Research Article

Cancer Epidemiology, Biomarkers & Prevention

Maternal Alcohol Consumption during Pregnancy and Risk of Childhood Leukemia: Systematic Review and Meta-analysis

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Abstract

Background: Leukemia is the most frequently occurring cancer in children. Although its etiology is largely unknown, leukemia is believed to result from an interaction between genetic and environmental factors. Among different potential risk factors, the possible role of maternal alcohol consumption during pregnancy has been questioned.

Methods: To assess the association between maternal alcohol consumption during pregnancy and childhood leukemia, a systematic review and meta-analysis of published studies was done.

Results: Twenty-one case-control studies were included in categorical and dose-response meta-analyses. No cohort study was identified. Analyses were conducted by type of leukemia, children's age at diagnosis, and type of alcoholic beverage and trimester of pregnancy at alcohol use. Alcohol intake during pregnancy (yes versus no) was statistically significantly associated with childhood acute myeloid leukemia (AML) [odds ratio (OR), 1.56; 95% confidence interval (CI), 1.13-2.15] but not with acute lymphoblastic leukemia (OR, 1.10; 95% CI, 0.93-1.29). Heterogeneity between studies was observed. The OR of AML for an increase of a drink per week was 1.24 (95% CI, 0.94-1.64). The association of alcohol intake during pregnancy with AML was observed for cancers diagnosed at age 0 to 4 years (OR, 2.68; 95% CI, 1.85-3.89) in five studies without heterogeneity ($I^2 \leq 0.1\%$).

Conclusions: The results of case-control studies indicate that maternal alcohol consumption during pregnancy is associated with a significantly increased risk of AML in young children.

Impact: Avoidance of maternal alcohol drinking during pregnancy might contribute to a decrease in the risk of childhood AML. *Cancer Epidemiol Biomarkers Prev; 19(5); 1238–60. ©2010 AACR.*

Introduction

Leukemia is the most common childhood cancer. The incidence rate of leukemia in children has increased in the United States and Europe in the last decades (1, 2). Among acute leukemia (AL), acute lymphoblastic leukemia (ALL) is the most frequent, followed by acute myeloid leukemia (AML) also called acute non-lymphoblastic leukemia, for which eight different subtypes of AML (M0-M7) have been characterized.

Some evidence from descriptive and etiologic epidemiology suggests that leukemia could be initiated during prenatal development or early childhood. First, early incidence peaks are observed for both ALL and AML. In developed countries, the incidence of ALL is characterized by a peak among 2- to 3-year-old children, it declines until age 8 to 10 years and remains stable thereafter. In contrast, the incidence rates of AML are highest in children ages 0 to 2 years, is fairly uniform in older children, and then increases through the adolescent years (3). Second, although the etiology of childhood leukemia remains largely unknown, it may result from an interaction between host susceptibility genetic factors and environmental carcinogenic factors during pregnancy. On one hand, it is now considered that similar with other cancers, the natural history of leukemia includes two or more genetic and/or epigenetic events (4). Children with certain genetic conditions have a higher risk of developing leukemia than those of the general population. In particular, children with Down syndrome (DS) are highly susceptible to AL (5). Studies in twins with concordant leukemias and in archived newborn blood spots have provided evidence that childhood leukemia is initiated *in utero* (6). The majority of chromosome translocations arise during fetal hematopoiesis. In addition, at least one mutation type has been found to occur prenatally in DS patients with AML-M7 (7). On the other hand, few prenatal nongenetic risk factors of childhood leukemia have been identified thus far. Prenatal exposure to

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X-rays is a generally accepted risk factor. Maternal exposures during pregnancy to tobacco, alcohol, viruses, pesticides and medications have been also suspected to play a role but the evidence is still limited or inconsistent (8).

Among the potential nongenetic risk factors, *in utero* exposure to alcohol is of particular interest. Indeed, alcoholic beverages are recognized as carcinogenic for humans (9). The ethanol consumed by a pregnant woman crosses the placental barrier. Acetaldehyde, its metabolite, could exert a mutagenic activity in the fetus. Outside the ethanol metabolism, acetaldehyde could also be directly ingested by the mother from alcoholic beverages (10). In addition, alcohol could modify the methylation status of the genome in interaction with the folate status. Such mechanisms have been reported to be involved in fetal alcohol syndrome (11), and in the development of co-occurring childhood neuroblastoma (12). It can be hypothesized that they might also cooperate with genetic lesions inherited or induced by other environmental factors and contribute to the development of childhood leukemia.

The association of maternal alcohol consumption during pregnancy and the risk of childhood leukemia has been investigated in several epidemiologic studies. We did a systematic review and meta-analysis of published data to summarize the existing evidence and contribute to clarify the possible association between the risk of childhood leukemia and maternal alcohol intake during pregnancy.

Materials and Methods

Data sources. We searched PubMed for studies published up to May 7, 2009. Indexed publications were searched with the limits "MeSH terms" and "all child: 0-18 years", without language restriction, using the following terms: leukemia AND ([(alcohol drinking OR alcoholic beverages OR ethanol OR acetaldehyde OR risk OR risk factor OR risk assessment OR food) AND (pregnancy OR maternal exposure OR prenatal exposure delayed effects OR maternal-fetal exchange OR prenatal nutrition physiology OR parents)] OR fetal alcohol syndrome). In-process publications (not yet indexed in PubMed), were searched using the corresponding entry terms. In addition, we examined the reference list of relevant articles and reviews.

Inclusion criteria. Original research articles were selected when they provided the odds ratio (OR) and 95% confidence interval (95% CI) of childhood ALL, AML (or acute non-lymphoblastic leukemia), or grouped leukemias (GL) in relation to maternal alcohol consumption during pregnancy, or number of cases and controls required to calculate crude OR.

Unpublished data collection. We contacted authors to obtain complementary data when alcohol intake was mentioned but ORs and 95% CIs were not provided in the publication or when an overlap between studies was suspected.

Data extraction. Data from each study included was extracted independently by two investigators using a standardized data collection form, and then compared. Data extracted were study design, first author, publication year, country, case recruitment period, number and characteristics of cases and controls, alcohol consumption assessment (questionnaire or interview: level of intake, type of alcohol), participation rate of cases and controls, age of children, leukemia type (GL, ALL, AML), control for confounding, and additional information considered important for the analysis or discussion.

Statistical analysis. Summary OR associated with any alcohol intake during pregnancy compared with no alcohol intake (yes versus no) and corresponding 95% CI were estimated with the method of DerSimonian and Laird (13) when at least three studies were available. Random effects models were used to account for differences in population, leukemia type, type of control group, assessment method of alcohol intake, and control for potential confounders (13). Two studies did not provide OR for "yes versus no" comparison. We calculated the OR from the data reported in one study using the method of Hamling et al. (14) and by pooling the categorical results using a fixed effect model in another study that did not provide the number of cases and controls per category level. Adjusted OR were used in all except for six studies for which only crude estimates were reported or could be calculated (Table 1). Meta-analyses were conducted by type of leukemia, age at diagnosis, alcoholic beverage, and pregnancy trimester if at least three studies were available.

Dose-response meta-analyses were done using the method proposed by Greenland and Longnecker (15). Dose-response slopes for an increment of one drink per week were estimated using the midpoint of each category of alcohol intake. Only studies with more than two intake levels and reporting number of cases and controls could be included in the dose-response meta-analyses. We converted alcohol intake to drinks per week, assuming that one glass or one can was equivalent to one drink.

Statistical heterogeneity between studies was evaluated with Cochran's Q test and I^2 statistics. Publication bias was assessed by constructing funnel plots and by Egger's regression asymmetry test. We investigated the following potential sources of heterogeneity: assessment method of alcohol consumption (self-reported or interview, pregnancy trimester, highest level of intake assessed), type of controls (population- or hospital-based), study size, participation rate, control for confounding, country, age at cancer diagnosis, and publication year. We conducted subgroup analyses when the number of studies allowed it or, alternatively, a visual inspection of the characteristics explaining the heterogeneity in study results. Meta-regression analyses were not conducted due to the low number of studies in each subgroup. Statistical analyses were done with Stata version 9 (Stata Corp.).

Table 1. Characteristics of case-control studies of exposure to alcohol from the mother during pregnancy and risk of leukemia in childhood

Reference, country, case recruitment period, cases, controls, study design	Age of the children	Maternal alcohol consumption during pregnancy: category	OR (95% CI)*			Matching factors	Adjusting factors	Comments
			GL	ALL	AML			
van Steensel-Moll et al. (22) The Netherlands, 1973-1979 519 ALL cases from the Nationwide morbidity register of childhood leukemia 507 population-based controls randomly selected Self-administered questionnaire Response rate: 90% (cases) and 70/68% (first/replacement controls) Assessment of alcohol consumption: not detailed	0-14 y	Total alcohol: yes		1.0 (0.8-1.2)		Date of birth, gender, residence	Age, gender	
Severson et al. (23) United States, Canada, 1980-1984 187 AML cases from CCG registration files 187 population-based controls randomly selected Exclusion criteria: no telephone, not English speaking Telephone interview Interview rate: 77.9% (cases) and 78.5% (controls) Assessment of alcohol consumption:	0-17 y	Total alcohol: ever			1.42 (0.91-2.23)	Date of birth, race, telephone area code and exchange number	No interaction with: age of the mother, education of the mother, use of mind altering drugs, gender of the child, ethnicity of the child	Dose-response: *P* trend = 0.63
	0-2 y	Total alcohol: ever			3.00 (1.23-8.35)			
		Total alcohol: 1-20 drinks/ pregnancy			2.1			
		Total alcohol: >20 drinks/ pregnancy			2.8			
	3-10 y	Total alcohol: ever			0.81 (0.36-1.80)			
	11-17 y	Total alcohol: ever			1.13 (0.53-2.44)			

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Table 1. Characteristics of case-control studies of exposure to alcohol from the mother during pregnancy and risk of leukemia in childhood (Cont'd)

Reference, country, case recruitment period, cases, controls, study design	Age of the children	Maternal alcohol consumption during pregnancy: category	OR (95% CI)*			Matching factors	Adjusting factors	Comments
			GL	ALL	AML			
numbers of glasses, cans, bottles or ounces consumed per day, week, or month; trimesters during which consumption occurred								
van Duijn et al. (24) The Netherlands, 1973-1979 517 ALL and 80 ANLL cases from registration of the Dutch Childhood leukemia Study Group 240 population-based controls from the same municipality Self-administered questionnaire Response rate: 86% (cases) and 66/67% (first/replacement controls) Assessment of alcohol consumption: abstainers, occasional drinkers (1 drink/wk), frequent drinkers (>1 drink/wk)	0-14 y	Total alcohol: yes			2.6 (1.4-4.6)	Age, gender	Gender, age, date of birth, social class, maternal smoking, occupational exposure to hydrocarbons, drugs, ultrasound, radiation, viral infections	For ALL, the sample is the same as in the study of van Steensel-Moll et al. (22), but data are stratified by age
		Total alcohol: 1 drink/wk			2.4 (1.3-4.5)			
		Total alcohol: >1 drink/wk			2.9 (1.1-7.4)			
	0-4 y	Total alcohol: yes		1.1 (0.8-1.9)	2.8 (1.2-6.5)			
	5-9 y	Total alcohol: yes		0.8 (0.5-1.5)	3.0 (1.1-8.4)			
	10-14 y	Total alcohol: yes		1.0 (0.4-2.1)	0.8 (0.3-2.3)			

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Table 1. Characteristics of case-control studies of exposure to alcohol from the mother during pregnancy and risk of leukemia in childhood (Cont'd)

Reference, country, case recruitment period, cases, controls, study design	Age of the children	Maternal alcohol consumption during pregnancy: category	OR (95% CI)* GL	ALL	AML	Matching factors	Adjusting factors	Comments
Ross et al. (25) United States, 1983-1994 84 AL, 54 ALL and 30 AML cases from CCG registration files CCG-E09 (1983-1988), CCG-E14 (1989-1993) and CCG-E15 (1989-1994) 97 population-based controls randomly selected Exclusion criteria: no telephone, not English speaking, Canadian mothers Telephone interview Interview rate: 45% (cases) and 50% (controls) Assessment of alcohol consumption frequency: never, <1/mo, 1-3/mo, <1/wk, 1-3/wk, 4-6/wk, daily	0-1 y	Beer: ever Wine: ever Spirits: ever	0.8 (0.4-1.9) 1.0 (0.5-2.1) 1.0 (0.3-3.2)	0.7 (0.2-2.1) 0.8 (0.3-1.9) 1.0 (0.2-4.2)	1.1 (0.3-3.8) 2.0 (0.6-7.0) 1.2 (0.2-8.9)	E09: year of birth, geography; E14 and E15: year of birth, ethnicity, geography	Maternal education	See Shu et al. (26)
Shu et al. (26) United States, Canada, Australia, 1983-1988 302 GL, 203 ALL and 88 AML cases from CCG registration files 558 population-based controls randomly selected	0-1.5 y	Total alcohol: ever Total alcohol: ever (Tri 1) Total alcohol: ever (Tri 2) Total alcohol: ever (Tri 3) Total alcohol: 1-20 drinks/ pregnancy	1.60 (1.18-2.18) 1.29 (0.94-1.78) 1.50 (1.04-2.16) 1.35 (0.92-1.98) 1.77 (1.23-2.55)	1.43 (1.00-2.04) 1.18 (0.81-1.72) 1.25 (0.81-1.95) 1.13 (0.72-1.78) 1.76 (1.14-2.72)	2.64 (1.36-5.06) 1.90 (1.00-3.62) 2.49 (1.17-5.32) 2.41 (1.05-5.52) 2.36 (1.11-5.03)	Year of birth, telephone area code and exchange number	Gender, maternal age, maternal education, maternal smoking during pregnancy	Only a subset of cases overlap between the study of Ross et al. (25); 0-1 y, American, E09-E14-E15 and the one of Shu et al.(26); 0-1.5 y, American Canadian and Australian, E09

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Table 1. Characteristics of case-control studies of exposure to alcohol from the mother during pregnancy and risk of leukemia in childhood (Cont'd)

Reference, country, case recruitment period, cases, controls, study design	Age of the children	Maternal alcohol consumption during pregnancy: category	OR (95% CI)*			Matching factors	Adjusting factors	Comments
			GL	ALL	AML			
Exclusion criteria: no telephone, not English speaking Telephone interview using a structured questionnaire Interview rate: 79.1% (cases) and 75.1% (controls) Assessment of alcohol consumption: during each trimester of the index pregnancy, type and frequency (0, 1-4 drinks/mo, >4 drinks/mo)		Total alcohol: >20 drinks/ pregnancy	1.27 (0.80-2.01)	0.93 (0.53-1.62)	3.13 (1.20-8.06)			
		Beer: 1-4 cans/mo	1.16 (0.68-1.98)	1.23 (0.65-2.33)	1.24 (0.43-3.60)			
		Beer: >4 cans/mo	0.99 (0.52-1.88)	0.68 (0.30-1.54)	2.21 (0.70-6.96)			
		Wine: 1-4 glasses/mo	1.39 (0.92-2.10)	1.42 (0.86-2.34)	1.95 (0.81-4.70)			
		Wine: >4 glasses/mo	1.06 (0.59-1.91)	0.71 (0.34-1.49)	2.33 (0.72-7.52)			
		Liquor: 1-4 drinks/mo	2.46 (1.41-4.29)	1.88 (0.96-3.67)	6.37 (1.95-20.80)			
		Liquor: >4 drinks/mo	0.96 (0.37-2.54)	0.54 (0.17-1.74)	—			
Petridou et al. (27) Greece, 1993-1994 153 GL cases from the Nationwide network of childhood hematologists/ oncologists 300 controls from the same hospital Interview using a structured questionnaire Interview rate: 95% (cases) and 96% (controls) Assessment of alcohol consumption: no, ≥2 glasses/wk	0-14 y	Total alcohol: yes	0.57 (0.34-0.95)			Gender, age, residence	Mutually adjusted variables: sociodemographic, lifestyle, environmental, and biomedical variables	No woman consumed more than a glass of alcoholic beverages per day during her pregnancy

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Table 1. Characteristics of case-control studies of exposure to alcohol from the mother during pregnancy and risk of leukemia in childhood (Cont'd)

Reference, country, case recruitment period, cases, controls, study design	Age of the children	Maternal alcohol consumption during pregnancy: category	OR (95% CI)*			Matching factors	Adjusting factors	Comments
			GL	ALL	AML			
Schüz et al. (28) Germany, 1980-1994 (NI) 1992-1994 (NW) 964 AL cases from a German childhood cancer registry in Mainz, with a nationwide part (NW) and a part living in the vicinity of nuclear installations (NI) 647 population-based controls randomly selected Mailed questionnaire and telephone interview Response rate: 80.2/81.7% (NI/NW cases) 61.6/68.6% (NI/NW controls) Assessment of weekly alcohol consumption (beer, wine and strong liquor)	0-14 y	Total alcohol: 1-7 glasses/wk Total alcohol: >7 glasses/wk	0.9 (0.7-1.1) 0.6 (0.3-1.3)			Gender, date of birth, district	Gender, date of birth, district	
Wen et al. (29) United States, 1989-1993 1,842 ALL cases from CCG registration files 1,986 population-based controls randomly selected Telephone interview using a structured questionnaire Interview rate: 92% (cases) and 76.5% (controls) Assessment of alcohol consumption: not detailed	0-17 y	Total alcohol: yes		1.0 (0.9-1.2)		Age, ethnicity, telephone area code and exchange number		

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Table 1. Characteristics of case-control studies of exposure to alcohol from the mother during pregnancy and risk of leukemia in childhood (Cont'd)

Reference, country, case recruitment period, cases, controls, study design	Age of the children	Maternal alcohol consumption during pregnancy: category	OR (95% CI)*			Matching factors	Adjusting factors	Comments
			GL	ALL	AML			
Alexander et al. (30) International: Italy, Greece, Egypt, Brazil, Chile, mainland China, Hong Kong, Japan; period and modalities of recruitment not reported 136 GL, 49 ALL and 74 AML cases 266 controls from the same or similar hospitals Telephone interview using a structured questionnaire Interview rate: >98% (cases) and >90% (controls) Assessment of alcohol consumption: not detailed	0-1.5 y	Total alcohol: yes	1.23 (0.68-2.23)	0.63 (0.25-1.60)	1.92 (0.90-4.10)	Gender, date of birth	Gender, region of residence	
Costas et al. (31) United States, 1969-1989 19 GL from hospitals of Massachusetts 37 population-based controls randomly selected from residents Face to face interview Interview rate: 91% (cases) and 97% (controls) Assessment of alcohol consumption: not detailed	0-9 y	Total alcohol: ever	1.5 (0.54-4.20)			Ethnicity, sex, date of birth, age		

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Table 1. Characteristics of case-control studies of exposure to alcohol from the mother during pregnancy and risk of leukemia in childhood (Cont'd)

Reference, country, case recruitment period, cases, controls, study design	Age of the children	Maternal alcohol consumption during pregnancy: category	OR (95% CI)* GL	OR (95% CI)* ALL	OR (95% CI)* AML	Matching factors	Adjusting factors	Comments
Infante-Rivard et al. (32) Canada, 1980-1993 491 ALL cases from tertiary children cancer care centers of the Province of Quebec 491 population-based controls selected from family allowance files Telephone interview using a structured questionnaire Participation rate: 96% (cases) and 84% (controls) Assessment of alcohol consumption (wine, beer or spirits): no, yes, number of glasses during each pregnancy trimester, <1 drink/d, ≥1 drink/d	0-9 y	Total alcohol: ever Total alcohol: ever (Tri 1) Total alcohol: ever (Tri 2) Total alcohol: ever (Tri 3) Total alcohol: <1 drink/d Total alcohol: ≥1 drink/d Beer: ever Wine: ever Spirits: ever		0.7 (0.5-0.9) 0.7 (0.5-1.0) 0.7 (0.5-0.9) 0.7 (0.5-0.9) 0.7 (0.5-1.0) 0.8 (0.5-1.6) 0.7 (0.5-1.1) 0.7 (0.5-0.9) 0.9 (0.5-1.3)		Age and gender of the child	Maternal age, level of schooling	No woman consumed more than a glass of alcoholic beverages per day during her pregnancy
Mejia-Arangure et al. (33) Mexico, from 1995 27 AL cases from seven children cancer care institutions in Mexico City 58 controls from institutions that treat children with DS Interview using a questionnaire	7.5 y (median age)	Total alcohol: yes	0.85 (0.15-4.68)					Children with DS The crude OR being estimated for a 90% CI, it has been calculated for a 95% CI

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Table 1. Characteristics of case-control studies of exposure to alcohol from the mother during pregnancy and risk of leukemia in childhood (Cont'd)

Reference, country, case recruitment period, cases, controls, study design	Age of the children	Maternal alcohol consumption during pregnancy: category	OR (95% CI)* GL	ALL	AML	Matching factors	Adjusting factors	Comments
Response rate: not mentioned Assessment of alcohol consumption frequency: no, <1 beverage/wk, >1 beverage/wk								
Clavel et al. (34) France, 1995-1999 219 AL cases from hospital (Paris, Lyon, Lille, Nancy) 105 controls from orthopedic departments Face-to-face interview using a standardized questionnaire Interview rate: 99% (cases and controls) Assessment of weekly alcohol consumption	0-14 y	Total alcohol: ever Total alcohol: 1 drink/wk Total alcohol: 2 drinks/wk Total alcohol: >2 drinks/wk	1.5 (0.9-2.5) 1.4 (0.8-2.6) 1.7 (0.6-4.7) 1.4 (0.6-3.4)			Age, gender, hospital, ethnicity	Age, gender, center origin, parental socio-professional category	See Menegaux et al. (35)
Menegaux et al. (35) France, 1995-1999 240 ALL and 40 ANLL cases from hospitals (Paris, Lyon, Lille, Nancy) 288 controls from orthopedic departments	0-14 y	Total alcohol: ever Total alcohol: 1 glass/wk Total alcohol: 2 glasses/wk Total alcohol: >2 glasses/wk Beer: ever		2.0 (1.4-3.0) 2.0 (1.3-3.0) 2.8 (1.3-6.0) 1.9 (0.9-3.5) 1.4 (0.9-2.3)	2.6 (1.2-5.8) 2.8 (1.2-6.6) — 2.4 (0.8-7.1) 0.7 (0.3-2.1)	Age, gender, hospital, ethnicity	Stratification variables, age, gender, center origin	

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Table 1. Characteristics of case-control studies of exposure to alcohol from the mother during pregnancy and risk of leukemia in childhood (Cont'd)

Reference, country, case recruitment period, cases, controls, study design	Age of the children	Maternal alcohol consumption during pregnancy: category	OR (95% CI)*			Matching factors	Adjusting factors	Comments
			GL	ALL	AML			
Face-to-face interview using a standardized questionnaire Participation rate: 95% (cases) and 95% (controls) Assessment of daily alcohol consumption: total number of drinks of any type of alcohol	0-2 y	Wine: ever		1.4 (1.0-2.1)	1.4 (0.7-3.0)			
		Spirits: ever		1.8 (1.3-2.9)	1.4 (0.7-3.1)			
		Total alcohol: ever			5.1 (1.5-17.5)			Confirmed by authors
Ross et al. (36) United States, 1997-2002 158 AL cases from registration files of the Children's Oncology Group 173 controls are children with DS and without leukemia Exclusion criteria: no telephone, not English speaking Telephone interview using a structured questionnaire Interview rate: 75% (cases) and 80.5% (controls) Assessment of alcohol consumption: not detailed	0-19 y	Total alcohol: yes	0.98 (0.56, 1.74)			Age at diagnosis		Children with DS
Kabuto et al. (37) Japan, 1999-2001 250 ALL and 61 AML cases from five major children's cancer study groups	0-15 y	Total alcohol: yes		0.82 (0.59-1.16)	0.71 (0.35-1.43)	Age, gender, residence		Numbers of cases and controls were used to calculate the crude OR

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Table 1. Characteristics of case-control studies of exposure to alcohol from the mother during pregnancy and risk of leukemia in childhood (Cont'd)

Reference, country, case recruitment period, cases, controls, study design	Age of the children	Maternal alcohol consumption during pregnancy: category	OR (95% CI)* GL	OR (95% CI)* ALL	OR (95% CI)* AML	Matching factors	Adjusting factors	Comments
495 controls population-based controls randomly selected Interview using a questionnaire Participation rate: 49% (cases) and 28.6% (controls) Assessment of alcohol consumption: not detailed								
Menegaux et al. (38) France, 1995-1998 472 AL, 407 ALL and 62 AML cases from the National Registry of Childhood Malignancies 567 population-based controls randomly selected Self-administered questionnaire Participation rate: 73% (cases) and 70% (controls) Assessment of daily alcohol consumption of any type	0-14 y	Total alcohol: yes	1.1 (0.8-1.7)	1.3 (0.8-2.0)	0.4 (0.1-1.3)	Age, gender, region	Stratification variables, age, gender, region, socio-professional category, birth order	The sample does not include cases from hospitals in Paris, Lyon, Lille, and Nancy: no overlap with the sample of the study of Menegaux et al. (35)
		Total alcohol: ≤1 glass/d	0.8 (0.5-1.3)	0.8 (0.5-1.5)	0.4 (0.1-1.6)			
		Total alcohol: >1 glass/d	2.4 (1.1-5.0)	2.8 (1.3-5.9)	—			
		Beer, wine, cider: any	1.3 (0.9-2.1)	1.5 (0.9-2.3)	0.4 (0.1-1.5)			
		Beer, wine, cider: ≤1 glass/d	1.0 (0.6-1.6)	1.0 (0.6-1.7)	0.5 (0.1-1.7)			
		Beer, wine, cider: >1 glass/d	2.8 (1.2-5.6)	3.3 (1.4-7.6)	—			
		Spirits: any	0.6 (0.2-1.8)	0.7 (0.2-2.2)				
		Spirits: ≤1 glass/d	0.7 (0.2-2.0)	0.8 (0.3-2.4)				
Monge et al. (39) Costa Rica, 1995-2000	0-14 y	Total alcohol: yes	0.77 (0.39-1.53)			Date of birth		Numbers of cases and controls were used to calculate the crude OR

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Table 1. Characteristics of case-control studies of exposure to alcohol from the mother during pregnancy and risk of leukemia in childhood (Cont'd)

Reference, country, case recruitment period, cases, controls, study design	Age of the children	Maternal alcohol consumption during pregnancy: category	OR (95% CI)* GL	ALL	AML	Matching factors	Adjusting factors	Comments
297 GL cases from the Cancer Registry and Children's Hospital of Costa Rica 549 population-based controls randomly selected from residents Face to face interview and questionnaire Participation rate: 90% (cases) and 90.5% (controls) Assessment of alcohol consumption: not detailed								
MacArthur et al. (40) Canada, 1990-1995 395 AL, 348 ALL and 38 AML cases from pediatric oncology treatment centers (British Columbia, Alberta, Saskatchewan, Manitoba, and Quebec) and cancer registries	0-14 y	Total alcohol: yes Total alcohol: 1-2 drinks/wk Total alcohol: >2 drinks/wk Total alcohol: yes (Tri 1) Total alcohol: 1-2 drinks/wk (Tri 1)	1.39 (1.01-1.93) 1.57 (1.11-2.23) 0.74 (0.39-1.44) 0.96 (0.63-1.45) 1.05 (0.63-1.74)	1.43 (1.03-1.99) 1.57 (1.10-2.25) 0.88 (0.46-1.67) 0.95 (0.62-1.45) 0.99 (0.58-1.67)	1.34 (0.55-3.27) 1.93 (0.77-4.84) — 0.79 (0.23-2.68) 1.12 (0.27-4.67)	Age, gender, area	Maternal age at birth, maternal education, household income, ethnicity, number or residences since birth	Possibility that a subset of cases overlap with the sample of the study of Infante-Rivard et al. (32): not confirmed by authors who were contacted

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Table 1. Characteristics of case-control studies of exposure to alcohol from the mother during pregnancy and risk of leukemia in childhood (Cont'd)

Reference, country, case recruitment period, cases, controls, study design	Age of the children	Maternal alcohol consumption during pregnancy: category	OR (95% CI)* GL	OR (95% CI)* ALL	OR (95% CI)* AML	Matching factors	Adjusting factors	Comments
393 population-based controls randomly selected from provincial government health insurance or family allowance rolls Face to face interview using a standardized questionnaire Participation rate: 90% (cases) and 76% (controls) Assessment of weekly alcohol consumption of any type		Total alcohol: >2 drinks/wk (Tri 1) Total alcohol: yes (Tri 2) Total alcohol: 1-2 drinks/wk (Tri 2) Total alcohol: >2 drinks/wk (Tri 2) Total alcohol: yes (Tri 3) Total alcohol: 1-2 drinks/wk (Tri 3) Total alcohol: >2 drinks/wk (Tri 3)	0.76 (0.40-1.47) 0.93 (0.58-1.48) 1.06 (0.61-1.83) 0.68 (0.30-1.54) 0.82 (0.51-1.33) 0.91 (0.51-1.60) 0.67 (0.29-1.52)	0.82 (0.42-1.59) 0.88 (0.54-1.43) 0.94 (0.53-1.69) 0.76 (0.33-1.73) 0.78 (0.47-1.28) 0.79 (0.43-1.45) 0.75 (0.33-1.71)	0.44 (0.05-3.76) 1.34 (0.43-4.24) 2.26 (0.67-7.66) — 1.10 (0.32-3.78) 1.87 (0.51-6.86) —			
Rudant et al. (41) France, 2003-2004 647 ALL and 102 AML cases from pediatric oncology hospital departments and the French national registry of childhood blood malignancies 1,681 population-based controls randomly selected	0-14 y	Total alcohol: yes Total alcohol: ≤1 glass/wk Total alcohol: 2-6 glasses/wk Total alcohol: ≥7 glasses/wk Beer: yes Wine: yes		1.1 (0.9-1.4) 1.1 (0.9-1.4) 1.1 (0.8-1.7) 1.0 (0.7-1.7) 1.3 (1.0-1.8) 1.1 (0.9-1.4)	1.4 (0.9-2.2) 1.5 (0.9-2.4) 1.2 (0.4-2.6) 1.4 (0.5-3.6) 1.2 (0.7-2.2) 1.6 (1.0-2.5)	Age, gender	Stratification variables, age, gender, parental professional category, maternal age at child's birth	

(*Continued on the following page*)

Table 1. Characteristics of case-control studies of exposure to alcohol from the mother during pregnancy and risk of leukemia in childhood (Cont'd)

Reference, country, case recruitment period, cases, controls, study design	Age of the children	Maternal alcohol consumption during pregnancy: category	OR (95% CI)*			Matching factors	Adjusting factors	Comments
			GL	ALL	AML			
Face to face interview using a standardized questionnaire Participation rate: 91% (cases) and 71.2% (controls) Assessment of alcohol consumption: number of drinks of any type per day or per week		Spirits: yes		1.3 (1.1-1.7)	0.8 (0.4-1.5)			
Liu et al. (42) Taiwan, 1997-2005 112 ALL and 33 AML cases from large referral hospitals (Kaohsiung) and registration files of the Department of Health of Kaohsiung 370 population-based controls randomly selected from the same area Face to face interview using a standardized questionnaire Participation rate: 94% (cases) and 56% (controls) Assessment of alcohol consumption: never, ever (≥1 beverage/wk for >6 mo)	0-20 y	Total alcohol: ever		1.2 (0.12-11.62)		Age and gender	Age and gender (no confounding was seen with: maternal age, birth weight, breast-feeding, parental education levels, parental and subjects' smoking history, maternal vitamins and iron supplements intake status, and all the other food items)	Data concerning maternal drinking during pregnancy (data not shown in the article) were communicated by the authors. None of the mothers of AML cases and the matched controls reported alcohol drinking during pregnancy

Abbreviations: ANLL, acute non-lymphoblastic leukemia; CCG, Children's Cancer Group; Tri, trimester of pregnancy.
*Reference group is the nonconsumers.

Results

Characteristics of the studies. Our search yielded a total number of 478 articles (Fig. 1). After reviewing each publication, we identified 27 potentially eligible studies (16-42) among which 6 studies were excluded. One study (16) was excluded for inappropriate outcome (leukemia grouped with lymphomas). Two studies (17, 18) were excluded for inappropriate exposure (alcohol drinking before pregnancy or alcohol use in general). One study was not included because no cases had been exposed to maternal alcohol consumption (19). The studies of Shu et al. (20) and Canfield et al. (21) were not included because their samples were the same as those of Shu et al. (26) and Ross et al. (36), respectively. Although based on the same sample, the study of Clavel et al. (34) examined GL and the one of Menegaux et al. (35) examined ALL and AML separately, and therefore, both reports were included in different analyses. From the article of Schüz et al., the "overall results", which comprised results from a nationwide sample and a population living in the vicinity of nuclear installations, were selected (28). Finally, 21 studies from 20 different study populations with a total of 8,128 cases and 10,207 controls were selected and included in the meta-analyses (22-42). All studies were of case-control design. No cohort study was identified.

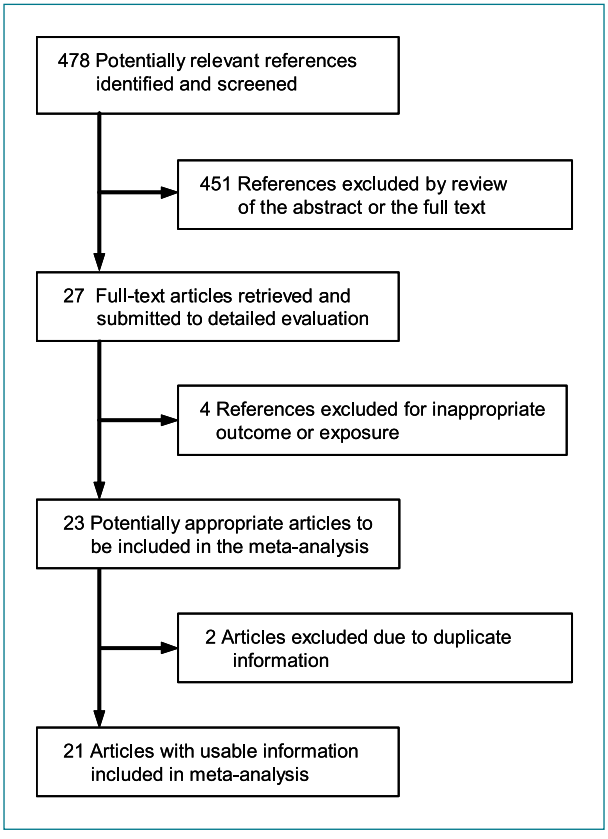

Figure 1. Flow diagram of study selection process.

Table 1 presents the main characteristics of the 21 case-control studies. Nineteen studies included children from the general population and analyzed GL, ALL, or AML. Two studies were on children with DS and reported data on GL only (33, 36). Eight studies were conducted in Europe (22, 24, 27, 28, 34, 35, 38, 41), eight in the United States and/or Canada and Australia (23, 25, 26, 29, 31, 32, 36, 40), two in Mexico or Costa Rica (33, 39), one in Japan (37), one in Taiwan (42) and one was international (30) involving eight countries. Control subjects were population-based in 15 studies and they were matched to cases on age, gender, and residence in most studies. Participation rates, mentioned only in recent studies, were above 80% in three studies (32, 35, 39) and below 50% in two studies (25, 37). In six studies, they were lower in controls than in cases (32, 37, 38, 40-42).

Twelve studies reported results for different types of leukemia combined. In seven of these, only acute leukemia was investigated (25, 28, 33, 34, 36, 38, 40), in three studies (26, 30, 39), a small percentage of other leukemias were also included, and in two studies (27, 31), the leukemia type was not specified. Overall, the proportion of cases with ALL in these studies ranged from 36% to 89%.

Maternal alcohol consumption during pregnancy was assessed by interview in all but three studies (22, 24, 38) that used self-administered questionnaires. One third of the studies were focused on other risk factors and provided limited data on alcohol consumption (22, 29-31, 36, 37, 39). Nineteen studies reported results of the comparison "yes versus no" alcohol intake during pregnancy. Nine studies reported results for more than two categories of alcohol intake (24, 26, 28, 32, 34, 35, 38, 40, 41). The highest category of maternal alcohol consumption reported varied across studies, ranging from more than 0.5 drinks/week to more than 7 drinks/week.

Total alcohol consumption. For children from the general population, the summary of nine studies (26-28, 30, 31, 34, 38-40) including 2,940 cases indicated that alcohol consumption during pregnancy was not statistically significantly associated with risk of GL (OR "yes versus no", 1.11; 95% CI, 0.88-1.40; Fig. 2). The heterogeneity between studies (I^2 = 62.1%) was mainly attributable to one study in a Greek population (27) showing a significant inverse association of childhood leukemia in relation to alcohol intake during pregnancy. In this study, the range of alcohol intake assessed was low and the control population was hospital-based. For children with DS, the two available studies also reported nonsignificant estimates for the risk of GL (33, 36).

Overall, the risk of ALL was not significantly related to alcohol consumption during pregnancy compared

with no consumption (OR, 1.10; 95% CI, 0.93-1.29) in 11 studies including 5,108 cases (refs. 22, 26, 29, 30, 32, 35, 37, 38, 40-42; Table 2, ALL; Fig. 3). There was significant heterogeneity (I^2 = 66%) attributable to one study in Quebec, in which a significant inverse association with alcohol intake was observed (32). This Canadian study seems to be a well-conducted study with a large sample size, an appropriate control group, and controls for confounding. Although high, the participation rate was lower in controls (84%) than in cases (96%), thus a non-response bias cannot be excluded. In addition, the difference in assessment of alcohol consumption played a role as this study queried the number of drinks per day whereas other studies queried the number of drinks per week or month. Two other studies reported inverse but not statistically significant results. One was an international study (30) including only 49 cases. The other was a Japanese study (37), for which crude ORs for alcohol were calculated from the number of cases and controls. In this study investigating the relation of magnetic fields and childhood leukemia, participation rates were very low (49% in cases, 28.6% in controls), which raises the issue of potential selection bias (37).

Overall, childhood AML was significantly positively associated with maternal alcohol consumption during pregnancy (OR, 1.56; 95% CI, 1.13-2.15) in nine studies (23, 24, 26, 30, 35, 37, 38, 40, 41) including 731 cases (Table 2, AML; Fig. 4). The association was statistically significant in three studies (24, 26, 35), positive but not statistically significant in four studies (23, 30, 40, 41), and not significantly inverse in two studies (37, 38). Heterogeneity of results (I^2 = 52.5%) was mainly attributable to the Japanese study on magnetic fields and childhood leukemia with very low participation rates, as mentioned previously (37), and a study in which only three mothers of index cases recalled any alcohol consumption during pregnancy (38).

To investigate if the difference of association of maternal alcohol consumption during pregnancy with ALL and AML was explained by study differences, we restricted the analysis to eight studies reporting data for both ALL (22, 26, 30, 35, 37, 38, 40, 41) and AML (24, 26, 30, 35, 37, 38, 40, 41). Again, a nonsignificant association with ALL (OR, 1.19; 95% CI, 0.98-1.45) and a significant positive association with AML (OR, 1.57; 95% CI, 1.07-2.32) were observed (Table 2).

Only a few studies provided enough information to be included in the dose-response meta-analyses. The results were consistent with a stronger association with AML compared with ALL, although the results were heterogeneous. The OR for an increase of a drink per

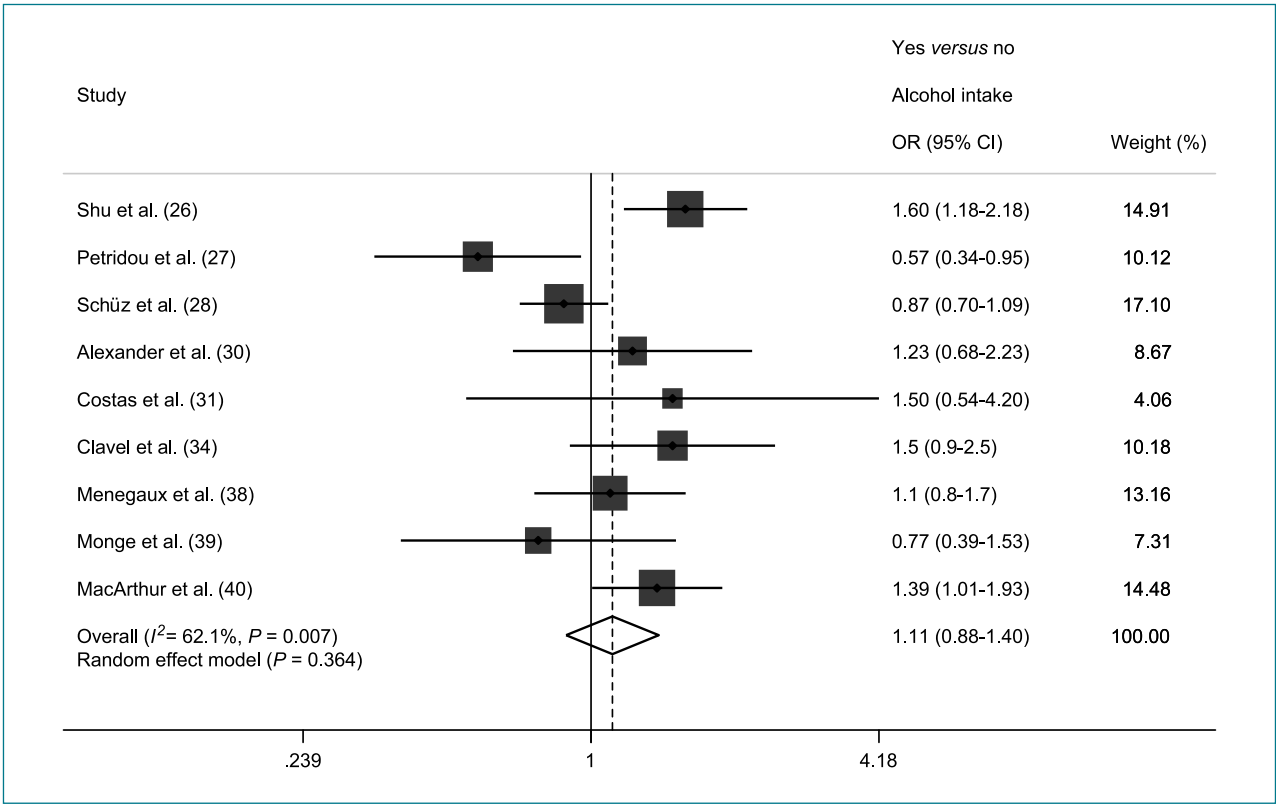

Figure 2. Meta-analysis of studies on maternal alcohol consumption during pregnancy (yes versus no) and risk of all childhood leukemia (GL) in children without Down syndrome.

Table 2. Summary of results of the meta-analyses of case-control studies on leukemia in childhood and maternal alcohol intake during pregnancy (yes vs. no)

Subgroup	No. of studies	Study references	No. of cases	Summary OR (95% CI) yes vs. no	Heterogeneity, *P*
Total alcohol consumption					
ALL	11	22, 26, 29, 30, 32, 35, 37, 38, 40, 41, 42	5,108	1.10 (0.93-1.29)	0.001
AML	9	23, 24, 26, 30, 35, 37, 38, 40, 41	731	1.56 (1.13-2.15)	0.032
Total alcohol consumption, analyses restricted to studies reporting data for both ALL and AML*					
ALL	8	22, 26, 30, 35, 37, 38, 40, 41	2,663	1.19 (0.98-1.45)	0.008
AML	8	24, 26, 30, 35, 37, 38, 40, 41	651	1.57 (1.07-2.32)	0.020
By children's age at diagnosis					
0 to 4 y					
ALL	3	24, 26, 30	539	1.17 (0.83-1.65)	0.231
AML	5	23, 24, 26, 30, 35	295	2.68 (1.85-3.89)	0.761
By type of alcoholic beverage					
Beer					
ALL	5	25, 26, 32, 35, 41	1,635	1.04 (0.77-1.40)	0.091
AML	4	25, 26, 35, 41	260	1.18 (0.79-1.75)	0.625
Wine					
ALL	5	25, 26, 32, 35, 41	1,635	1.02 (0.79-1.32)	0.039
AML	4	25, 26, 35, 41	260	1.67 (1.21-2.32)	0.870
Spirits					
ALL	6	25, 26, 32, 35, 38, 41	1,984	1.29 (1.05-1.59)	0.308
AML	4	25, 26, 35, 41	260	1.62 (0.68-3.81)	0.029

*The two references (22, 24), corresponding to analyses of ALL and AML data, respectively, refer to the same population.

week was 1.02 (95% CI, 0.95-1.09; four studies; refs. 28, 34, 38, 40) for GL, 1.04 (95% CI, 0.97-1.12; five studies; refs. 32, 35, 38, 40, 41) for ALL, and 1.24 (95% CI, 0.94-1.64; three studies; refs. 24, 35, 41; *P* heterogeneity = 0.016) for AML (Table 3).

Children's age. Overall, no association was found between maternal alcohol intake during pregnancy and ALL at age 0 to 4 years (OR, 1.17; 95% CI, 0.83-1.65) in three studies (24, 26, 30). In contrast, a statistically significant association was observed for AML (OR, 2.68; 95% CI, 1.85-3.89) in five studies without heterogeneity ($I^2 \leq 0.1\%$; refs. 23, 24, 26, 30, 35; Table 2, Fig. 5). Only two studies reported results of leukemia with other ages at diagnosis (23, 24). For ALL, one study found no association in children ages 5 to 9 and 10 to 14 years (23). For AML, one study observed no association in children ages 3 to 10 years (23), whereas the other study found a significant positive association in children ages 5 to 9 years (24); both studies found no association in older children (Table 1).

Type of alcoholic beverage. Five studies (25, 26, 32, 35, 41) provided data on beer, wine, or spirits intake, separately, whereas in one study (38), beer and wine were combined into one group and spirits were investigated separately. Statistically significant associations were observed only for AML and wine intake (OR, 1.67; 95% CI, 1.21-2.32) and for ALL and spirits (OR, 1.29; 95% CI, 1.05-1.59; Table 2).

Pregnancy trimester. The risks associated with maternal alcohol consumption at different trimesters of pregnancy were examined in two studies (26, 40) for GL, three studies (26, 32, 40) for ALL, and two studies (26, 40) for AML. Overall, childhood ALL was not associated with alcohol consumption during the first trimester (OR, 0.91; 95% CI, 0.67-1.25), the second trimester (OR, 0.89; 95% CI, 0.63-1.27), or the third trimester (OR, 0.82; 95% CI, 0.62-1.10). For AML, the limited data did not allow any conclusions, although in both studies (26, 40), the OR tended to be slightly higher when alcohol was consumed in the second and third trimesters compared with the first trimester (Table 1).

Publication bias. No evidence of publication bias was found when assessed by funnel plots (data not shown). However, we identified 12 studies on risk factors of childhood leukemia, other than alcohol intake during pregnancy, in which maternal alcohol consumption was considered as a potential confounder (43-54). The corresponding OR or the number of cases and controls for their computation were not given in the articles. The authors were contacted, but no workable information could be retrieved.

Discussion

To our knowledge, this is the first meta-analysis that investigated the role of *in utero* exposure to alcohol associated with childhood leukemia. The results of this meta-analysis indicate that the risk of childhood AML increases with maternal alcohol consumption during pregnancy. The summary OR from nine studies for the comparison of alcohol intake during pregnancy versus no intake was 1.56 (95% CI, 1.13-2.15).

We did not observe a statistically significant association between childhood ALL and maternal alcohol intake during pregnancy. The difference of association with alcohol observed for ALL and AML was not attributable to differences between studies. When a sensitivity analysis including only the eight studies reporting data on both ALL and AML was run, alcohol intake was associated with an increased risk of AML, but not of ALL.

Due to the low number of studies with appropriate published data, the dose-response meta-analyses were not conclusive, although they are consistent with a stronger association with AML as compared with ALL. It was not possible to identify whether there was a threshold of alcohol intake in the association. Additional studies with more detailed data on alcohol exposure are thus necessary.

Only a few studies reported results according to type of alcoholic beverage, and these were mutually adjusted in only two studies (35, 41). The existing evidence does not suggest that one type of alcohol could be more related to leukemia risk than others.

One of the limitations of this study was that all the studies included in the meta-analyses were case-control studies. Recall bias due to the stigma of drinking during pregnancy cannot be excluded. Nevertheless, any recall bias should be assumed to operate similarly for studies on ALL or AML, and particularly in those investigating both types of leukemia. Another limitation concerns the control of potential confounding factors. In the case of AML in young children (Fig. 5), the ORs were adjusted for maternal smoking during pregnancy in only two of five studies (24, 26). Nevertheless, the size of the association reported in the tobacco-adjusted studies was similar to the estimates reported in the other studies. Other potentially uncontrolled confounding factors are maternal household use of pesticides, as suggested by Rudant et al. (41), folate intake during pregnancy, birth weight, allergy after birth (55, 56), and maternal age (57).

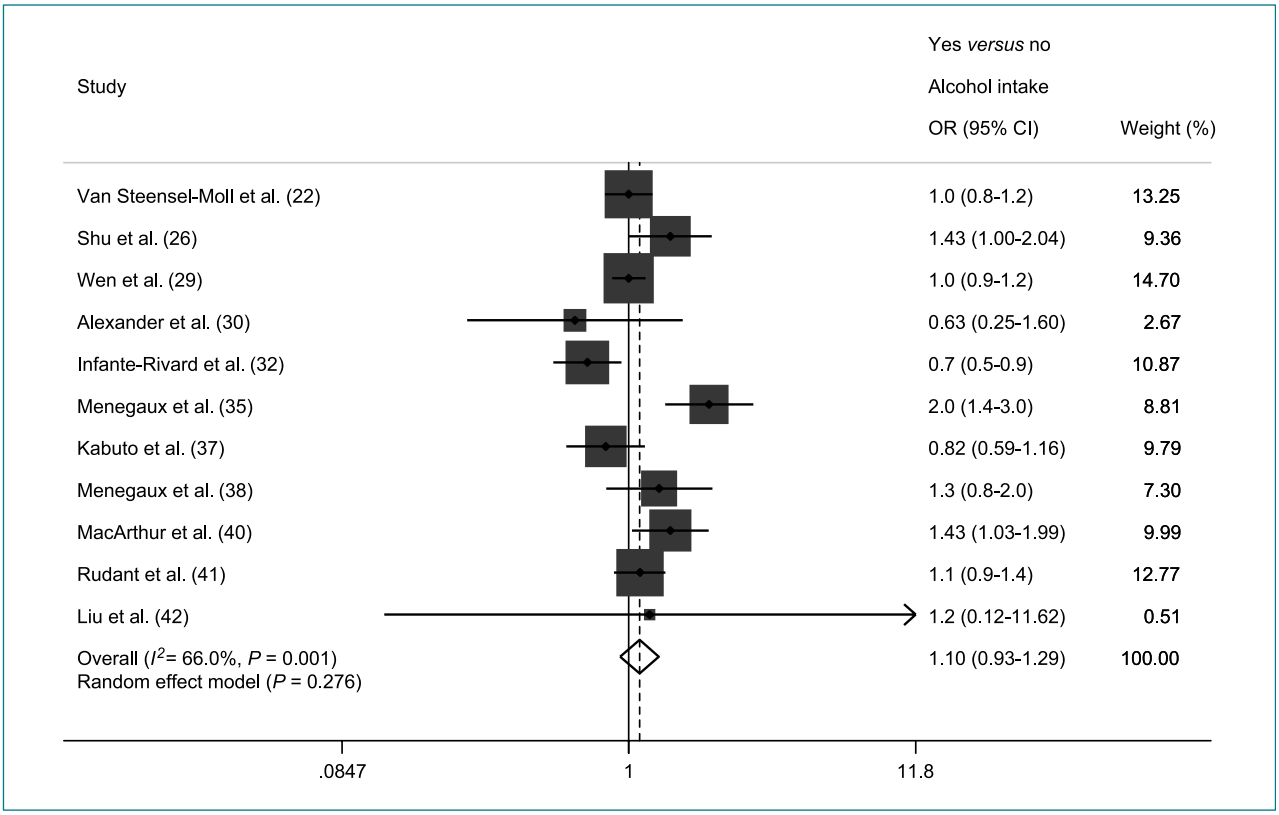

Figure 3. Meta-analysis of studies on maternal alcohol consumption during pregnancy (yes versus no) and risk of childhood ALL.

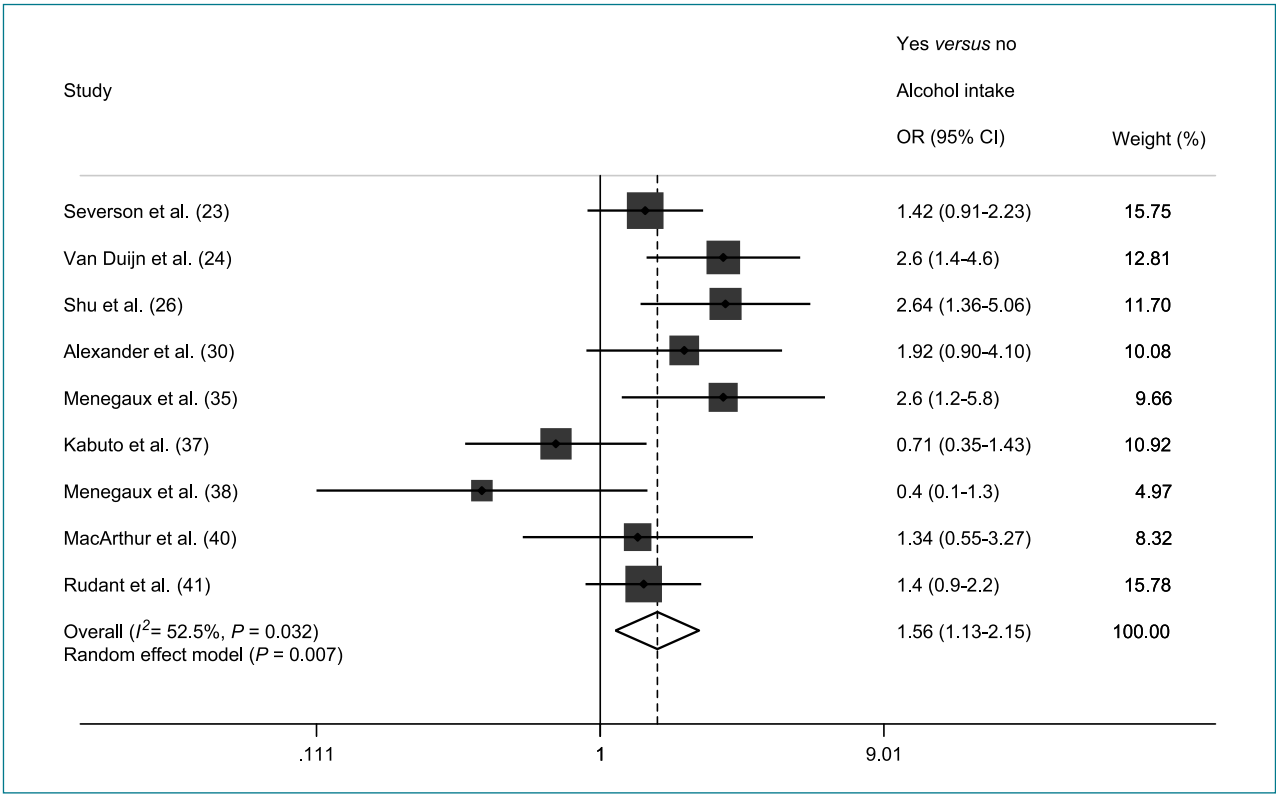

Figure 4. Meta-analysis of studies on maternal alcohol consumption during pregnancy (yes versus no) and risk of childhood AML.

Study results were heterogeneous. It was not possible to statistically assess the source of heterogeneity using meta-regression analyses due to the low number of studies. Qualitative analysis of the data indicated that studies with a low number of cases exposed and low participation rates tended to report associations in opposite directions compared with other studies.

The association of maternal alcohol consumption during pregnancy and AML risk was observed in children ages 0 to 4 years (OR, 2.68; 95% CI, 1.85-3.89), which is consistent with the potential role of prenatal exposure to alcohol in the etiology of AML. The biological plausibility of this association is supported by the fact that alcoholic beverages are recognized as carcinogenic for humans (9) and are involved in several fetal alcohol-related diseases (11, 12). The reason why *in utero* exposure to alcohol may specifically modify the risk of AML in young children is unknown. The incidence peak is observed at a younger age in AML compared with ALL, suggesting a stronger association or shorter latency of AML with prenatal exposures. However, a possible effect on subtypes of ALL and AML cannot be ruled out, as suggested recently for B mature or Burkitt ALL, with a few cases (41) and two studies in which the association of maternal alcohol intake for AML was predominant with M4/M5 subtypes (23) and M1/M2 subtypes (41), respectively.

Table 3. Summary of results of the meta-analyses of case-control studies on leukemia in childhood and maternal alcohol intake during pregnancy (dose-response) in children without Down syndrome

Subgroup	No. of studies	Study references	No. of cases	Summary OR (95% CI) Increase of one drink per week	Heterogeneity, *P*
GL	4	28, 34, 38, 40	2,034	1.02 (0.95-1.09)	0.095
ALL	5	32, 35, 38, 40, 41	2,133	1.04 (0.97-1.12)	0.095
AML	3	24, 35, 41	222	1.24 (0.94-1.64)	0.016

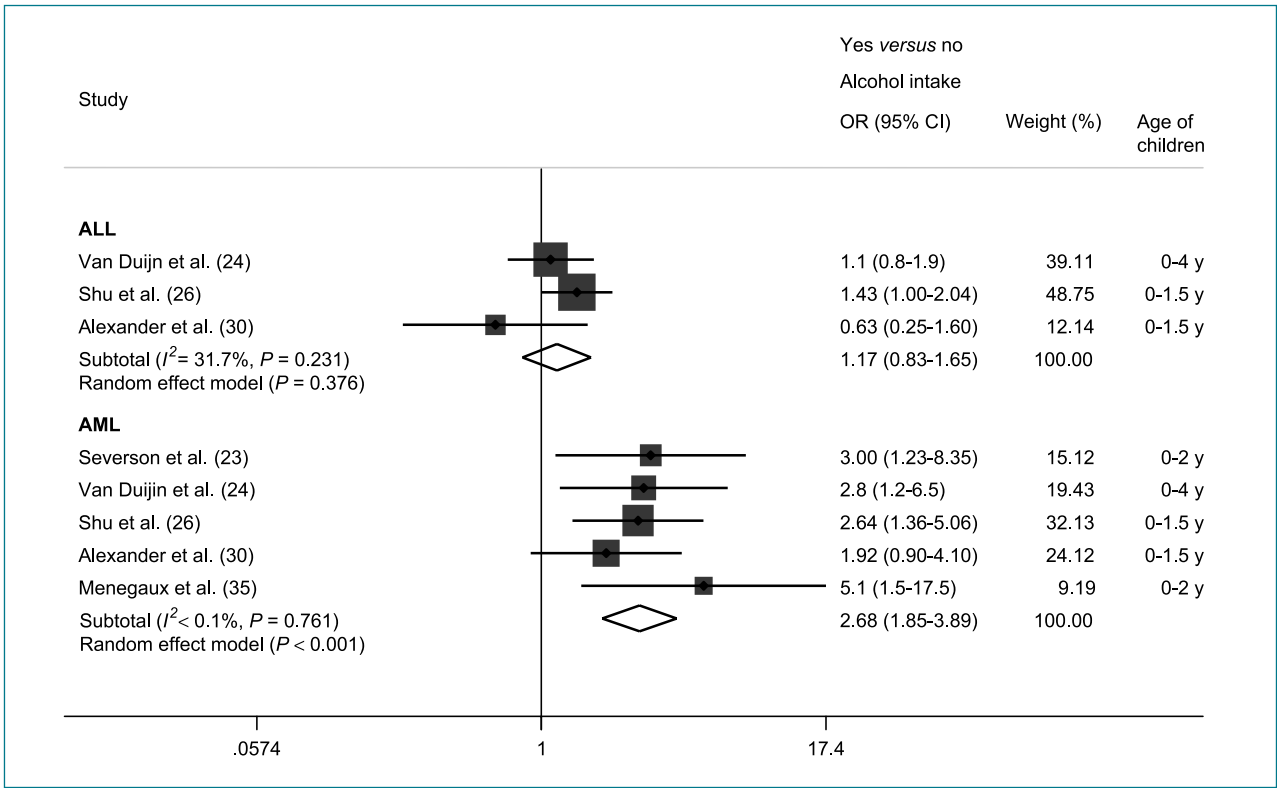

Figure 5. Meta-analysis of studies on maternal alcohol consumption during pregnancy (yes versus no) and risk of ALL and AML for children ages 0 to 4 years at diagnosis.

Although in most countries, pregnant women and women who are trying to conceive are advised to avoid drinking alcohol, to prevent fetal alcohol syndrome, recent studies indicate that the prevalence of women reporting alcohol drinking during pregnancy in some countries is still high: as reviewed by de Chazeron et al. (58), it has been estimated to be 12% in the United States, 30% in Sweden, 52% in France, 59% in Australia, and 60% in Russia. Binge-drinking before pregnancy has been found to be a strong predictor of both drinking and binge-drinking during pregnancy (59). In addition to actions directed to pregnant women, acting before pregnancy to reduce alcohol drinking might contribute to reduce the occurrence of harmful effects including AML in young children.

In the future, large birth cohort studies should investigate the influence of maternal alcohol drinking and the risk of childhood leukemia, in particular, AML. Such studies may integrate accurate data collection not only on fetal exposure to alcohol allowing dose-response analyses, but also the collection of detailed potential confounding factors. Because ALL and AML are rare diseases, the creation of an international consortium of birth cohort studies could provide the statistical power required to investigate the interaction of alcohol drinking with other environmental and genetic factors in relation to the risk of acute leukemia in children.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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