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Coffee and tea consumption during pregnancy and risk of childhood acute myeloid leukemia: A Childhood Leukemia International Consortium (CLIC) study

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ABSTRACT

Background: Dietary habits during pregnancy have been inconsistently linked to childhood acute myeloid leukemia (AML), given the putative intrauterine onset of the disease as a result of triggering events during the critical period of fetal hematopoiesis. We investigated the potential association of maternal coffee and tea consumption during pregnancy with childhood AML risk, pooling primary data from eight case-control studies participating in the Childhood Leukemia International Consortium.

Methods: Information on coffee and/or tea consumption was available for 444 cases and 1255 age- and sex-matched controls, on coffee consumption for 318 cases and 971 controls and on tea consumption for 388 cases and 932 controls. Categories for cups of daily coffee/tea consumption were created in order to explore potential dose-response associations. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were estimated using logistic regression.

Results: Associations were found neither in the analysis on coffee or tea nor in the analysis on coffee only consumption (any versus no). A positive association with increasing coffee intake was observed (> 1 cup per day; OR: 1.40, 95% CI: 1.03–1.92, increment of one cup per day; OR: 1.18, 95% CI: 1.01–1.39). No associations were observed with tea consumption. Interaction analyses showed non-significant associations between coffee/tea and smoking. Hyperdiploidy was inversely associated with tea consumption, with other cytogenetic markers having no association with coffee/tea.

Conclusion: Given the widespread consumption of caffeinated beverages among pregnant women, our finding is of important public health relevance, suggesting adverse effects of maternal coffee consumption during pregnancy in the offspring.

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1. Introduction

Acute myeloid leukemia (AML) accounts for 9% of all hematological malignancies in children 0–14 years of age and 15% of all childhood leukemia cases [1,2]. Despite extensive research, the biological mechanisms of leukemogenesis remain indefinite apart from intrauterine exposure to ionizing radiation and few chromosomal and genetic abnormalities [3]. A growing body of recent research is directed towards parental exposure to known environmental carcinogens. Among the latter, maternal smoking and alcohol consumption during pregnancy have been intensively explored with previous studies yielding conflicting results [4,5].

Coffee and tea consumption have been associated both positively and negatively with cancer risk in adults [6–8], whereas there are indications that maternal coffee consumption during pregnancy may also result in leukemia in the offspring [9,10]. Two recent meta-analyses on coffee consumption and childhood leukemia reported statistically significant dose-response associations for the risk of AML [11,12]. The possible harmful effect of coffee might be due to the high concentration of caffeine, a known topoisomerase II inhibitor, which may lead to translocations, especially in the 11q23 locus (Mixed Lineage Leukemia; MLL gene) *in utero* [13]. Regarding maternal tea consumption, most studies have shown null associations for AML [14–17], whereas a statistically significant inverse association with childhood leukemia has once been reported for low to moderate tea consumption [12].

Pooling of primary data is expected to overcome important limitations of previous studies including small statistical power, especially for the rarer childhood AML subtype, inability to investigate a dose-response association and the interactive effect of other exposures, such as maternal smoking during pregnancy. We assessed the potential association of coffee and tea consumption during pregnancy with AML in the offspring in a collaborative study comprising primary raw data derived from the Childhood Leukemia International Consortium (CLIC) [18].

2. Methods

2.1. Study population

Eight CLIC case-control studies on childhood AML (0–14 years) were included in the pooled analysis. Four studies were conducted in France (ADELE, ELECTRE, ESCALE, ESTELLE) [14,15,17,19], one in the US [California Childhood Leukemia Study (CCLS)] [20] and one in Germany [cases from the German Childhood Cancer Registry (GCCR)] [21]; in addition, a study from Greece contributed data for two time points: the Nationwide Registry of Childhood Hematological Malignancies (NARECHEM, 1999–2003) including children 0–5 years and the Nationwide Registry of Childhood Hematological Malignancies and Solid Tumors (NARECHEM-ST, 2011–2016) including also children 0–14 years. Supplemental Table 1 presents descriptive data on a total of 554 patients with AML and 1419 age- and sex-matched controls included in this pooled study. Given the age distribution of AML cases, we opted to use 1:3 frequency matched controls to cases for the French, German and Greek studies, whereas the CCLS study contributed mostly 1:1 individually matched controls. Children with Down syndrome (N = 28 cases and N = 4 controls) were excluded given the particular biological mechanisms of AML leukemogenesis in these patients [22].

2.2. Data collection and harmonization

Data on socio-demographic and parental lifestyle characteristics of cases and controls including maternal consumption of coffee and tea during pregnancy were obtained for each study. Information on socio-demographic characteristics and exposures of interest was assessed using self-administered food frequency or general questionnaires. Interviews were conducted at the time of diagnosis for cases and recruitment for controls.

Information on primary exposures was available for any consumption of coffee or tea during the whole period of pregnancy, as well as by cups of daily consumption. Only two studies (ESTELLE and GCCR) provided additional data by pregnancy trimester, whereas in GCCR information was available only for black tea and/or coffee as a combined variable, without further clarifying whether these study subjects were predominantly coffee drinkers who occasionally drank tea or vice versa. No data on tea consumption was available for the ELECTRE study. In GCCR, decaffeinated coffee was assessed as a separate variable, whereas consumption of tea other than black tea was not included in the questionnaire.

A mediation model (Supplemental Fig. 1) was constructed following an *a priori* literature search, and was thereafter tested on the basis of our data using the Structural Equation Modeling (SEM) in the STATA software [23,24]. Confounding factors with significant mediating paths included age at diagnosis or recruitment, sex and ethnicity of the index child, maternal age at child's birth, household socioeconomic status (SES) and maternal smoking during pregnancy. Cytogenetic information was provided for some cases by all studies, except for GCCR. Availability of cytogenetic data across studies relied on the calendar study period. In particular, data on ETV6-RUNX1 (or TEL/AML1), the most common chimeric fusion gene in childhood cancer, were not routinely provided for cases diagnosed before 2000. Likewise, no data were provided on AML morphology French-American-British (FAB) subtypes.

Data were reviewed by the CLIC principal investigators and thereafter harmonized for the pooled analysis. Variables with potential different definitions across studies were eventually categorized as follows: White/Caucasian/European versus Other (African, Caribbean, Maghreb, African or Native Americans, Asian or Pacific Islander, Mixed) for index child ethnicity and low, medium or high for SES. Specifically, in three French (ADELE, ELECTRE and ESCALE) and the Greek studies, SES was based on socio-professional ranking provided by source study. In ESTELLE, SES was derived from data used in census collections; in CCLS and GCCR, from self-reported income level or phone interviews. Categories for coffee and tea by cups of daily consumption were created in order to explore potential dose-response associations.

2.3. Statistical analysis

The distributions of exposures, socio-demographic and lifestyle characteristics were initially assessed using chi-square tests.

Logistic regressions were used to calculate the study-specific and pooled odds ratios (ORs) along with 95% confidence intervals (95% CIs) for childhood AML compared to frequency matched controls. The core multivariable model included significant mediating factors as potential confounders derived from the SEM (Supplemental Fig. 1) and the chi-square testing to ensure maximal adjustment: child's age at diagnosis or recruitment (< 1, 1–4, 5–9, 10–14 years), sex (male, female), child's ethnicity (Caucasian, non-Caucasian), maternal age at child's birth (< 25, 25–34, ≥35 years), household SES (low, medium, high), maternal smoking during pregnancy (yes, no) and birthweight (< 2500, 2500–3999, ≥4000 g). The exposures of interest, namely (i) coffee or tea, (ii) coffee and (iii) tea consumption during pregnancy, were separately introduced into the core model. Analyses were run categorically (any vs. no consumption), by cup increments of daily consumption [coffee or tea: 1, 2, 3, 4 and more vs. 0 cup per day; coffee: 1, 2 or more vs. 0 cup per day; tea: 1, 2 or more vs. 0 cup per day] and as a quantitative variable (increment of 1 cup per day) based on data availability. Alternative analyses were also performed including the study site as a potential covariate in the core model. Sensitivity analyses were run excluding one study at a time. The possible interaction between coffee or tea and smoking was also examined. Finally, sub-group analyses by cytogenetic abnormality were undertaken.

Meta-analysis of the individual study effect estimates was performed and summary effect estimates were calculated using the fixed-effects (Mantel-Haenszel) or random-effects (DerSimonian–Laird) models as appropriate. Between-study heterogeneity was assessed by estimating the I^2 and using the Cochran Q statistic. The Z-test was applied for the overall effect and the statistical significance level was set at $p < 0.05$. Using the generalized least square method described by Orsini and Greenland [[25]], dose-response meta-analysis was conducted to explore any differential levels of caffeinated beverages consumption among CLIC studies.

Statistical analyses were performed using SAS [26] and meta-analysis using STATA [27].

3. Results

3.1. Characteristics of the study population

Overall, 554 AML cases and 1419 originally- or frequency-matched controls were available for analyses. Specifically, analyses on maternal coffee or tea consumption during pregnancy included 444 cases and 1255 controls, on coffee consumption 318 cases and 971 controls and on tea consumption 388 cases and 932 controls. Overall, 78.6% of cases and 79.5% of controls reported consumption of either coffee or tea during pregnancy (Table 1). Among control mothers, the percentage of coffee consumption during pregnancy varied between 48.2% (NARECHEM-ST) and 75.2% (ADELE) and for tea consumption between 17.6% (NARECHEM-ST) and 44.8% (ADELE) (Supplemental Table 1).

Table 1 presents the distribution of the 554 AML cases and 1419 controls by the study variables. Child's ethnicity ($p = 0.0002$), maternal age at child's birth ($p = 0.02$), household SES ($p = 0.0001$) and birthweight ($p = 0.05$) were associated with AML risk. The multivariable logistic regression analysis replicated the established associations of child's ethnicity, maternal age at child's birth and SES with childhood AML risk (Table 2).

3.2. Maternal coffee and/or tea consumption during pregnancy

The overall analysis of "coffee and/or tea consumption" during pregnancy as a combined variable and childhood AML risk showed no association (OR: 0.94, 95% CI: 0.72–1.23), neither did the dose-response analyses (Table 2).

In separate analyses, any versus no consumption of "coffee only" during pregnancy was positively associated with increased risk of childhood AML (OR: 1.21, 95% CI: 0.92–1.59; Table 2). A statistically significant association was found in the analysis by daily coffee consumption ($OR_{>1 vs. 0 \text{ cups per day}}$: 1.40, 95% CI: 1.03–1.92), as well as in the one more cup/quantitative analysis ($OR_{1+ \text{ cups per day}}$: 1.18, 95% CI: 1.01–1.39). Likewise, the meta-analysis of CLIC studies (Fig. 1a, b) showed positive associations regarding any versus no (OR: 1.23, 95% CI: 0.92–1.66; 6 study arms) and > 1 cup per day versus no coffee consumption (OR: 1.65, 95% CI: 0.92–2.96; 6 study arms). Results of the dose-response meta-analysis suggested a positive, albeit not statistical significance, dose-response relationship of coffee consumption with AML risk (Supplemental Fig. 2).

Maternal tea consumption during pregnancy was not significantly associated with AML risk, either in the "any versus no" or in the dose-response analyses (Table 2). The results of the meta-analysis of individual CLIC studies were consistent with these findings (Fig. 2, OR: 0.91, 95% CI: 0.69–1.20; 6 study arms).

Results of the pooled analysis were virtually the same when the study site was introduced into the models. The interaction analyses showed non-significant associations between coffee (p interaction = 0.28) or tea consumption (p interaction = 0.92) and smoking. Sensitivity analysis excluding one study at a time did not change the findings of our study.

Limited data was available on cytogenetics among the participating CLIC studies. Thus, analyses were restricted to cases with MLL translocation (coffee, N = 40 cases; tea, N = 54 cases), hypodiploidy (coffee, N = 14 cases; tea, N = 20 cases) and low or high hyperdiploidy (coffee, N = 58 cases; tea, N = 74 cases), defined as 47–49 and ≥50 chromosomes, respectively. Hyperdiploidy showed an inverse association with tea consumption (any tea consumption, OR: 0.53, 95% CIs: 0.31-0.92; one more cup/quantitatively, OR: 0.57, 95% CI: 0.34-0.96), whereas null results were yielded for other cytogenetic markers (Supplemental

Table 1
Characteristics of the 554 children (0–14 years) with acute myeloid leukemia and the 1419 controls.

Variable	Cases		Controls		*p*-value (chi-square)
	N	%	N	%	
Child's age at diagnosis/recruitment					0.59
< 1 year	80	14.4	193	13.6	
1-4 years	180	32.5	493	34.7	
5-9 years	139	25.1	367	25.9	
10-14 years	155	28.0	366	25.8	
Missing	–		–		
Child's sex					0.95
Female	259	46.8	661	46.6	
Male	295	53.2	758	53.4	
Missing	–		–		
Child's ethnicity					0.0002
Caucasian	454	82.9	1259	89.2	
Other	94	17.1	153	10.8	
Missing	6 (1.1%)		7 (0.5%)		
Maternal age at child's birth					0.02
< 25 years	123	22.3	226	16.0	
25-34 years	347	62.8	976	68.9	
≥35 years	82	14.9	215	15.1	
Missing	2 (0.4%)		2 (0.1%)		
Household socioeconomic status					0.0001
Low	134	24.2	238	16.8	
Medium	200	36.2	514	36.3	
High	219	39.6	664	46.9	
Missing	1 (0.2%)		3 (0.2%)		
Birth weight					0.05
< 2500 grams	22	4.0	80	5.7	
2500-3999 grams	453	83.3	1183	84.0	
≥4000 grams	69	12.7	145	10.3	
Missing	10 (1.8%)		11 (0.8%)		
Maternal smoking during pregnancy					0.42
No	453	82.7	1146	81.1	
Yes	95	17.3	267	18.9	
Missing	6 (1.1%)		6 (0.4%)		
Coffee or tea consumption (either of them) during pregnancy					0.68
No	95	21.4	257	20.5	
Yes	349	78.6	998	79.5	
Cups of daily coffee or tea consumption (either of them) during pregnancy					0.89
0	95	26.8	257	23.7	
1	85	23.9	280	25.8	
2	67	18.9	232	21.4	
3	49	13.8	153	14.1	
> 3	59	16.6	162	15.0	
Coffee consumption during pregnancy[1]					0.24
No	116	36.5	390	40.2	
Yes	202	63.5	581	59.8	
Cups of daily coffee consumption during pregnancy					0.06
0	116	36.5	390	40.2	
1	84	26.4	284	29.2	
> 1	118	37.1	297	30.6	
Tea consumption during pregnancy[2]					0.49
No	251	64.7	584	62.7	
Yes	137	35.3	348	37.3	
Cups of daily tea consumption during pregnancy[3]					0.25
0	172	65.6	501	63.3	
1	67	25.6	196	24.7	
> 1	23	8.8	95	12.0	

[1]Data on coffee consumption not available for CCLS and GCCR; [2]Data on tea consumption not available for ELECTRE and GCCR; [3]Data on cups of daily tea consumption not available for CCLS and GCCR.

Table 2
Logistic regression derived Odds Ratios (ORs) and 95% Confidence Intervals (95% CIs) for the risk of childhood acute myeloid leukemia by socio-demographic and parental life-style variables.

Variable	ORs (95% CIs)
Child's age at diagnosis/recruitment	
< 1 year	1.19 (0.87, 1.64)
1-4 years	1.00 (reference)
5-9 years	1.01 (0.77, 1.32)
10-14 years	1.20 (0.92, 1.56)
Child's sex	
Female	1.00 (reference)
Male	0.96 (0.78, 1.18)
Child's ethnicity	
Caucasian	1.00 (reference)
Other	1.57 (1.17, 2.09)
Maternal age at child's birth	
< 25 years	1.38 (1.05, 1.80)
25-34 years	1.00 (reference)
≥35 years	1.13 (0.85, 1.52)
Household socioeconomic status	
Low	1.42 (1.08, 1.88)
Medium	1.00 (reference)
High	0.89 (0.70, 1.12)
Maternal smoking during pregnancy	
No	1.00 (reference)
Yes	0.90 (0.69, 1.17)
Birthweight	
< 2500 grams	0.69 (0.42, 1.13)
2500-3999grams	1.00 (reference)
≥4000grams	1.26 (0.92, 1.72)
Additionally introduced exposure variables	
Coffee or tea consumption (combined variable) during pregnancy*	
No	1.00 (reference)
Yes	0.94 (0.72, 1.23)
Cups of daily coffee or tea consumption (combined variable) during pregnancy*	
0	1.00 (reference)
1	0.85 (0.60, 1.20)
2	0.79 (0.55, 1.14)
3	0.91 (0.60, 1.36)
> 3	1.00 (0.67, 1.48)
1 cup per day increment	1.00 (0.91, 1.09)
Coffee consumption during pregnancy*	
No	1.00 (reference)
Yes	1.21 (0.92, 1.59)
Cups of daily coffee consumption during pregnancy*	
0	1.00 (reference)
1	1.03 (0.74, 1.43)
> 1	1.40 (1.03, 1.92)
1 cup per day increment	1.18 (1.01, 1.39)
Tea consumption during pregnancy*	
No	1.00 (reference)
Yes	0.91 (0.70, 1.17)
Cups of daily tea consumption during pregnancy*	
0	1.00 (reference)
1	0.95 (0.68, 1.33)
> 1	0.70 (0.42, 1.15)
1 cup per day increment	0.87 (0.70, 1.08)

*All models adjusted for child's age at diagnosis/recruitment, sex, child's ethnicity, maternal age at child's birth, household socioeconomic status, maternal smoking during pregnancy and birth weight.

Table 2).

4. Discussion

4.1. Principal findings

The largest to-date study pooling primary international data from eight CLIC studies, provides a slight evidence for an increased risk for AML among children born to mothers consuming coffee during pregnancy, particularly among those drinking > 1 cup of coffee per day. However, our results do not support a dose-response relationship, possibly due to the small number of AML cases in the respective subgroups. No associations were found for maternal coffee and/or tea consumption as a combined variable or for tea consumption only.

4.2. Strengths and limitations

Apart from inclusion of unpublished data from the NARECHEM-ST studies in Greece, the main strengths of this study which used robust methodology in the analyses include: 1) a large size for a rare disease, such as AML; 2) harmonization of the primary raw data included in the main and subgroup pooled analyses and meta-analyses; 3) control for main confounders derived from the Structural Equation Modeling (SEM), such as smoking during pregnancy; 4) lack of heterogeneity across the participating studies, which comprise populations of variable SES and diverse cultural habits regarding consumption of the main exposures; and 5) use of the generalized least square method in the meta-analysis.

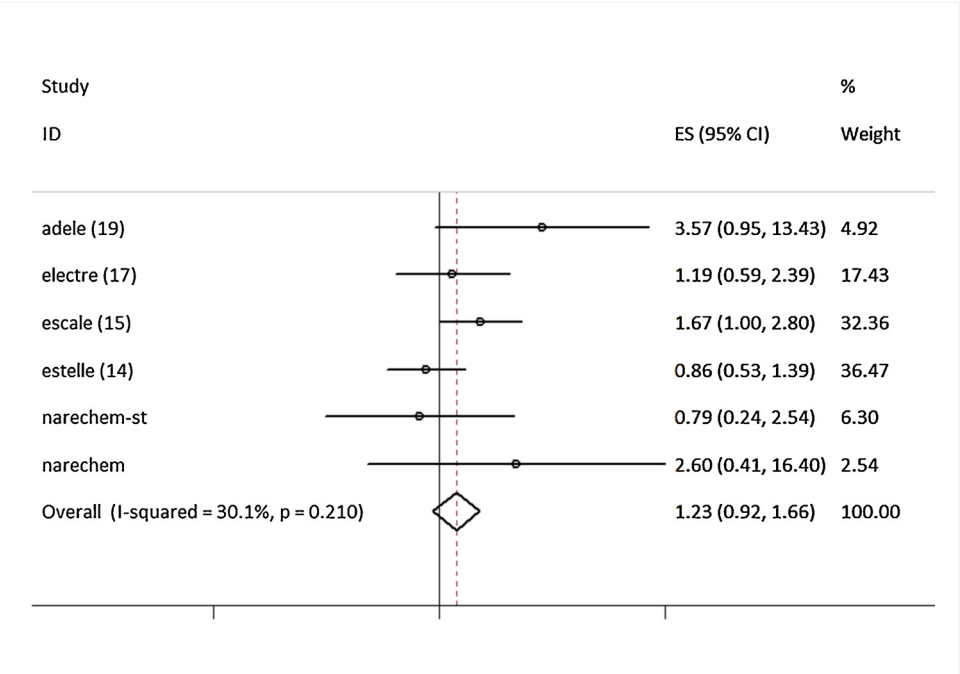
Self-report of exposure data in all participating studies may raise concerns about their accuracy. Recall bias, an issue of concern in case-control studies, cannot be excluded; however, differential reporting error in this study seems unlikely due to the limited public awareness regarding a tentative association of caffeine with childhood leukemia and AML risk, in particular. Pooling data from different populations with diverse cultural habits regarding the consumption of the main exposures may also raise concerns about the robustness of the results. Nevertheless, although the range of coffee and tea consumption was quite broad by study site, we observed non-significant variations in coffee/tea consumption within each study site, as was also the between-study heterogeneity in the meta-analyses. Lack of specificity regarding the content of certain beverages, namely caffeinated versus decaffeinated coffee or black versus other types of tea, should be considered when interpreting our findings; however, the proportion of decaffeinated consumption, at least in Greece, was minimal during the respective time period. Furthermore, residual confounding cannot be excluded; indeed, data on additional potential confounders, such as maternal alcohol consumption and prematurity, were not available. Generalization of our findings is rather limited, as the coffee-only analyses relied solely on data derived from Greece and France, although both countries contributed studies spanning variable study periods and from different populations. Last, sub-analyses by trimester of pregnancy consumption or by cytogenetic abnormalities were limited by the small sample size and the paucity of available indices.

4.3. Interpretations

Consumption of caffeine during pregnancy has been implicated in the pathogenesis of several childhood cancers including central nervous system tumors, Wilms tumor and leukemia [1,28,29]. Our results are consistent with a recent CLIC study on coffee consumption and ALL risk in childhood, as well as with previous literature showing a consistent dose-response relationship of coffee, but not tea consumption [14,17]. In the same context, two previously published meta-analyses, which included four of the participating studies [14,15,17,19] in the current CLIC analysis, showed a significant association of coffee consumption with childhood AML risk, specifically in the "low to moderate versus never/lowest consumption" analysis (OR: 1.28, 95% CI: 1.01–1.63) [11,12]; these findings are in line with ours, which include, however, primary and unpublished data from a larger number of studies.

Caffeine-containing beverages, including coffee and tea, have both been associated with adverse health outcomes; yet, the magnitude of the potentially harmful impact of caffeine depends on its levels which are lower in tea [30]. More importantly, potential anti-carcinogenic effects have been invoked due to anti-carcinogenic agents included in tea beverages, such as folate and polyphenolic compounds [23,31,32]; the latter, have been reported to exert cancer inhibition activities by reducing DNA hypermethylation of key cancer-causing genes [23,24]. Regarding coffee consumption, several studies have focused on the

(a)



(b)

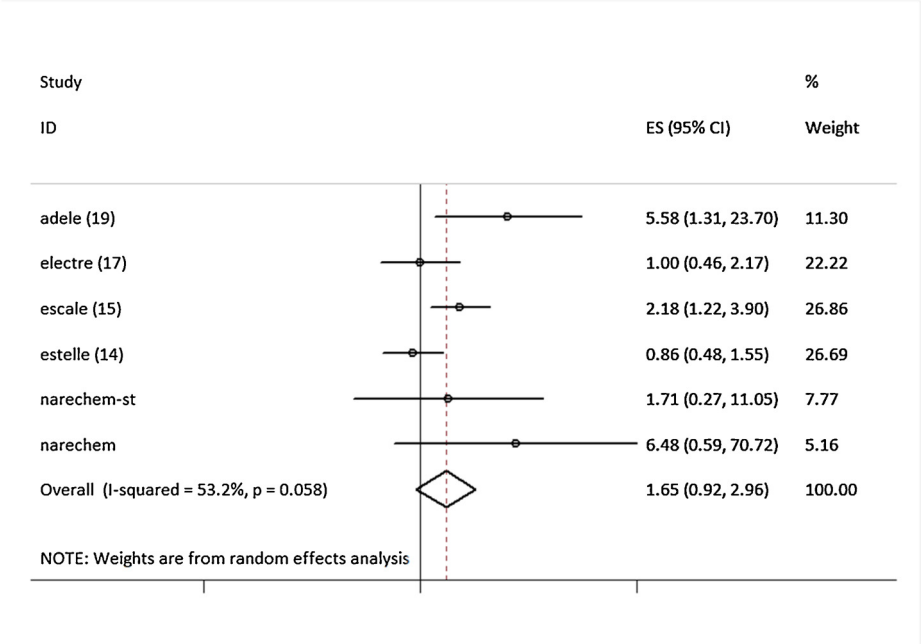


Fig. 1. Meta-analysis of study-specific Odds Ratios (ORs) for maternal coffee consumption [(a) any consumption and (b) > 1 cup per day consumption] and the risk of acute myeloid leukemia. ORs are indicated by the data markers; 95% Confidence Intervals (CIs) are indicated by the error bars; summary-effect estimates with their 95% CIs are depicted as a diamond.

inhibitory effect of caffeine on the ataxia telangiectasia mutated (ATM) gene [33] and the tumor suppressor gene p53 [34], both linked to childhood leukemia onset [35,36]. Caffeine and related substances are also likely to block the release of DNA topoisomerase II (topo II), an enzyme protecting DNA double strand breaks [37]. Topo II inhibition has been postulated as a potential risk factor in the development of infant leukemia [13] due to chromosomal abnormalities and translocations involving the MLL gene located at chromosome 11q23. Although our sub-analysis on cases with MLL translocations showed null results, the small sample size in the respective subgroups leading to

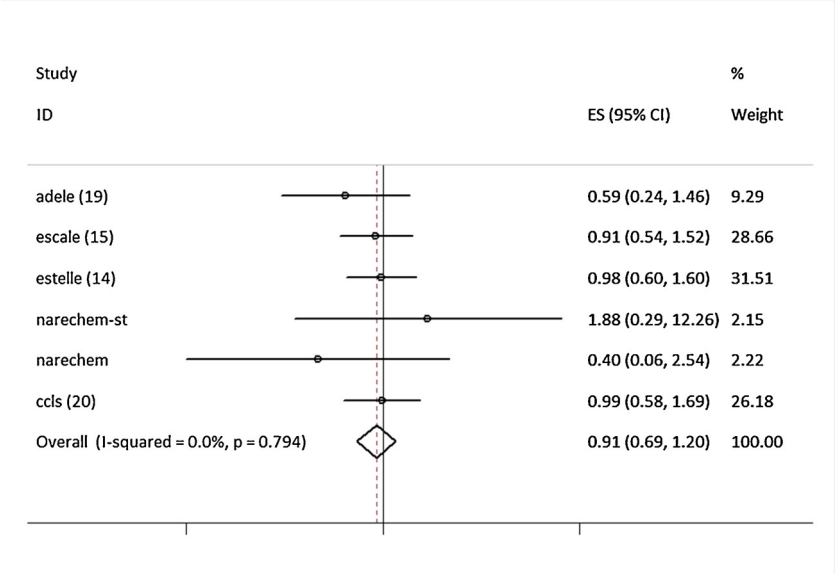


Fig. 2. Meta-analysis of study-specific Odds Ratios (ORs) for maternal any tea consumption and the risk of acute myeloid leukemia. ORs are indicated by the data markers; 95% confidence intervals (CIs) are indicated by the error bars; summary-effect estimates with their 95% CIs are depicted as a diamond.

reduced power did not allow us to draw sound conclusions. In addition, cytochrome P-4501A2 (CYP1A2) which catalyses N-oxidation, and acetyltransferase (NAT2) which catalyses N- and O-acetylation, both appear to be polymorphically distributed in human populations; slow and rapid NAT2 phenotypes have been implicated as risk factors for coffee-induced carcinogenesis. Such results were yielded by a recent CLIC study on coffee/tea consumption and ALL risk suggesting that slow acetylators may be linked to an increased risk of ALL among mothers consuming > 2 cups of coffee per day (OR:1.95, 95% CI: 1.08–3.52). Similar were the results on maternal tea consumption and ALL risk in children with slow acetylator genotype (OR: 2.22, 95% CI: 1.14–4.32). However, analysis of these polymorphisms in our AML dataset was not feasible.

4.4. Conclusions

Our results are indicative of a tentative relationship between maternal coffee consumption and childhood AML risk, whereas there seems to be no association of tea consumption with the disease onset. Given the widespread consumption of caffeinated beverages among pregnant women, these findings merit further consideration; specifically, studies with population coverage and availability of linkage systems between the indicated maternal exposures, tentative confounding factors and AML, its subtypes and cytogenetics could address several limitations of our study. Furthermore, basic research could clarify whether the observed associations reflect a causal relationship exploring the potential underlying causal mechanisms between coffee consumption and childhood leukemogenesis.

Author's contribution

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Declaration of Competing Interest

The authors declare no conflict of interest related to this study.

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Appendix A. Supplementary data

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References

[1] M. Plichart, F. Menegaux, B. Lacour, O. Hartmann, D. Frappaz, F. Doz, A.I. Bertozzi, A.S. Defaschelles, A. Pierre-Kahn, C. Icher, P. Chastagner, D. Plantaz, X. Rialland, D. Hemon, J. Clavel, Parental smoking, maternal alcohol, coffee and tea consumption during pregnancy and childhood malignant central nervous system tumours: the ESCALE study (SFCE), Eur. J. Cancer Prev. 17 (4) (2008) 376–383.

[2] E. Steliarova-Foucher, M. Colombet, L.A.G. Ries, F. Moreno, A. Dolya, F. Bray, P. Hesseling, H.Y. Shin, C.A. Stiller, I.-. Contributors, International incidence of childhood cancer, 2001-10: a population-based registry study, Lancet Oncol. 18 (6) (2017) 719–731.

[3] J. Schuz, F. Erdmann, Environmental exposure and risk of childhood leukemia: an overview, Arch. Med. Res. 47 (8) (2016) 607–614.

[4] C. Metayer, E. Petridou, J.M. Arangure, E. Roman, J. Schuz, C. Magnani, A.M. Mora, B.A. Mueller, M.S. de Oliveira, J.D. Dockerty, K. McCauley, T. Lightfoot, E. Hatzipantelis, J. Rudant, J. Flores-Lujano, P. Kaatsch, L. Miligi, C. Wesseling, D.R. Doody, M. Moschovi, M. Group, L. Orsi, S. Mattioli, S. Selvin, A.Y. Kang, J. Clavel, Parental tobacco smoking and acute myeloid leukemia: the childhood leukemia international consortium, Am. J. Epidemiol. 184 (4) (2016) 261–273.

[5] M.A. Karalexi, N. Dessypris, T.P. Thomopoulos, E. Ntouvelis, M. Kantzanou, A.A. Diamantaras, M. Moschovi, M. Baka, E. Hatzipantelis, M. Kourti, S. Polychronopoulou, E. Stiakaki, A.M. Mora, V. Wunsch-Filho, C. Infante-Rivard, D. Loutradis, E.T. Petridou, Parental alcohol consumption and risk of leukemia in the offspring: a systematic review and meta-analysis, Eur. J. Cancer Prev. 26 (5) (2017) 433–441.

[6] G. Alicandro, A. Tavani, C. La Vecchia, Coffee and cancer risk: a summary overview, Eur. J. Cancer Prev. 26 (5) (2017) 424–432.

[7] T. Ugai, K. Matsuo, N. Sawada, M. Iwasaki, T. Yamaji, T. Shimazu, A. Goto, M. Inoue, Y. Kanda, S. Tsugane, G. Japan Public Health Center-based Prospective Study, Coffee and green tea consumption and subsequent risk of acute myeloid leukemia and myelodysplastic syndromes in Japan, Int. J. Cancer 142 (6) (2018) 1130–1138.

[8] S.K. Bohn, R. Blomhoff, I. Paur, Coffee and cancer risk, epidemiological evidence, and molecular mechanisms, Mol. Nutr. Food Res. 58 (5) (2014) 915–930.

[9] E. Milne, K.R. Greenop, E. Petridou, H.D. Bailey, L. Orsi, A.Y. Kang, M. Baka, A. Bonaventure, M. Kourti, C. Metayer, J. Clavel, Maternal consumption of coffee and tea during pregnancy and risk of childhood ALL: a pooled analysis from the childhood Leukemia International Consortium, Cancer Causes Control 29 (6) (2018) 539–550.

[10] D. Loomis, K.Z. Guyton, Y. Grosse, B. Lauby-Secretan, F. El Ghissassi, V. Bouvard, L. Benbrahim-Tallaa, N. Guha, H. Mattock, K. Straif, G. International Agency for Research on Cancer Monograph Working, Carcinogenicity of drinking coffee, mate, and very hot beverages, Lancet Oncol. 17 (7) (2016) 877–878.

[11] J. Cheng, H. Su, R. Zhu, X. Wang, M. Peng, J. Song, D. Fan, Maternal coffee consumption during pregnancy and risk of childhood acute leukemia: a metaanalysis, Am. J. Obstet. Gynecol. 210 (2) (2014) 151 e1-151 e10.

[12] T.P. Thomopoulos, E. Ntouvelis, A.A. Diamantaras, M. Tzanoudaki, M. Baka, E. Hatzipantelis, M. Kourti, S. Polychronopoulou, V. Sidi, E. Stiakaki, M. Moschovi, M. Kantzanou, E.T. Petridou, Maternal and childhood consumption of coffee, tea and cola beverages in association with childhood leukemia: a meta-analysis, Cancer Epidemiol. 39 (6) (2015) 1047–1059.

[13] J.A. Ross, J.D. Potter, G.H. Reaman, T.W. Pendergrass, L.L. Robison, Maternal exposure to potential inhibitors of DNA topoisomerase II and infant leukemia (United States): a report from the Children's Cancer group, Cancer Causes Control: CCC 7 (6) (1996) 581–590.

[14] L. Orsi, J. Rudant, R. Ajrouche, G. Leverger, A. Baruchel, B. Nelken, M. Pasquet, G. Michel, Y. Bertrand, S. Ducassou, V. Gandemer, P. Lutz, L. Saumet, P. Moreau, D. Hemon, J. Clavel, Parental smoking, maternal alcohol, coffee and tea consumption during pregnancy, and childhood acute leukemia: the ESTELLE study, Cancer Causes Control: CCC 26 (7) (2015) 1003–1017.

[15] A. Bonaventure, J. Rudant, S. Goujon-Bellec, L. Orsi, G. Leverger, A. Baruchel, Y. Bertrand, B. Nelken, M. Pasquet, G. Michel, N. Sirvent, P. Bordigoni, S. Ducassou, X. Rialland, D. Zelenika, D. Hemon, J. Clavel, Childhood acute leukemia, maternal

beverage intake during pregnancy, and metabolic polymorphisms, Cancer Causes Control: CCC 24 (4) (2013) 783–793.
[16] E. Milne, J.A. Royle, L.C. Bennett, N.H. de Klerk, H.D. Bailey, C. Bower, M. Miller, J. Attia, R.J. Scott, M. Kirby, B.K. Armstrong, Maternal consumption of coffee and tea during pregnancy and risk of childhood ALL: results from an Australian case-control study, Cancer Causes Control: CCC 22 (2) (2011) 207–218.
[17] F. Menegaux, M. Ripert, D. Hemon, J. Clavel, Maternal alcohol and coffee drinking, parental smoking and childhood leukaemia: a French population-based case-control study, Paediatr. Perinat. Epidemiol. 21 (4) (2007) 293–299.
[18] C. Metayer, E. Milne, J. Clavel, C. Infante-Rivard, E. Petridou, M. Taylor, J. Schuz, L.G. Spector, J.D. Dockerty, C. Magnani, M.S. Pombo-de-Oliveira, D. Sinnett, M. Murphy, E. Roman, P. Monge, S. Ezzat, B.A. Mueller, M.E. Scheurer, B.K. Armstrong, J. Birch, P. Kaatsch, S. Koifman, T. Lightfoot, P. Bhatti, M.L. Bondy, J. Rudant, K. O'Neill, L. Miligi, N. Dessypris, A.Y. Kang, P.A. Buffler, The childhood leukemia international consortium, Cancer Epidemiol. 37 (3) (2013) 336–347.
[19] F. Menegaux, C. Steffen, S. Bellec, A. Baruchel, B. Lescoeur, G. Leverger, B. Nelken, N. Philippe, D. Sommelet, D. Hemon, J. Clavel, Maternal coffee and alcohol consumption during pregnancy, parental smoking and risk of childhood acute leukaemia, Cancer Detect. Prev. 29 (6) (2005) 487–493.
[20] K. Bartley, C. Metayer, S. Selvin, J. Ducore, P. Buffler, Diagnostic X-rays and risk of childhood leukaemia, Int. J. Epidemiol. 39 (6) (2010) 1628–1637.
[21] J. Schuz, P. Kaatsch, U. Kaletsch, R. Meinert, J. Michaelis, Association of childhood cancer with factors related to pregnancy and birth, Int. J. Epidemiol. 28 (4) (1999) 631–639.
[22] M.K. Mateos, D. Barbaric, S.A. Byatt, R. Sutton, G.M. Marshall, Down syndrome and leukemia: insights into leukemogenesis and translational targets, Transl. Pediatr. 4 (2) (2015) 76–92.
[23] C. Metayer, E. Milne, J.D. Dockerty, J. Clavel, M.S. Pombo-de-Oliveira, C. Wesseling, L.G. Spector, J. Schuz, E. Petridou, S. Ezzat, B.K. Armstrong, J. Rudant, S. Koifman, P. Kaatsch, M. Moschovi, W.M. Rashed, S. Selvin, K. McCauley, R.J. Hung, A.Y. Kang, C. Infante-Rivard, Maternal supplementation with folic acid and other vitamins and risk of leukemia in offspring: a Childhood Leukemia International Consortium study, Epidemiology 25 (6) (2014) 811–822.
[24] C.S. Yang, H. Wang, Mechanistic issues concerning cancer prevention by tea catechins, Mol. Nutr. Food Res. 55 (6) (2011) 819–831.
[25] N. Orsini, R. Li, A. Wolk, P. Khudyakov, D. Spiegelman, Meta-analysis for linear and nonlinear dose-response relations: examples, an evaluation of approximations, and software, Am. J. Epidemiol. 175 (1) (2012) 66–73.
[26] SAS v9.2, SAS Statistical Software, Version 9, SAS Institute, Carry, NC, 2019.
[27] StataCorp, STATA Statistical Software, Version 14, Stata Corporation, College Station, TX, 2014.
[28] K.R. Greenop, M. Miller, J. Attia, L.J. Ashton, R. Cohn, B.K. Armstrong, E. Milne, Maternal consumption of coffee and tea during pregnancy and risk of childhood brain tumors: results from an Australian case-control study, Cancer Causes Control 25 (10) (2014) 1321–1327.
[29] G.R. Bunin, Nongenetic causes of childhood cancers: evidence from international variation, time trends, and risk factor studies, Toxicol. Appl. Pharmacol. 199 (2) (2004) 91–103.
[30] J.J. Barone, H.R. Roberts, Caffeine consumption, Food Chem. Toxicol. 34 (1) (1996) 119–129.
[31] S.M. Henning, P. Wang, C.L. Carpenter, D. Heber, Epigenetic effects of green tea polyphenols in cancer, Epigenomics 5 (6) (2013) 729–741.
[32] P. Chen, C. Li, X. Li, J. Li, R. Chu, H. Wang, Higher dietary folate intake reduces the breast cancer risk: a systematic review and meta-analysis, Br. J. Cancer 110 (9) (2014) 2327–2338.
[33] J.N. Sarkaria, E.C. Busby, R.S. Tibbetts, P. Roos, Y. Taya, L.M. Karnitz, R.T. Abraham, Inhibition of ATM and ATR kinase activities by the radiosensitizing agent, caffeine, Cancer Res. 59 (17) (1999) 4375–4382.
[34] H. Carvalho, T.G. Ortolan, T. dePaula, R.A. Leite, R. Weinlich, G.P. Amarante-Mendes, C.F. Menck, Sustained activation of p53 in confluent nucleotide excision repair-deficient cells resistant to ultraviolet-induced apoptosis, DNA Repair (Amst) 7 (6) (2008) 922–931.
[35] T.N. Do, E. Ucisik-Akkaya, C.F. Davis, B.A. Morrison, M.T. Dorak, TP53 R72P and MDM2 SNP309 polymorphisms in modification of childhood acute lymphoblastic leukemia susceptibility, Cancer Genet. Cytogenet. 195 (1) (2009) 31–36.
[36] F. Gumy-Pause, P. Wacker, P. Maillet, D.R. Betts, A.P. Sappino, ATM variants and predisposition to childhood T-lineage acute lymphoblastic leukaemia, Leukemia 20 (3) (2006) 526–527 author reply 527.
[37] J.E. Deweese, N. Osheroff, The DNA cleavage reaction of topoisomerase II: wolf in sheep's clothing, Nucleic Acids Res. 37 (3) (2009) 738–748.