott, R.J.; Armstrong, B.K.; Milne, E. Maternal dietary intake of folate and vitamins B6 and B12 during pregnancy and the risk of childhood acute lymphoblastic leukemia. *Nutr. Cancer* **2012**, *64*, 1122–1130. [CrossRef]

*Int. J. Environ. Res. Public Health* **2023**, *20*, 5428

27 of 28

29. Singer, A.W.; Selvin, S.; Block, G.; Golden, C.; Carmichael, S.L.; Metayer, C. Maternal prenatal intake of one-carbon metabolism nutrients and risk of childhood leukemia. *Cancer Causes Control* **2016**, *27*, 929–940. [CrossRef]

30. Bonaventure, A.; Simpson, J.; Ansell, P.; Roman, E.; Lightfoot, T. Prescription drug use during pregnancy and risk of childhood cancer - is there an association? *Cancer Epidemiol.* **2015**, *39*, 73–78. [CrossRef]

31. Abudaowd, O.A.G.; Subki, S.; Alsaaedi, R.; Alsiyoufi, A.; Al-Khotany, B.; Altaifi, R.; Al-Kadi, H. Breast feeding and its association with childhood leukemia: A retrospective casecontrol study among children attending King Abdulaziz University Hospital in Jeddah, Saudi Arabia. *Med. Sci.* **2021**, *25*, 2624–2634.

32. McKinney, P.A.; Juszczak, E.; Findlay, E.; Smith, K.; Thomson, C.S. Pre- and perinatal risk factors for childhood leukaemia and other malignancies: A Scottish case control study. *Br. J. Cancer* **1999**, *80*, 1844–1851. [CrossRef]

33. Robison, L.L.; Buckley, J.D.; Daigle, A.E.; Wells, R.; Benjamin, D.; Arthur, D.C.; Hammond, G.D. Maternal drug use and risk of childhood nonlymphoblastic leukemia among offspring. An epidemiologic investigation implicating marijuana (a report from the Childrens Cancer Study Group). *Cancer* **1989**, *63*, 1904–1911. [PubMed]

34. Van Steensel-Moll, H.A.; Valkenburg, H.A.; Vandenbroucke, J.P.; van Zanen, G.E. Are maternal fertility problems related to childhood leukaemia? *Int. J. Epidemiol.* **1985**, *14*, 555–559.

35. Kwan, M.L.; Metayer, C.; Crouse, V.; Buffler, P.A. Maternal illness and drug/medication use during the period surrounding pregnancy and risk of childhood leukemia among offspring. *Am. J. Epidemiol.* **2006**, *165*, 27–35. [CrossRef] [PubMed]

36. Linabery, A.M.; Puumala, S.E.; Hilden, J.M.; Davies, S.M.; Heerema, N.A.; Roesler, M.A.; Ross, J.A.; Children's Oncology, G. Maternal vitamin and iron supplementation and risk of infant leukaemia: A report from the Children's Oncology Group. *Br. J. Cancer* **2010**, *103*, 1724–1728. [CrossRef] [PubMed]

37. Schuz, J.; Weihkopf, T.; Kaatsch, P. Medication use during pregnancy and the risk of childhood cancer in the offspring. *Eur. J. Pediatr.* **2007**, *166*, 433–441. [CrossRef] [PubMed]

38. Shaw, A.K.; Infante-Rivard, C.; Morrison, H.I. Use of medication during pregnancy and risk of childhood leukemia (Canada). *Cancer Causes Control* **2004**, *15*, 931–937. [CrossRef]

39. Wen, W.; Shu, X.O.; Potter, J.D.; Severson, R.K.; Buckley, J.D.; Reaman, G.H.; Robison, L.L. Parental medication use and risk of childhood acute lymphoblastic leukemia. *Cancer* **2002**, *95*, 1786–1794. [CrossRef]

40. Ajrouche, R.; Rudant, J.; Orsi, L.; Petit, A.; Baruchel, A.; Nelken, B.; Pasquet, M.; Michel, G.; Bergeron, C.; Ducassou, S.; et al. Maternal reproductive history, fertility treatments and folic acid supplementation in the risk of childhood acute leukemia: The ESTELLE study. *Cancer Causes Control* **2014**, *25*, 1283–1293. [CrossRef]

41. Amigou, A.; Rudant, J.; Orsi, L.; Goujon-Bellec, S.; Leverger, G.; Baruchel, A.; Bertrand, Y.; Nelken, B.; Plat, G.; Michel, G.; et al. Folic acid supplementation, MTHFR and MTRR polymorphisms, and the risk of childhood leukemia: The ESCALE study (SFCE). *Cancer Causes Control* **2012**, *23*, 1265–1277. [CrossRef]

42. Dockerty, J.D.; Herbison, P.; Skegg, D.C.; Elwood, M. Vitamin and mineral supplements in pregnancy and the risk of childhood acute lymphoblastic leukaemia: A case-control study. *BMC Public Health* **2007**, *7*, 136. [CrossRef] [PubMed]

43. Milne, E.; Royle, J.A.; Miller, M.; Bower, C.; de Klerk, N.H.; Bailey, H.D.; van Bockxmeer, F.; Attia, J.; Scott, R.J.; Norris, M.D.; et al. Maternal folate and other vitamin supplementation during pregnancy and risk of acute lymphoblastic leukemia in the offspring. *Int. J. Cancer* **2010**, *126*, 2690–2699. [CrossRef] [PubMed]

44. Ognjanovic, S.; Blair, C.; Spector, L.G.; Robison, L.L.; Roesler, M.; Ross, J.A. Analgesic use during pregnancy and risk of infant leukaemia: A Children's Oncology Group study. *Br. J. Cancer* **2011**, *104*, 532–536. [CrossRef] [PubMed]

45. Thompson, J.R.; Gerald, P.F.; Willoughby, M.L.; Armstrong, B.K. Maternal folate supplementation in pregnancy and protection against acute lymphoblastic leukaemia in childhood: A case-control study. *Lancet* **2001**, *358*, 1935–1940. [CrossRef]

46. Metayer, C.; Milne, E.; Dockerty, J.D.; Clavel, J.; Pombo-de-Oliveira, M.S.; Wesseling, C.; Spector, L.G.; Schuz, J.; Petridou, E.; Ezzat, S.; et al. Maternal supplementation with folic acid and other vitamins and risk of leukemia in offspring: A Childhood Leukemia International Consortium study. *Epidemiology* **2014**, *25*, 811–822. [CrossRef] [PubMed]

47. Higgins, J.P.T.; Green, S.; Cochrane, C. *Cochrane Handbook for Systematic Reviews of Interventions*; Wiley-Blackwell: Chichester, UK, 2008; pp. 245–246.

48. Higgins, J.P.; Thompson, S.G.; Deeks, J.J.; Altman, D.G. Measuring inconsistency in meta-analyses. *Brit. Med. J.* **2003**, *327*, 557–560. [CrossRef] [PubMed]

49. RevMan Web. *Review Manager Web (RevMan Web), Version 5.4*; The Cochrane Collaboration: London, UK, 2020.

50. Dessypris, N.; Karalexi, M.A.; Ntouvelis, E.; Diamantaras, A.A.; Papadakis, V.; Baka, M.; Hatzipantelis, E.; Kourti, M.; Moschovi, M.; Polychronopoulou, S.; et al. Association of maternal and index child's diet with subsequent leukemia risk: A systematic review and meta analysis. *Cancer Epidemiol.* **2017**, *47*, 64–75. [CrossRef]

51. Charalampopoulou, A.; Petridou, E.; Spyridopoulos, T.; Dessypris, N.; Oikonomou, A.; Athanasiadou-Piperopoulou, F.; Baka, M.; Kalmanti, M.; Polychronopoulou, S.; Trichopoulos, D. An integrated evaluation of socioeconomic and clinical factors in the survival from childhood acute lymphoblastic leukaemia: A study in Greece. *Eur. J. Cancer Prev.* **2004**, *13*, 397–401. [CrossRef]

52. Thomopoulos, T.P.; Ntouvelis, E.; Diamantaras, A.A.; Tzanoudaki, M.; Baka, M.; Hatzipantelis, E.; Kourti, M.; Polychronopoulou, S.; Sidi, V.; Stiakaki, E.; et al. Maternal and childhood consumption of coffee, tea and cola beverages in association with childhood leukemia: A meta-analysis. *Cancer Epidemiol.* **2015**, *39*, 1047–1059. [CrossRef]

*Int. J. Environ. Res. Public Health* **2023**, *20*, 5428

28 of 28

53. Yan, K.; Xu, X.; Liu, X.; Wang, X.; Hua, S.; Wang, C.; Liu, X. Corrigendum: The Associations Between Maternal Factors During Pregnancy and the Risk of Childhood Acute Lymphoblastic Leukemia: A Meta-Analysis. *Pediatr. Blood Cancer* **2016**, *63*, 953–954. [CrossRef]

54. Wan Ismail, W.R.; Abdul Rahman, R.; Rahman, N.A.A.; Atil, A.; Nawi, A.M. The Protective Effect of Maternal Folic Acid Supplementation on Childhood Cancer: A Systematic Review and Meta-analysis of Case-control Studies. *J. Prev. Med. Public Health* **2019**, *52*, 205–213. [CrossRef] [PubMed]

55. Liu, X.; Ye, F.; Wu, J.; How, B.; Li, W.; Zhang, D.Y. Signaling proteins and pathways affected by flavonoids in leukemia cells. *Nutr. Cancer* **2015**, *67*, 238–249. [CrossRef] [PubMed]

56. Greenwald, P.; Clifford, C.K.; Milner, J.A. Diet and cancer prevention. *Eur. J. Cancer* **2001**, *37*, 948–965. [CrossRef]

57. Cacciatore, I.; Cornacchia, C.; Pinnen, F.; Mollica, A.; Di Stefano, A. Prodrug approach for increasing cellular glutathione levels. *Molecules* **2010**, *15*, 1242–1264. [CrossRef] [PubMed]

58. Tricker, A.R. Carcinogenic N-nitrosamines in the diet: Occurrence, formation, mechanisms and carcinogenic potential. *Mutat. Res.* **1991**, *259*, 277–289. [CrossRef] [PubMed]

59. Dietrich, M.; Block, G.; Pogoda, J.M.; Buffler, P.; Hecht, S.; Preston-Martin, S. A review: Dietary and endogenously formed N-nitroso compounds and risk of childhood brain tumors. *Cancer Causes Control* **2005**, *16*, 619–635. [CrossRef] [PubMed]

60. Cantarella, C.D.; Ragusa, D.; Giammanco, M.; Tosi, S. Folate deficiency as predisposing factor for childhood leukaemia: A review of the literature. *Genes Nutr.* **2017**, *12*, 14. [CrossRef]

61. Jang, S.; Bae, J.; Lee, Y.; Oh, K.; Park, K.; Bae, Y. Caffeic acid and quercitrin purified from Houttuynia cordata inhibit DNA topoisomerase I activity. *Nat. Prod. Res.* **2011**, *25*, 222–231. [CrossRef]

62. Naowaratwattana, W.; De-Eknamkul, W.; De Mejia, E.G. Phenolic-containing organic extracts of mulberry (*Morus alba* L.) leaves inhibit HepG2 hepatoma cells through G2/M phase arrest, induction of apoptosis, and inhibition of topoisomerase IIα activity. *J. Med. Food.* **2010**, *13*, 1045–1056. [CrossRef]

63. Burgos-Moron, E.; Calderon-Montano, J.M.; Orta, M.L.; Pastor, N.; Perez-Guerrero, C.; Austin, C.; Mateos, S.; Lopez-Lazaro, M. The coffee constituent chlorogenic acid induces cellular DNA damage and formation of topoisomerase I- and II-DNA complexes in cells. *J. Agric. Food Chem.* **2012**, *60*, 7384–7391. [CrossRef]

64. Kleinjans, J.; Botsivali, M.; Kogevinas, M.; Merlo, D.F. Fetal exposure to dietary carcinogens and risk of childhood cancer: What the NewGeneris project tells us. *Bmj* **2015**, *351*, h4501. [CrossRef] [PubMed]

65. Page, M.J.; McKenzie, J.E.; Bossuyt, P.M.; Boutron, I.; Hoffman, T.C.; Mulrow, C.D.; Shamseer, L.; Tetzlaff, J.K.; Akl, E.A.; Brenan, S.E.; et al. The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *Int. J. Surg.* **2021**, *88*, 105906.