REVIEW

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Maternal Alcohol Consumption and Risk of Childhood Cancers: A Systematic Review and Meta-Analysis

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Abstract

Background: Childhood cancers are a leading cause of death among children worldwide. Maternal alcohol consumption before and during pregnancy has been suggested as a potential risk factor for childhood cancers. However, the evidence to support this association is inconsistent. A systematic review and meta-analysis were conducted to clarify this association. **Methods:** We performed a systematic search of PubMed, Web of Science, and Scopus databases until May 2023 to identify observational studies reporting associations between maternal alcohol consumption and childhood cancers. Heterogeneity between studies was evaluated using the χ^2, τ^2, and I^2 statistics. Publication bias was assessed using Begg and Egger tests. We calculated the odds ratio (OR) with a 95% confidence interval (CI) using a random-effects model. **Results:** Out of 18,583 studies retrieved from the search, 31 studies involving 47,277 participants met the eligibility criteria. Our meta-analysis found that maternal alcohol consumption before and during pregnancy was associated with an increased risk of childhood cancers with OR of 1.15 (95% CI: 1.00, 1.33) and 1.11 (95% CI: 1.03, 1.20), respectively. **Conclusions:** Our meta-analysis found evidence of a positive association between maternal alcohol consumption before and during pregnancy and the risk of childhood cancers. These findings suggest a need for public health interventions aimed at reducing alcohol consumption during pregnancy to potentially prevent childhood cancers.

Keywords: Maternal risk factor- alcohol consumption- childhood cancers- meta-analysis

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Introduction

In 2020, cancer emerged as a prominent global cause of death, accounting for almost 10 million fatalities, which amounts to approximately one in every six deaths [1]. Childhood cancer affects approximately 400,000 children and adolescents under the age of 20 globally each year [2]. Among the most common childhood cancers are acute lymphoblastic leukemia, astrocytoma, neuroblastoma, non-Hodgkin's lymphoma, and nephroblastoma [3].

Approximately 10% of childhood cancers have a genetic basis, while the majority have no known cause [4]. While childhood cancers are generally not strongly linked to environmental and lifestyle risk factors, some maternal factors, such as iron deficiency anemia, thyroid diseases, gestational diabetes, and exposure to pesticides, smoking, and alcohol consumption during pregnancy, may contribute to their development [5-10].

The potential association between maternal alcohol consumption during pregnancy and the risk of childhood cancers has been the subject of interest in recent years. The potential carcinogenic nature of alcohol metabolites and the occurrence of leukemia during fetal development provide valid reasons to investigate alcohol consumption as a potential risk factor for the development of childhood cancer [11].

The biological plausibility of alcohol consumption as a carcinogen for humans has been demonstrated [12]. Ethanol has been shown to disrupt normal hematopoiesis and lead to leukopenia, anemia, and thrombocytopenia, making a person more susceptible to diseases such as acute leukemia [13]. However, the association between maternal alcohol consumption and childhood cancers remains unclear. Some studies have reported a positive association [14-16] while others have reported an inverse association [17-19]. The purpose of this study is to determine whether maternal alcohol consumption during pregnancy can be considered a risk factor for childhood cancers.

A previous systematic review and meta-analysis of published studies assessed the association between maternal alcohol consumption during pregnancy and childhood leukemia and found a statistically significant association with childhood acute myeloid leukemia [20]. However, the evidence on the association between maternal alcohol use and the risk of childhood cancers is conflicting. In this review, we aim to summarize the

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epidemiological evidence on the association between parental alcohol exposure and the risk of childhood cancers. Our meta-analysis provides an updated, comprehensive, and unbiased assessment of this association, which could inform public health interventions aimed at reducing the incidence of childhood cancers.

Materials and Methods

PICOS criteria

Population: We included children and adolescents under the age of 20 who were affected by any type of childhood cancer, regardless of sex, race, ethnicity, and geography.

Intervention (exposure)

The exposure of interest in our study was maternal alcohol consumption before or during pregnancy.

Control

Our control group consisted of children and adolescents without any type of childhood cancer.

Outcome

The primary outcome of interest in our study was the incidence of any type of childhood cancer, including leukemia, lymphoma including acute lymphocytic lymphoma (ALL) and acute myeloid lymphoma (AML), neuroblastoma, retinoblastoma, rhabdomyosarcoma, and Wilms tumor.

Study

We included observational studies, such as case-control or cohort studies, that investigated the association between maternal alcohol consumption before and during pregnancy and the risk of childhood cancers. We did not restrict studies based on publication status or language.

Information sources and search

We conducted a comprehensive search of PubMed, Web of Science, and Scopus databases up to May 2023 and also explored the reference lists of the included studies. The following terms were used in the search: (ethanol or alcohol or pregnancy or "maternal exposure" or "prenatal exposure") and (leukemia or lymphoma or neuroblastoma or retinoblastoma or rhabdomyosarcoma or Wilms tumor).

Study selection

After combining the search results from all databases using EndNote and removing duplicates, two authors (R.R. and F.G.) independently screened the titles and abstracts to exclude studies that did not meet the eligibility criteria. The complete texts of studies that may be relevant were obtained for further assessment.

Data extraction

Data from the relevant studies were extracted by two authors (R.R. and J.P.) using an electronic data collection form prepared in Stata. The extracted data included the first author's name, year of publication, country, language, mean or range of age, type of childhood cancer (leukemia, lymphoma, neuroblastoma, retinoblastoma, rhabdomyosarcoma, or Wilms tumor), exposure (maternal alcohol consumption before or during pregnancy), study design (case-control or cohort), sample size, analysis of potential confounders (adjusted or unadjusted), and effect size (odds ratio) with their corresponding 95% confidence intervals (CIs).

Methodological quality

We used the Newcastle-Ottawa Scale (NOS) [21] to assess the quality of the included studies. The NOS is a tool designed to evaluate the quality of non-randomized studies, such as case-control and cohort studies. The NOS (Newcastle-Ottawa Scale) evaluates the quality of studies by considering three main categories: the selection of study groups, the comparability of study groups, and the ascertainment of either the exposure or outcome of interest. These criteria are used to assess the methodological rigor and potential biases in the studies under evaluation. Each study was evaluated on a scale of 0 to 9 stars, with high-quality studies receiving 7 or more stars and low-quality studies receiving fewer stars.

Heterogeneity and publication bias

We assessed heterogeneity across studies using the chi-square (χ^2) test and tau-square (τ^2) test [22] and quantified it by the I^2 statistic [23]. Based on the I^2 value, heterogeneity was classified as low (<50%), moderate (50-74%), or high (≥75%). We also explored the possibility of publication bias using the Egger [24] and Begg [25] tests.

Data synthesis

We used both Review Manager 5 and Stata software version 14 (StataCorp, College Station, TX, USA) for data analysis. The overall effect size was reported as an odds ratio (OR). We conducted a meta-analysis to obtain a summary measure using the random-effects model [26] at a 0.05 significance level.

The random-effects model is based on the assumption that the true effect size can vary among studies due to variations in study design, population characteristics, and other factors. This model considers both within-study and between-study variability, resulting in a more cautious estimation of the effect size and a wider confidence interval. By accounting for these sources of variability, the random-effects model provides a more comprehensive and conservative approach to analyzing data from multiple studies.

Results

Description of articles

Of the 18,583 studies initially identified, 18,093 were retrieved through electronic database searches and 490 were identified through screening the reference lists of included studies. After removing duplicates, 17,268 studies underwent title and abstract screening. Following a full-text review, 31 studies [27-32, 18, 33-35, 16, 36-38, 15, 39-47, 14, 19, 48-52] met the inclusion criteria and were included in the analysis, comprising a total of 47,277 participants (Figure 1). The characteristics of the included

studies are presented in Table 1.

Synthesis of results

Overall, based on the analysis of 14 studies (Figure 2), the meta-analysis revealed an overall OR of 1.15 (95% CI: 1.00, 1.33) for the association between maternal alcohol consumption before pregnancy and childhood cancers, including leukemia, ALL, and AML. This indicated a non-significant increase in the risk of childhood cancers by approximately 15% (P=0.060). Notably, between-study heterogeneity was low (I^2=42%). Both the Begg test (P=0.702) and the Egger test (P=0.530) showed no evidence of publication bias.

Based on the analysis of 51 studies (Figure 3), the meta-analysis revealed an overall OR of 1.11 (95% CI: 1.03, 1.20) for the association between maternal alcohol consumption during pregnancy and childhood cancers, including leukemia, acute ALL, AML, and neuroblastoma. This indicated a significant increase in the risk of childhood cancers by approximately 11% (P=0.008). Notably, between-study heterogeneity was low (I^2=46%), and neither the Begg test (P=0.948) nor the Egger test (P=0.369) showed evidence of publication bias.

A single article reported on the relationship between maternal alcohol consumption during pregnancy and childhood Hodgkin lymphoma with an OR of 0.8 (95% CI: 0.5, 1.4) [43]. Meanwhile, two articles reported on the relationship between maternal alcohol consumption during pregnancy and childhood non-Hodgkin lymphoma, with ORs of 1.5 (95% CI: 1.0, 2.1) and 0.8 (95% CI: 0.6, 1.2), respectively [43, 44].

Discussion

The present meta-analysis examined the association between maternal alcohol consumption before and during pregnancy and childhood cancers. Our findings revealed a non-significant increase in the risk of childhood cancers by approximately 15% in children whose mothers consumed alcohol before pregnancy and a significant increase in the risk of childhood cancers by approximately 11% in children whose mothers consumed alcohol during pregnancy. Interestingly, a single article reported no significant association between maternal alcohol consumption during pregnancy and childhood Hodgkin lymphoma, while two other articles reported conflicting results for the relationship between maternal alcohol consumption during pregnancy and childhood non-Hodgkin lymphoma. These findings suggest that the association between maternal alcohol consumption during pregnancy and childhood cancers may vary depending on the type of cancer.

It is important to note that the present meta-analysis found low between-study heterogeneity, indicating that the studies included in the analysis were relatively consistent in their findings. Moreover, the Begg and Egger tests

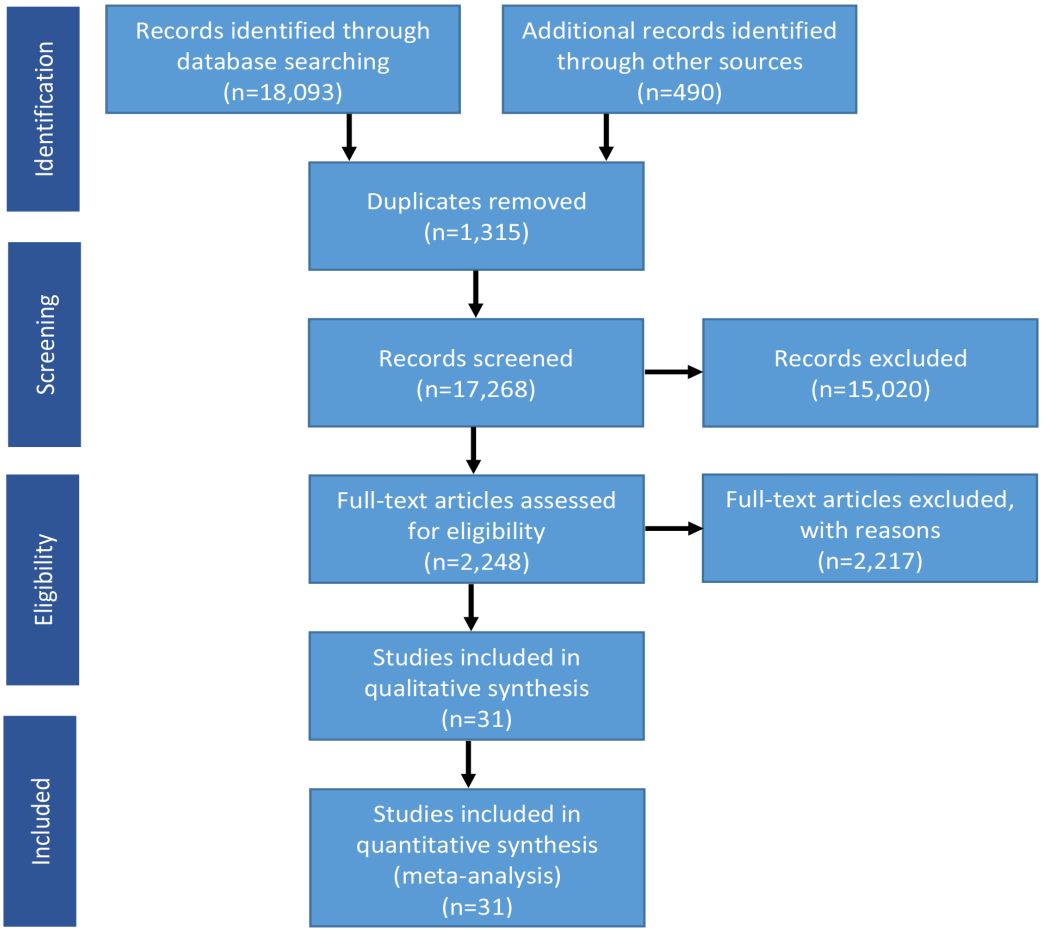

Figure 1. Flow of Information through the Various Phases of the Systematic Review

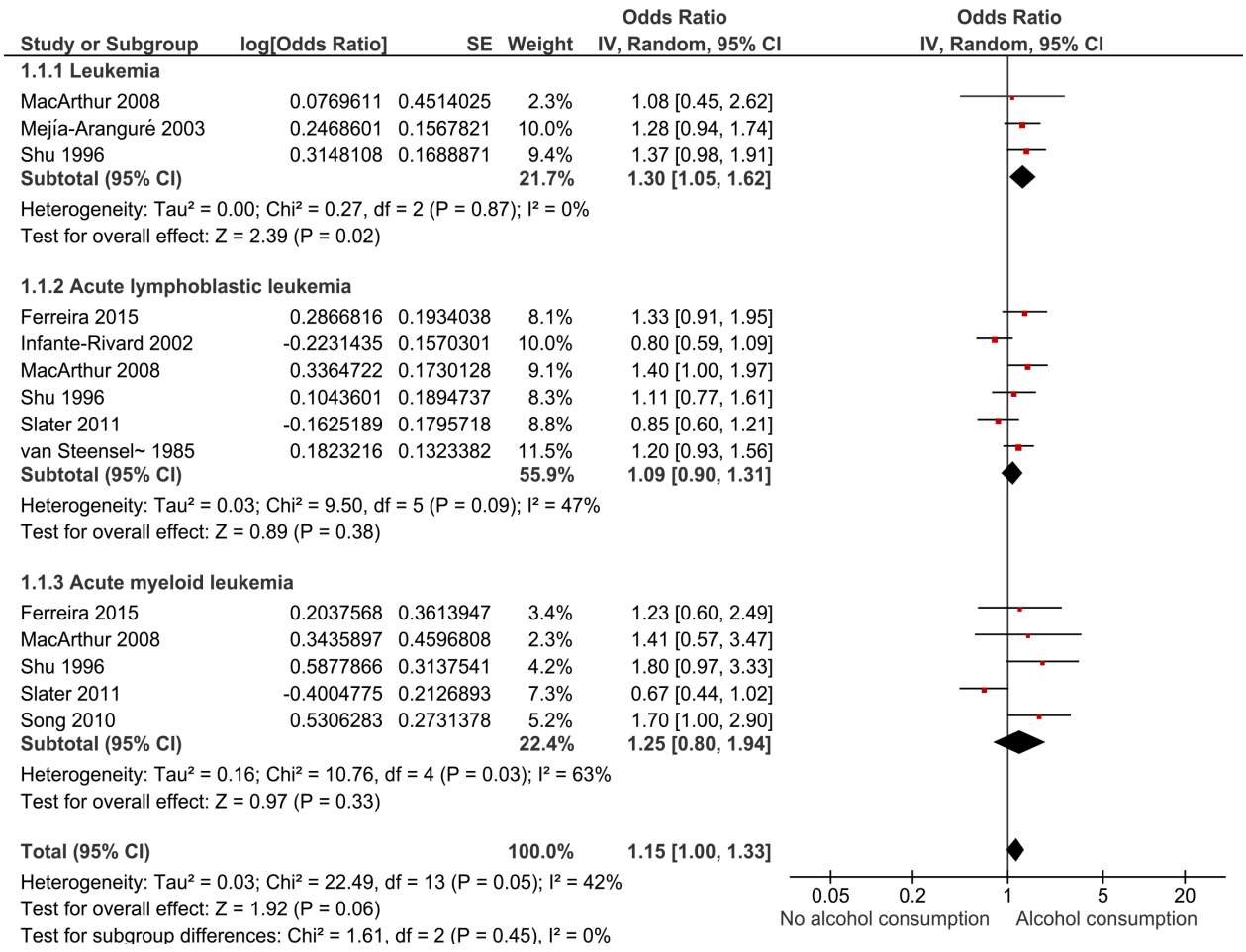

Figure 2. Forest Plot of the Association between Maternal Alcohol Consumption before Pregnancy and Childhood Cancers

revealed no evidence of publication bias, suggesting that the results are unlikely to be influenced by selective reporting of studies.

A meta-analysis study by Latino-Martel et al. reported similar findings to our study, showing that maternal alcohol consumption during pregnancy has been found to be significantly associated with an increased risk of acute myeloid leukemia (AML) in young children [20]. In a systematic review by Jin et al., the incidence of AML related to maternal alcohol consumption was found to be twice as high as that of ALL [53]. These studies provide further evidence for the potential association between maternal alcohol consumption during pregnancy and childhood cancers, highlighting the need for continued research to better understand the underlying mechanisms and to develop effective prevention strategies.

Childhood cancers can be caused by both genetic and non-genetic (environmental) risk factors. A systematic review by Spector et al. investigated the effect of demographic and environmental risk factors on all childhood cancers, as well as the effect of environmental risk factors on ALL. The review found that, apart from high-dose radiation therapy and prior chemotherapy, there were few strong extrinsic risk factors with relative risks greater than 2. Intrinsic risk factors, such as birth weight, parental age, and congenital anomalies, were consistently associated with most types of childhood cancer. These findings suggest that intrinsic factors may play a more significant role in the development of childhood cancers than extrinsic factors and highlight the importance of considering both genetic and non-genetic risk factors in the design of future research studies and prevention strategies.

This study had several limitations and potential biases as follows. Firstly, the studies included in this meta-analysis were observational, which limits our ability to establish causality. While the meta-analysis found a significant association between maternal alcohol consumption during pregnancy and childhood cancers, it is possible that other factors not accounted for in the studies may have contributed to the observed association. Secondly, the studies included in this meta-analysis used a variety of methods to assess maternal alcohol consumption during pregnancy, which may have introduced measurement error or misclassification bias. This heterogeneity in exposure assessment may have contributed to the observed between-study heterogeneity, although it was relatively low in this meta-analysis. Thirdly, the studies included in this meta-analysis were conducted in different populations with varying levels of prenatal alcohol exposure and other risk factors, which

Table 1. Characteristics of the Included Studies

Author, yr	Country	Age (yr)	Study	Matching	Adjustment	Type of cancer	Effect size	Sample	NOS score	Quality
Alexander, 2001	Global	<15	Case-control	Yes	Yes	Leukemia, ALL, AML	Odds Ratio	402	*********	High
Bonaventure, 2013	France	<15	Case-control	No	Yes	Leukemia, ALL, AML	Odds Ratio	2,445	*******	High
Buck, 2001	New York	<5	Case-control	Yes	No	Neuroblastoma	Odds Ratio	465	********	High
Clavel, 2005	France	<15	Case-control	Yes	Yes	Leukemia	Odds Ratio	324	********	High
Costas, 2002	USA	<9	Case-control	Yes	No	Leukemia	Odds Ratio	56	********	High
Ferreira, 2015	Brazil	<2	Case-control	Yes	Yes	ALL, AML	Odds Ratio	675	*********	High
Infante-Rivard, 2002	Canada	>9	Case-control	Yes	Yes	AML	Odds Ratio	982	*********	High
Johnson, 2008	Minnesota	<15	Case-cohort	Yes	Yes	Neuroblastoma	Odds Ratio	4,811	*********	High
Kabuto, 2006	Japan	<15	Case-control	Yes	No	ALL, AML	Odds Ratio	915	*******	High
Kramer, 1987	USA	NR	Case-control	Yes	No	Neuroblastoma	Odds Ratio	186	*******	High
Mac Arthur, 2008	Canada	<15	Case-control	Yes	Yes	Leukemia, ALL, AML	Odds Ratio	798	********	High
Mc Laughlin, 2009	New York	<15	Case-cohort	Yes	Yes	Neuroblastoma	Odds Ratio	12,539	*********	High
Mejía-Aranguré, 2003	Mexico	7.5	Case-control	No	No	Leukemia	Odds Ratio	85	*******	High
Menegaux, 2005	France	<15	Case-control	Yes	No	ALL, AML	Odds Ratio	568	*******	High
Menegaux, 2007	France	<15	Case-control	Yes	Yes	Leukemia, ALL, AML	Odds Ratio	1,039	********	High
Monge, 2007	Costa Rica	<14	Case-control	Yes	No	Leukemia	Odds Ratio	879	*******	High
Orsi, 2015	France	<15	Case-control	Yes	Yes	Leukemia, ALL, AML	Odds Ratio	2,168	*********	High
Ross, 1996	USA	<1y	Case-control	Yes	Yes	Leukemia, ALL, AML	Odds Ratio	181	********	High
Ross, 2005	North America	<20	Case-control	Yes	No	Leukemia	Odds Ratio	331	********	High
Rudant, 2008	France	<15	Case-control	Yes	Yes	ALL and AML	Odds Ratio	2,437	*********	High
Schuz, 1999	Germany	>15	Case-control	Yes	Yes	Leukemia, Neuroblastoma	Odds Ratio	2,688	*********	High
Schuz, 2001	Germany	<8	Case-control	Yes	Yes	Neuroblastoma	Odds Ratio	1968	*********	High
Schwartzbaum, 1992	USA	<9	Case-control	No	Yes	Neuroblastoma	Odds Ratio	791	*******	High
Severson, 1993	USA	NR	Case-control	Yes	Yes	AML	Odds Ratio	374	********	High
Shu, 1996	United States	1.5	Case-control	Yes	Yes	Leukemia, ALL, AML	Odds Ratio	860	*********	High
Slater, 2011	Canada	<1y	Case-control	Yes	Yes	ALL and AML	Odds Ratio	768	*********	High
Song, 2010	Korea	<18	Case-control	Yes	No	Leukemia, ALL, AML	Odds Ratio	923	********	High
Wen, 2000	USA	<15	Case-control	Yes	No	ALL	Odds Ratio	3828	*********	High
Yang, 2000	USA & Canada	NR	Case-control	NR	Yes	Neuroblastoma	Odds Ratio	1008	********	High
Van Duijn, 1994	Netherlands	0-4	Case-control	Yes	Yes	AML	Odds Ratio	757	*********	High
Van Steensel~ 1985	Netherlands	<15	Case-control	Yes	Yes	ALL	Odds Ratio	1026	*********	High

NR, not reported; ALL, acute lymphocytic leukemia; AML, acute lymphocytic leukemia

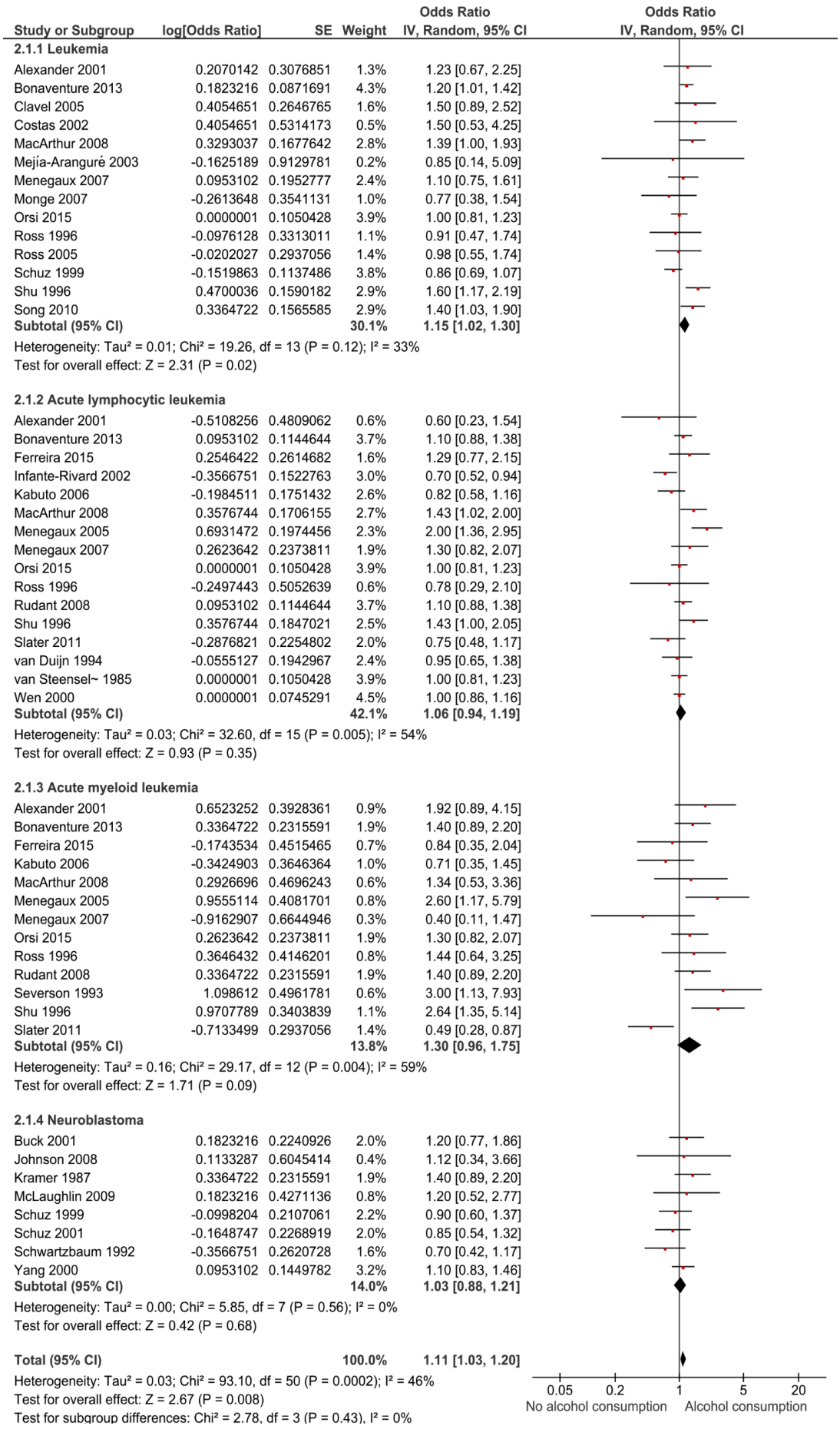

Figure 3. Forest Plot of the Association between Maternal Alcohol Consumption during Pregnancy and Childhood Cancers

may limit the generalizability of the findings to other populations or settings. Finally, while the Begg and Egger tests revealed no evidence of publication bias, it is possible that some studies were not identified or included in the analysis. This may have affected the overall estimate of the association between maternal alcohol consumption during pregnancy and childhood cancers.

The results of this meta-analysis suggest that maternal alcohol consumption during pregnancy may increase the risk of childhood cancers. Given the potential health risks associated with prenatal alcohol exposure, health policies should aim to promote abstinence from alcohol during pregnancy. This could include public health campaigns to raise awareness about the risks of alcohol consumption during pregnancy, as well as targeted interventions for women who are known to consume alcohol during pregnancy. Healthcare providers should also play an active role in promoting abstinence from alcohol during pregnancy by providing education and counseling to pregnant women and their families. This could involve routine screening for alcohol use during prenatal care visits, as well as providing information about the risks of alcohol consumption during pregnancy and strategies for reducing or quitting alcohol use. Finally, given the potential variability in the association between maternal alcohol consumption during pregnancy and specific types of childhood cancers, further research is necessary to gain a better understanding of the underlying mechanisms involved and to identify any potential differences in risk across different cancer types. This research can inform the development of evidence-based health policies and interventions to reduce the risks of prenatal alcohol exposure and improve the health outcomes of children.

In conclusion, this meta-analysis found a significant association between maternal alcohol consumption during pregnancy and childhood cancers, including leukemia, ALL, AML, and neuroblastoma. The observed association was consistent across a large number of studies with low between-study heterogeneity, suggesting that the results are reliable. However, the limited ability to establish causality and potential sources of bias and heterogeneity should be considered when interpreting the findings. Further research is needed to confirm these findings and to determine the underlying mechanisms by which alcohol exposure during pregnancy may increase the risk of childhood cancers. These findings also highlight the importance of promoting abstinence from alcohol during pregnancy to reduce the risk of adverse health outcomes for children.

Author Contribution Statement

The idea for the study was conceived by J.P. and R.R.; R.R. and F.G. screened articles for inclusion; R.R. and J.P. extracted and analyzed the data; the first draft of the manuscript was prepared by R.R. and edited by J.P.; all authors reviewed the final version.

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Availability of data

The datasets used in this study are publicly available in international databases (PubMed, Web of Science, Scopus) and can be accessed using the search terms provided in the Methods section.

Conflict of interest

The authors declare that they have no conflict of interest regarding this study.

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