OBSTETRICS

# Maternal coffee consumption during pregnancy and risk of childhood acute leukemia: a metaanalysis

Jian Cheng, BMSc; Hong Su, PhD; Rui Zhu, BMSc; Xu Wang, BMSc; Meiling Peng, MD; Jian Song, BMSc; Dongdong Fan, MD

**OBJECTIVE:** This study was undertaken to explore the association between maternal coffee consumption during pregnancy and childhood acute leukemia (AL).

**STUDY DESIGN:** The PubMed database was used to search studies up to May 5, 2013, and the lists of references of retrieved articles were also screened to identify additional relevant studies. Studies were included if they reported the odds ratio and corresponding 95% confidence interval (CI) of childhood AL, including childhood acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML), with respect to maternal coffee consumption during pregnancy.

**RESULTS:** Compared with non/lowest drinkers, the combined odds ratio regarding the relationship of maternal coffee consumption during pregnancy and childhood AL was 1.22 (95% CI, 1.04—1.43) for ever drinkers, 1.16 (95% CI, 1.00—1.34) for low to moderate-level drinkers, and 1.72 (95% CI, 1.37—2.16) for high-level drinkers. When analysis was conducted by subtypes of childhood AL, maternal coffee consumption (high-level drinkers vs non/lowest drinkers) was statistically significantly associated with childhood ALL (1.65; 95% CI, 1.28—2.12) and childhood AML (1.58; 95% CI, 1.20—2.08). We observed the linear dose-response relationship of coffee consumption and childhood AL ($P$ for nonlinearity = .68), including childhood ALL and childhood AML; with increased coffee consumption, the risk of childhood AL increased.

**CONCLUSION:** The findings of the metaanalysis suggest that maternal coffee consumption during pregnancy may increase the risk of childhood AL. Because of limited studies, further prospective studies are urgently needed to explore the adverse effect of coffee consumption on childhood AL.

**Key words:** childhood leukemia, coffee consumption, metaanalysis

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Childhood cancer has been a major global health issue. Each year, nearly 100,000 children age <15 years die of cancer, >90% of them in resource-limited countries.[1] Acute leukemia (AL) is one of the most common childhood cancers, and morbidity has been increasing in Europe and the United States in past decades.[2-4] Among AL, acute lymphoblastic leukemia (ALL) was the most common subtype, followed by acute myeloid leukemia (AML), also called acute nonlymphoblastic leukemia.[5]

Despite decades of research, the cause of childhood AL remained unclear with the exception of radiation exposure and a few chromosomal and genetic abnormalities. The attention of recent research on finding risk factors of childhood AL has been focused on parental environmental exposures during pregnancy. Factors such as maternal alcohol consumption and smoking during pregnancy have been extensively explored. According to 2 recent metaanalyses, positive association was found between childhood leukemia and maternal alcohol during pregnancy,[6] but not maternal smoking.[7]

Among environmental exposures, the impact of maternal coffee consumption during pregnancy on childhood AL was another research hotspot. Coffee, one of the most widely consumed beverages in the world, contains caffeine, which may result in childhood AL. For instance, caffeine may act as a topoisomerase (topo) II inhibitor,[8] a DNA repair inhibitor or a carcinogen metabolism inhibitor.[9] It induces chromosomal aberrations and translocations, such as abnormalities of chromosome 11q23, which was taken as a cause for the pathogenesis of infant leukemia.[8] However, the results based on epidemiological studies on the association between coffee consumption during pregnancy with childhood AL were inconsistent. Although the risk estimates concerning the association of maternal coffee consumption during pregnancy and childhood ALL from previous published studies were pooled by Milne et al[10] in their original paper, but only 2 published studies were included and the impact of coffee consumption during pregnancy on childhood AL and childhood AML remains unknown. Therefore, we aimed to conduct a comprehensive metaanalysis of identified studies to evaluate the relationship of maternal coffee consumption during pregnancy and childhood AL and its subtypes (ALL, AML).

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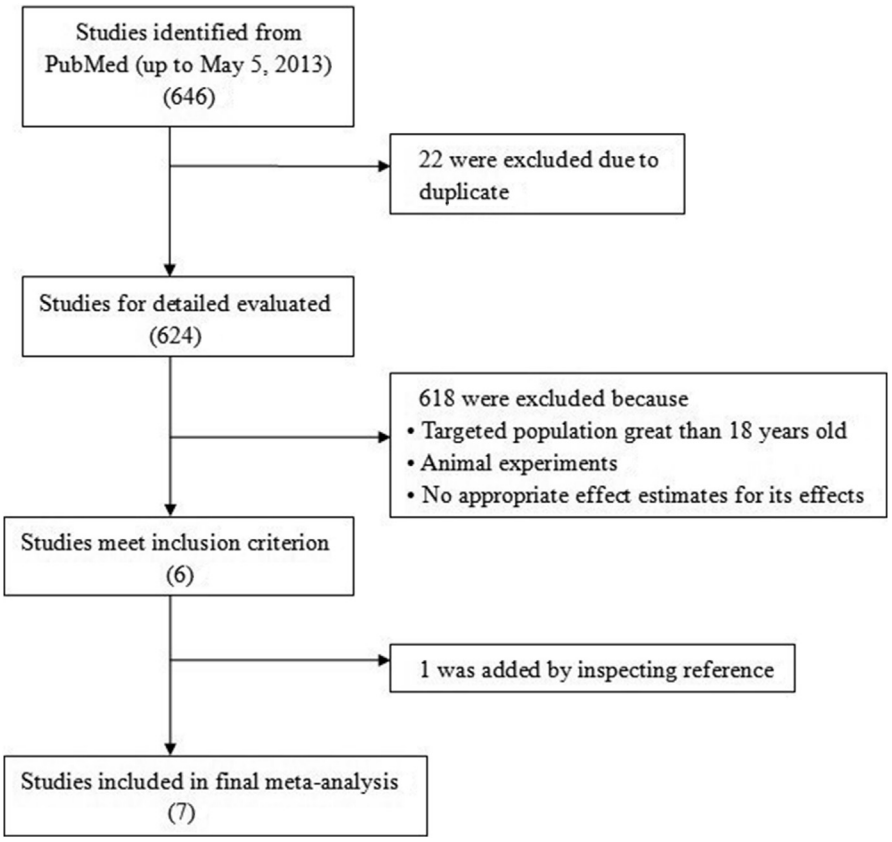
FIGURE 1
**Process of study selection**

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## MATERIALS AND METHODS

### Search strategy

The PubMed database was searched for studies up to May 5, 2013, with the following key words: "coffee," "caffeine," "beverage," "leukemia," and "AL." All subterms were included and no language restrictions were imposed. In addition, the lists of references in previous studies (including reviews) were also screened to identify additional relevant studies.

### Study selection

We included the identified studies that meet the following criteria: (1) case-control or cohort study design; (2) main exposure of interest was coffee consumption during pregnancy; (3) outcome of interest was childhood AL, ALL, or AML (or acute nonlymphoblastic leukemia); (4) targeted population was children <18 years; and (5) they provided the odds ratio (OR) and corresponding 95% confidence interval (CI) (or data allowed to recalculate them).

### Data extraction

Data from identified studies were extracted independently by 2 investigators using a standardized data collection form, and then compared. For each included study, the data extracted were the following: first author's last name, year of publication, location, study period, children's age range, the number of cases and controls, type of leukemia, level of coffee consumption during pregnancy, effect estimates (OR and 95% CI), adjustment for potential confounding factors, and assessment methods of coffee consumption (interview or self-administrated).

### Statistical analysis

We extracted study-specific risk estimates and calculated the summary estimates by combining log risk estimates weighted by the inverse of their variances. First, we compared the risk of childhood AL in ever drinkers with never/lowest drinkers. Several studies did not provide the risk of childhood AL for ever drinkers. For those studies, a summary OR was calculated for ever drinkers using the reported risk estimates for each coffee consumption level. Then the summary OR was used in final metaanalysis when pooling the overall risk of childhood AL for ever drinkers.

Second, to estimate the summary OR for various levels of coffee consumption during pregnancy, we also calculated the study-specific estimates for low to moderate coffee consumption (defined as >0 to ≤3 cups/d for Menegaux et al[5,11]; >0 to ≤1 cup/d and >1 to ≤2 cups/d for Bonaventure et al[12]; >0 to <3 cups/d for Clavel et al[4]; >0 to <2 cups/d for Milne et al[10]; >0 to <3 times/wk for Ross et al[8]) and for high coffee consumption (defined as >4 to ≤8 cups/d and ≥8 cups/d for Menegaux et al[5]; >3 cups/d for Menegaux et al[11]; >2 cups/d for Bonaventure et al[12]; ≥3 for Menegaux et al[11]; ≥2 cups/d for Milne et al[10]; ≥4 times/wk for Ross et al[8]). Statistical heterogeneity between studies was evaluated with Cochran Q and $I^2$ statistics with corresponding $P$ value and $P < .1$ was considered statistically significant. Fixed effect model was used to calculate the pooled OR if no heterogeneity was observed, otherwise, random effect model was used.

Since different levels of coffee consumption were analyzed in different studies, we also conducted a dose-response metaanalysis to explore the pooled dose-response relationship between coffee consumption during pregnancy and childhood AL. Studies included in final dose-response had to meet the following criteria: (1) at least 3 levels of coffee consumption, including the reference level were presented; and (2) number of cases and controls, and OR (for case-control study) with corresponding 95% CI for each level of coffee consumption were reported. The median or mean coffee consumption for each level was assigned to each corresponding OR for each study. The midpoint of the upper and lower boundaries in each level was assigned as

TABLE 1
**Characteristics of studies included in metaanalysis**

| Reference | Country and study; period | Age range | Cases/controls | Type of leukemia (no.) | Coffee consumption | Effect estimation (95% CI) AL | ALL | AML (ANLL) | Adjustments |
|---|---|---|---|---|---|---|---|---|---|
| Ross et al,[8] 1996[a] | United States and Canada; NA | <12.5 mo | 84/97 | AL (84)<br>ALL (54)<br>AML (30) | Never<br>≤3 times/wk<br>≥4 times/wk | Reference<br>1.5 (0.7–3.3)<br>2.5 (1.0–6.2) | Reference<br>1.1 (0.4–3.0)<br>2.3 (0.7–8.2) | Reference<br>2.4 (0.6–9.2)<br>2.6 (0.7–10.0) | Socioeconomic status, maternal education |
| Petridou et al,[15] 1997[a] | Greece; 1993 through 1994 | 0–14 y | 153/300 | AL (153) | Never<br>Ever | Reference<br>0.89 (0.55–1.46) | | | Gender, age, place of residence |
| Clavel et al,[4] 2004[a] | France; 1995 through 1999 | <15 y | 219/105 | AL (219) | Never<br>Ever<br>≤3 cups/d<br>>3 cups/d | Reference<br>1.8 (1.0–3.3)<br>1.6 (0.9–2.9)<br>4.1 (1.6–10.1) | | | Gender, age, ethnic origin, hospital, socioeconomic status, maternal education |
| Menegaux et al,[5] 2005[a] | France; 1995 through 1999 | <15 y | 280/288 | AL (280)<br>ALL (240)<br>ANLL (40) | Never<br>≤3 cups/d<br>4-8 cups/d<br>>8 cups/d | | Reference<br>1.1 (0.7–1.8)<br>2.4 (1.3–4.7)<br>3.1 (1.0–9.5) | Reference<br>1.6 (0.6–4.3)<br>2.8 (0.7–10.4)<br>3.0 (0.3–35.1) | Gender, age, ethnic origin, socioeconomic status |
| Menegaux et al,[11] 2007[b] | France; 1995 through 1998 | <15 y | 472/567 | AL (472)<br>ALL (407)<br>AML (62) | Never<br>Ever<br>≤3 cups/d<br>>3 cups/d | Reference<br>1.1 (0.9–1.5)<br>1.1 (0.8–1.4)<br>1.5 (0.9–2.4) | Reference<br>1.1 (0.8–1.4)<br>1.1 (0.8–1.4)<br>1.5 (0.9–2.4) | Reference<br>1.6 (0.8–2.9)<br>1.6 (0.8–3.0)<br>1.4 (0.5–4.4) | Gender, age, region, socioprofessional category, and birth order |
| Milne et al,[10] 2011[b] | Australia; 2003 through 2006 | ≤14 y | 337/697 | ALL (337) | Never<br>Ever<br><2 cups/d<br>≥2 cups/d | | Reference<br>0.89 (0.61–1.30)<br>0.77 (0.51–1.16)<br>1.12 (0.72–1.74) | | Age, sex, state of residence, and maternal education |
| Bonaventure et al,[12] 2013[a] | France; 2003 through 2004 | ≤14 y | 764/1681 | AL (764)<br>ALL (648)<br>AML (101) | Never/occasional<br><1 cup/d<br>1-2 cups/d<br>>2 cups/d | Reference<br>1.0 (0.8–1.3)<br>1.3 (1.0–1.7)<br>1.6 (1.2–2.1) | Reference<br>1.3 (0.7–2.1)<br>1.8 (1.0–3.3)<br>2.4 (1.3–4.3) | Reference<br>1.0 (0.8–1.3)<br>1.3 (1.0–1.7)<br>1.5 (1.1–2.0) | Gender, age, maternal education, and socioeconomic status |

*AL*, acute leukemia; *ALL*, acute lymphoblastic leukemia; *AML*, acute myelocytic leukemia; *ANLL*, acute nonlymphocytic leukemia; *CI*, confidence interval; *NA*, no records.

[a] Studies used interview for coffee assessment; [b] Studies used self-administered questionnaire for coffee assessment.

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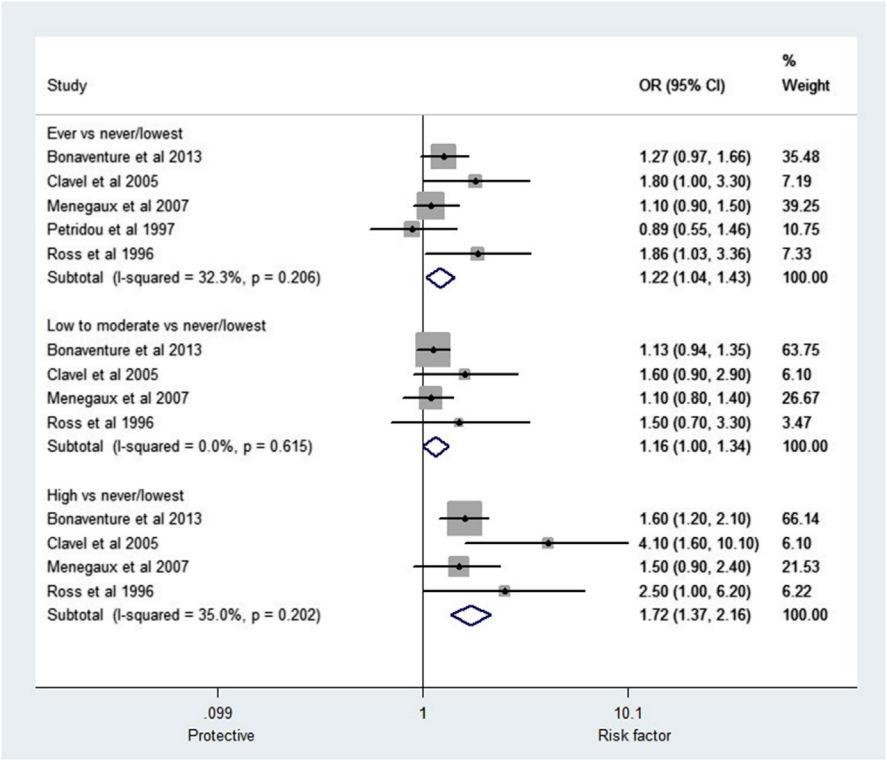
FIGURE 2
**Summary ORs of childhood acute leukemia for ever, low to moderate-level, and high-level drinkers vs never/lowest drinkers**




*Squares* indicate study-specific risk estimates; *diamond* indicates summary OR with corresponding 95% confidence interval (CI).

*OR*, odds ratio.

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the average intake if the median or mean coffee consumption for each level was not provided. If the upper boundary of the highest level was not provided, we assumed that the boundary had the same amplitude as the adjacent category.

To examine the nonlinear relationship between coffee consumption during pregnancy and childhood AL, a 2-stage random effects dose-response meta-analysis was performed, taking into account the heterogeneity among studies recently proposed by Orsini et al.[13] Briefly, for each identified study contributing to this metaanalysis, the log OR was calculated for various levels of coffee consumption. Then a restricted cubic spline model, with 4 knots at percentiles (5%; 35%; 65%; 95%) of levels of coffee consumption, was estimated using generalized least square regression, taking into account the correlation within each set of published ORs. The study-specific estimates were combined using fixed effects restricted cubic spline models with 4 knots and using the method of Greenland and Longnecker[14] to estimate the covariances of OR. If $P < .05$, the nonlinearity dose-response relationship was considered to exist.

We conducted stratified analysis by the subtype of childhood AL and investigated the following potential sources of heterogeneity: assessment methods of coffee consumption and study population. Meanwhile, publication bias was also assessed by constructing funnel plots and by Egger regression asymmetry test. $P < .05$ was considered representative of statistically significant publication bias. All statistical analyses were conducted using software (Stata, version 11; StataCorp, College Station, TX).

## RESULTS

A total of 7 published studies (Figure 1) regarding the relationship between coffee consumption during pregnancy and childhood AL were included in our metaanalysis. All the studies were case-control design (Table 1), of which 4 were conducted in France, 1 in Australia, 1 in Greece, and 1 in North America. Among these studies, 5 used self-administrated questionnaires for coffee consumption assessment, and the others used interview technology for coffee consumption assessment. Five evaluated the association between coffee consumption during pregnancy and childhood AL,[4,8,11,12,15] 5 assessed childhood ALL,[5,8,10-12] and 4 evaluated childhood AML.[5,8,11,12]

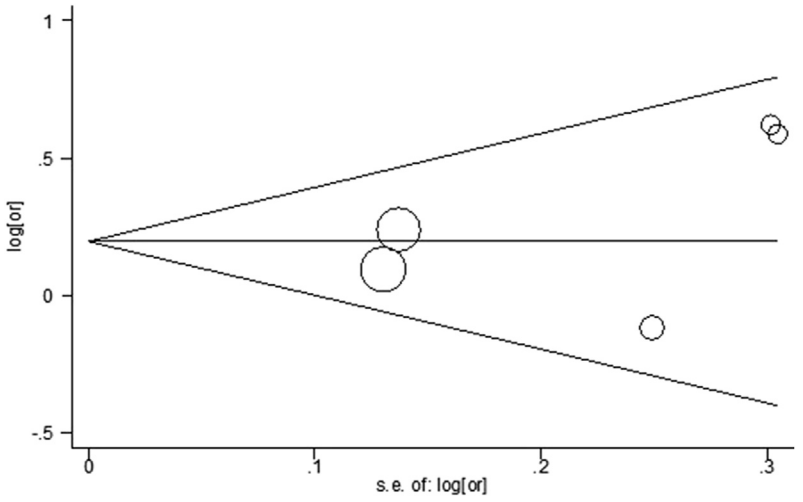
### Maternal coffee consumption during pregnancy on childhood AL

Risk estimates for childhood AL are shown in Figure 2. Compared with never/lowest drinkers, adverse effect of maternal coffee consumption during pregnancy on childhood AL was observed in ever drinkers (1.22; 95% CI, 1.04−1.43), low to moderate-level drinkers (1.16; 95% CI, 1.00−1.34), and high-level drinkers (1.72; 95% CI, 1.37−2.16). There was no statistically significant heterogeneity among studies ($I^2 = 32.3\%$, $P = .206$; $I^2 = 0.0\%$, $P = .615$; $I^2 = 35.0\%$, $P = .202$). Regarding the assessment of publication bias, neither Begg bias (Figure 3) nor Egger bias was observed ($P = .406$).

### Maternal coffee consumption during pregnancy on childhood ALL

Figure 4 presents the summary ORs for childhood ALL. Compared with the never/lowest drinkers, the summary OR was 1.26 (95% CI, 1.05−1.50) for ever drinkers, 1.09 (95% CI, 0.91−1.31) for low to moderate-level drinkers, and 1.65 (95% CI, 1.28−2.12) for high-level drinkers. Significant between-study heterogeneity was not noted in last 2 ($I^2 = 24.1\%$, $P = .261$; $I^2 = 47.0\%$, $P = .110$). When the results on ever drinkers were pooled in random effect model, the adverse effect of ever drinkers was not observed: 1.30 (95% CI, 0.97−1.73). With

FIGURE 3
**Begg funnel plot with 95% confidence interval**




No publication bias was noted from both visualization of funnel plot and Egger test ($P = .406$).

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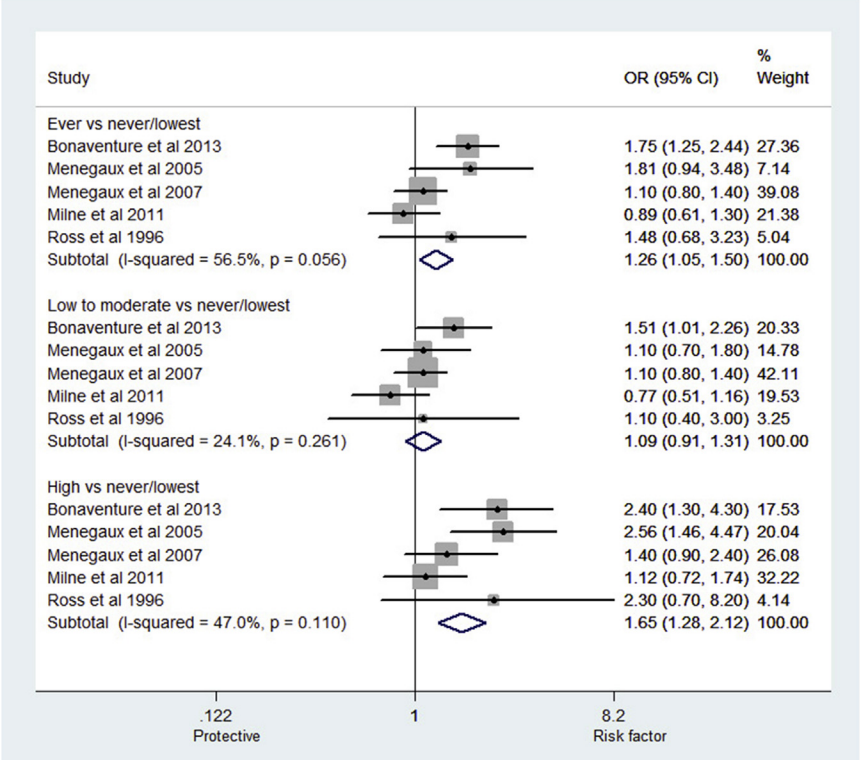
FIGURE 4
**Summary ORs of childhood acute lymphoblastic leukemia for ever, low to moderate-level, and high-level drinkers vs never/lowest drinkers**




*Squares* indicate study-specific risk estimates; *diamond* indicates summary OR with corresponding 95% confidence interval (CI).

*OR*, odds ratio.

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respect to publication bias, no bias was observed (Egger test, $P = .596$).

## Maternal coffee consumption during pregnancy on childhood AML

The summary ORs for childhood AML are presented in Figure 5. The significant association between childhood AML and coffee consumption during pregnancy was observed for ever drinkers (1.35; 95% CI, 1.10−1.66) and high-level drinkers (1.58; 95% CI, 1.20−2.08), but not for low to moderate-level drinkers (1.18; 95% CI, 1.00−1.40). No heterogeneity was observed ($I^2 = 17.0\%$, $P = .306$; $I^2 = 0.0\%$, $P = .643$; $I^2 = 0.0\%$, $P = .486$). There was publication bias among studies included in this metaanalysis (Egger test, $P = .018$).

## Dose-response relationship

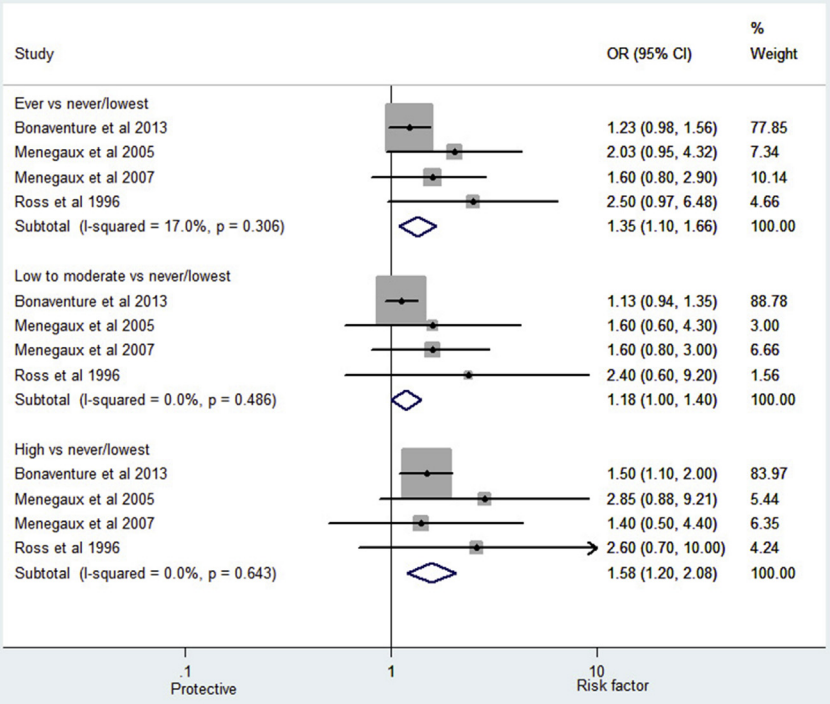
Six studies were included in final dose-response metaanalysis with one[8] removed due to no available data presented for cases and controls. Among these studies, 3,[4,11,12] 4,[5,10-12] and 3[5,11,12] were used to explore the dose-response relationship between coffee consumption during pregnancy and childhood AL, childhood ALL, and childhood AML, respectively.

For childhood AL, the nonlinearly relationship was not observed regarding maternal coffee consumption with childhood AL ($P$ for nonlinearity = .68) (Figure 6, A). Compared with never/lowest drinkers, the pooled ORs were 1.10 (95% CI, 0.94−1.29) for 1 cup/d, 1.24 (95% CI, 1.06−1.46) for 1-2 cups/d, 1.53 (95% CI, 1.21−1.93) for 2-3 cups/d, and 1.96 (95% CI, 1.32−2.92) for 4-5 cups/d.

The nonlinearly relationships of maternal coffee consumption during pregnancy with childhood ALL were also not noted ($P$ for nonlinearity = .67) (Figure 6, B), and the summary ORs were 1.00 (95% CI, 0.89−1.14) for 0-1 cup/d, 1.04 (95% CI, 0.86−1.25) for 1 cup/d, 1.10 (95% CI, 0.91−1.34) for 1-2 cups/d, 1.30 (95% CI, 1.05−1.60) for 2-3 cups/d, 1.41 (95% CI, 1.11−1.78) for 3 cups/d, 1.74 (95% CI, 1.29−2.35) for 4-5 cups/d, 2.08 (95% CI, 1.46−2.94) for 6 cups/d, and 3.02 (95% CI, 1.17−7.78) for 10 cups/d.

We found linear association between maternal coffee consumption and

FIGURE 5
**Summary ORs of childhood acute myeloid leukemia for ever, low to moderate-level, and high-level drinkers vs never/lowest drinkers**




*Squares* indicate study-specific risk estimates; *diamond* indicates summary OR with corresponding 95% confidence interval (CI).

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childhood AML (*P* for nonlinearity = .65) (Figure 6, C). The risk of childhood AML for coffee consumption was 1.10 (95% CI, 0.96−1.25), 1.15 (95% CI, 0.98−1.34), 1.24 (95% CI, 1.04−1.47), 1.39 (95% CI, 1.10−1.75), 1.48 (95% CI, 1.18−1.84), and 1.65 (95% CI, 1.26−2.16) for 1, 1-2, 2-3, 4-5, 6, and 10 cups/d, respectively.

### Subgroup and sensitivity analysis

The studies were stratified by study population and assessment methods of coffee consumption for ever drinkers (Table 2). In the subgroup analysis by study population, we noted that coffee consumption during pregnancy was significantly associated with increased risk of childhood ALL (OR, 1.45; 95% CI, 1.01−2.07) and childhood AML (OR, 1.31; 95% CI, 1.07−1.62) among Europeans, while no such association was observed among people in other countries. When stratified by assessment methods of coffee consumption, the adverse effects of coffee consumption for ever drinkers on childhood AL (OR, 1.72; 95% CI, 1.30−2.28) and childhood AML (OR, 1.33; 95% CI, 1.07−1.65) were observed for studies using interviewing techniques, but not among studies using self-administrated questionnaire. The heterogeneity was only observed ($P = .08$, $I^2 = 60.9\%$) when assessing the association between coffee consumption and childhood ALL among Europeans. When we conducted the analysis for low to moderate-level drinkers and high-level drinkers, the pooled effect estimates were similar with that for ever drinkers, and no heterogeneity was noted in all results (data not shown).

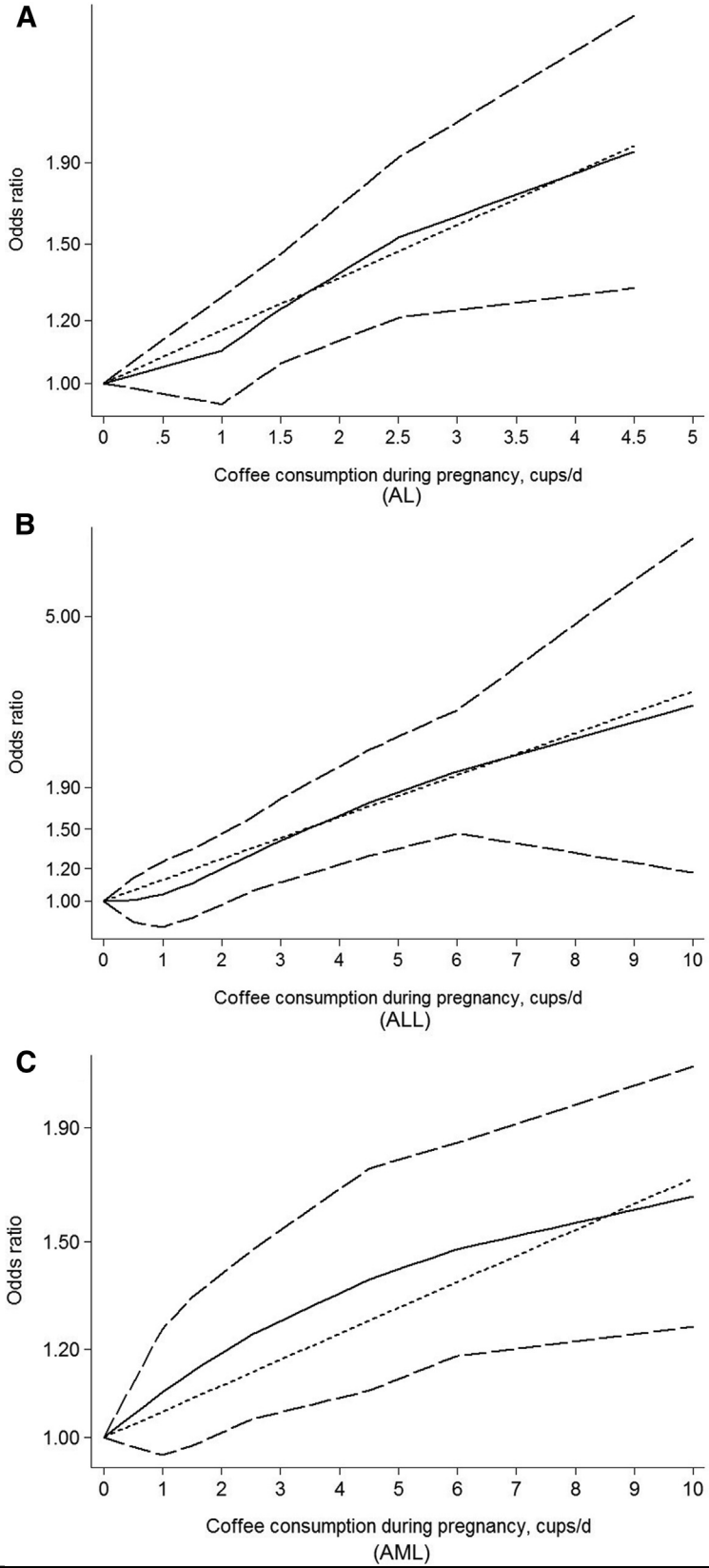
Because limited cases of AL (84) were analyzed by Ross et al,[8] the study was removed to observe the stability of the results. For high-level drinkers, the positive relationships with childhood AL (OR, 1.68; 95% CI, 1.33−2.12), ALL (OR, 1.71; 95% CI, 1.14−2.55), and AML (OR, 1.55; 95% CI, 1.17−2.05) remained statistically significant. For ever drinkers, the adverse effect of coffee consumption during pregnancy on childhood AML was observed (OR, 1.32; 95% CI, 1.07−1.62), but not on childhood AL and ALL. However, for low to moderate-level drinkers, the positive relationships with childhood AL, ALL, and AML were not noted.

## COMMENT

The current metaanalysis evaluated the potential association between maternal coffee consumption during pregnancy and childhood AL based on 7 case-control studies, with a pooled total of 2090 cases and 3630 controls. The results indicated that maternal coffee consumption during pregnancy was significantly associated with childhood AL. Overall, compared with never/lowest drinkers, the risk of childhood AL increased by 22% for ever drinkers and 72% for high-level drinkers. In addition, the statistically significant relationships between maternal coffee consumption during pregnancy and childhood ALL and childhood AML were also noted, especially for high-level drinkers with summary ORs ranging from 1.58 to 1.65.

There are some potential mechanisms through which coffee consumption may increase the risk of childhood AL. Coffee contains a large amount of caffeine, which is considered a topo II inhibitor.[8] According to previous studies, DNA topo II, an important enzyme in the unwinding and regulation of DNA, is necessary for gene transcription, DNA recombination, and replication.[16] Since the proliferation of cells during fetal development and topo II levels is greatest in rapidly dividing cells,[17] excessive exposure to topo II inhibitors, such as coffee, during pregnancy may lead to developmental abnormalities in the fetus. For instance, it is generally believed that DNA topo II inhibitors can cause illegitimate recombination or translocation preferentially at the 11q23 site,[18] resembling that induced by epipodophyllotoxins,[19] as has commonly been observed in

FIGURE 6
**Dose-response relationships between maternal coffee consumption and risk of childhood**




infants with leukemia[20] and postulated as a factor in the pathogenesis of the disease.[8] Previous studies have shown that caffeine has the capacity of inhibiting some genes, such as the tumor suppressor gene (P53)[21] and ataxia telangiectasia mutated gene,[22] which were associated with childhood AL.[23,24]

Furthermore, the interaction of coffee consumption and maternal lifestyle during pregnancy on childhood AL has been reported. Milne et al[10] has assessed the interaction of coffee consumption and maternal smoking during pregnancy in the development of childhood AL through pooling results with prior published studies. They found that smoking status might modify the association between coffee consumption and childhood ALL and the summary OR (2.32; 95% CI, 1.51−3.57) increased for >3 cups/d of coffee during pregnancy among nonsmokers, while that among smoking mothers was 1.01 (95% CI, 0.77−1.33). Later, Bonaventure et al[12] also explored the potential effect of maternal smoking status during pregnancy on the association between coffee consumption and childhood AL as well as its subtypes. They observed that for children born to nonsmoking mothers, the OR was 1.7 (95% CI, 1.3−2.3) [ALL 1.5 (95% CI, 1.1−2.1) and AML 3.2 (95% CI, 1.6−6.2); and for children born to smoking mothers: AL 1.2 (95% CI, 0.7−2.0); ALL 1.2 (95% CI, 0.7−2.1); and AML 1.6 (95% CI, 0.4−6.6)]. It has been shown that, for a given caffeine intake, blood caffeine concentrations were lower in smoking

**A,** Acute leukemia (AL) (*P* for nonlinearity = .68); **B,** acute lymphoblastic leukemia (ALL) (*P* for nonlinearity = .67); and **C,** acute myeloid leukemia (AML) (*P* for nonlinearity = .65). Data were modeled with fixed effects restricted cubic spline models with 4 knots (5%; 35%; 65%; 95%) and using Greenland and Longnecker[14] method to estimate covariances of odds ratio (OR). *Solid line* and *long dash line* represented estimated OR and its 95% confidence interval. Short dash line represented linear relationship.

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TABLE 2
**Stratified analysis by study population and coffee assessment for ever drinkers vs non/lowest drinkers**

| Variables | Study, n | Case, n | OR (95% CI) ALL | OR (95% CI) AML | Heterogeneity test ALL | Heterogeneity test AML |
|---|---|---|---|---|---|---|
| Study population | | | | | | |
| Europe | 5 | 1669 | 1.45 (1.01−2.07)[a] | 1.31(1.07−1.62) | $P = .08$, $I^2 = 60.9\%$ | $P = .38$, $I^2 = 0.0\%$ |
| Others | 2 | 421 | 0.98 (0.70−1.38) | 2.5 (0.97−6.48) | $P = .25$, $I^2 = 24.5\%$ | $P = .93$, $I^2 = 0.0\%$ |
| Coffee assessment | | | | | | |
| Interview | 5 | 1281 | 1.72 (1.30−2.28) | 1.33 (1.07−1.65) | $P = .92$, $I^2 = 0.0\%$ | $P = .19$, $I^2 = 39.9\%$ |
| Questionnaire | 2 | 809 | 1.02 (0.82−1.28) | 1.60 (0.80−2.90) | $P = .89$, $I^2 = 0.18\%$ | |

*ALL*, acute lymphocytic leukemia; *AML*, acute myelocytic leukemia; *CI*, confidence interval; *OR*, odds ratio.

[a] Random effect model.

*Cheng. Maternal coffee consumption and risk of childhood leukemia. Am J Obstet Gynecol 2014.*

than in nonsmoking women.[25] The different observation may be explained by the known accelerating effect of tobacco smoking on caffeine metabolism[26] and decreasing the exposure to caffeine.

Because of the wide array of measurement categories of coffee consumption reported among studies, we also conducted dose-response analysis of coffee consumption during pregnancy on risk of childhood AL. In the present metaanalysis, we noted the linearity association between childhood AL (including its subtypes) and coffee consumption during pregnancy. Although the threshold of coffee consumption was not identified in prior studies, which may due to the variation of ethnicity or coffee consumption category existing in pregnant women over the world, we observed the significant association between pregnant women who drank 1-2 cups/d of coffee and childhood AL. The similar adverse effects on childhood ALL and childhood AML were also noted for those who drank 2-3 cups/d of coffee. The results showed that with the coffee consumption increased, the risk of childhood AL and its subtypes elevated, which were similar with previous studies. Bonaventure et al[12] has reported that OR of coffee consumption increased linearly with daily intake ($P$ for trend .001). In a population-based study, Ross et al[8] has shown that there was a statistically significant positive association ($P$ for trend = .04) between childhood AML and the increasing consumption of DNA topo II inhibitors contained in foods. Thus, we speculated that for those born to nonsmoking mothers, coffee consumption might aggravate the accumulation of caffeine in the body and lead to a greater risk of childhood AL.

We also conducted a subgroup analysis by study population and coffee assessment for ever drinkers vs never/lowest drinkers. The pooled effect estimates indicated that the significant relationship of coffee consumption and childhood AL existed only in Europe, not in other countries. The difference observed may be explained, at least in part, by the variations of coffee consumption among people in Europe and other countries. Although the United States was one of the countries with the highest coffee consumption, only 1 study[8] was included in our metaanalysis and limited numbers of cases (84) were analyzed, therefore, it might be insufficient to detect the risk of childhood AL. In addition, a possible role of ethnic differences in genetic backgrounds, the differences of environment they lived in, and potential lifestyles should also be taken into account. When the subgroup analysis was performed by assessment methods of coffee consumption, we noted the positive association between coffee consumption and childhood ALL and childhood AML among studies using interviewing techniques, but not among studies using self-administrated questionnaire. The contrast may due to a consequence of information bias (mainly recall bias) because of different assessment techniques used in different studies.

Ross et al[8] reported no risk of childhood AL and childhood AML for decaffeinated coffee drinkers, but only 64 and 43 cases were included, respectively. Due to limited studies that examined the risk of decaffeinated coffee intake during pregnancy in relation to childhood AL, there were no available data for us to conduct a metaanalysis of decaffeinated coffee intake. Regarding the detailed sensitivity period during pregnancy, in which the risk of childhood AL for coffee drinkers may be greater, Ross et al[8] has proposed that a 9-month window was extremely important for epidemiologic studies. But few studies have explored it. Milne et al[10] has explored whether maternal coffee consumption during the last 6 months of pregnancy was associated with childhood ALL. But no association was found for drinkers (ever, <2 cups and >2 cups/d).

The strengths of this metaanalysis was that we have a systematic and quantitative assessment on the association between maternal coffee consumption during pregnancy and childhood AL (including its subtypes), and explore the potential dose-response relationship between

them. In addition, after removing the studies including the maximum[8] and minimum sample size,[12] the positive association of maternal coffee consumption and childhood leukemia still remained statistically significant. Subgroup analyses also confirmed the robustness of the pooled results.

Several limitations should also be taken into account when interpreting the results in current metaanalysis. First, as all the identified studies were case-control design, history of coffee consumption level was wholly based on self-report. The information bias may have appeared in studies using self-administered questionnaires. And the similar interviewing technology used in studies for case and control mothers reduced potential differential misclassifications. However, the recall bias could not be ruled out although there was no general awareness of a potential relationship between coffee consumption and childhood AL. Second, although most studies have adjusted for major potential confounders, such as gender, age, maternal education, and socioeconomic status, a metaanalysis was unable to remove potential confounding factors, such as alcohol consumption, which could be inherent in the included studies. Third, coffee exposure was mostly assessed with respect to the number of cups of coffee consumption daily. However, methods of coffee preparation (eg, filtered, boiled) and cup size may vary considerably. Our results were likely be affected by the misclassification of coffee consumption. Fourth, the risk of other sources of caffeine, such as cola, which may be associated with childhood AL, was not analyzed. Finally, only limited published studies were included and the method of control selection varied with studies. For instance, the controls were selected from the whole population by Menegaux et al,[11] while Clavel et al[4] selected the controls from the hospital. Publication bias may have occurred although only a publication bias was observed in the present study.

In summary, the results of this meta-analysis provided evidence that maternal coffee consumption during pregnancy may be associated with increased risk of childhood AL and its subtypes. Meanwhile, the linear dose-response relationships between coffee consumption during pregnancy and childhood ALL and childhood AML were also observed, with the increasing of coffee consumption and the risk of childhood ALL and childhood AML increased accordingly. In light of limited studies included in this metaanalysis, more prospective cohort studies with larger sample size, well-controlled confounding factors, and more accurate assessment of coffee consumption should be conducted to assess whether this association was causal. ■

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