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Systematic Reviews and Meta- and Pooled Analyses

Parental Tobacco Smoking and Acute Myeloid Leukemia

The Childhood Leukemia International Consortium

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The association between tobacco smoke and acute myeloid leukemia (AML) is well established in adults but not in children. Individual-level data on parental cigarette smoking were obtained from 12 case-control studies from the Childhood Leukemia International Consortium (CLIC, 1974–2012), including 1,330 AML cases diagnosed at age <15 years and 13,169 controls. We conducted pooled analyses of CLIC studies, as well as meta-analyses of CLIC and non-CLIC studies. Overall, maternal smoking before, during, or after pregnancy was not associated with childhood AML; there was a suggestion, however, that smoking during pregnancy was associated with an increased risk in Hispanics (odds ratio = 2.08, 95% confidence interval (CI): 1.20, 3.61) but not in other ethnic groups. By contrast, the odds ratios for paternal lifetime smoking were 1.34 (95% CI: 1.11, 1.62) and 1.18 (95% CI: 0.92, 1.51) in pooled and meta-analyses, respectively. Overall, increased risks from 1.2- to 1.3-fold were observed for pre- and postnatal smoking ($P < 0.05$), with higher risks reported for heavy smokers. Associations with paternal smoking varied by histological type. Our analyses suggest an association between paternal smoking and childhood AML. The association with maternal smoking appears limited to Hispanic children, raising questions about ethnic differences in tobacco-related exposures and biological mechanisms, as well as study-specific biases.

acute myeloid leukemia; childhood cancer; international collaboration; parental smoking

Abbreviations: AML, acute myeloid leukemia; CI, confidence interval; CLIC, Childhood Leukemia International Consortium; FAB, French-American-British; OR, odds ratio.

Acute lymphoblastic leukemia is the most common cancer in children 0–14 years of age, whereas acute myeloid leukemia (AML) represents 2%–5% of childhood cancers (1, 2). The incidence of childhood AML varies geographically, with higher rates in children from Asian and Hispanic descents (3). It is well established that exposure to tobacco smoke is a risk factor for AML in adults (4). Numerous studies demonstrate that myeloid cells can be damaged by tobacco smoke carcinogens, including benzene, formaldehyde, 1,3-butadiene, polycyclic aromatic hydrocarbons, and polonium (4–8). Although it has been hypothesized that tobacco smoke may affect both somatic cells and germ cells

during critical periods of a child's development (7), the potential contribution of tobacco smoke to the development of AML in children has not been as well studied as it has in adults. Most studies of childhood AML report no associations with maternal smoking during pregnancy (9–22), although modest increased risks were observed in 2 small case-control studies (11, 12) and 2 registry-based Swedish cohort studies (23, 24). Studies on paternal smoking and childhood AML have yielded mixed results, some reporting elevated risks for lifetime smoking (18, 25), some for pre-conception smoking (17), and others no associations (9, 12, 26, 27).

Table 1. Clinical and Sociodemographic Characteristics of Acute Myeloid Leukemia Cases and Controls, Childhood Leukemia International Consortium, 1974–2012^a

Variable	Controls (n = 13,169)		Cases (n = 1,330)	
	No.	%	No.	%
FAB subtype (cases only)				
M0			46	3
M1			94	7
M2			256	19
M3			140	11
M4			162	12
M5			158	12
M6			28	3
M7			101	2
Unspecified/missing			346	26
Child's age, years ^b				
<1	1,174	9	176	13
1–4	5,752	44	474	36
5–9	3,566	27	330	25
10–14	2,677	20	350	26
Child's sex				
Male	7,299	55	706	53
Female	5,870	45	624	47
Parent's highest educational level ^c				
None/primary	2,611	20	284	22
Secondary	4,710	37	458	35
Tertiary	5,386	42	533	41
Missing	154	1	21	2

Table continues

Individual studies of childhood AML to date are based on small numbers because of the rarity of the disease and have included mostly Caucasian children. To overcome these shortcomings, we pooled data on maternal and paternal tobacco smoking from 12 case-control studies participating in the Childhood Leukemia International Consortium (CLIC) (28) and examined the associations of pre- and postnatal exposures to tobacco smoke with risk of childhood AML. Additionally, we conducted meta-analyses of CLIC and non-CLIC studies.

METHODS

Study population

Twelve case-control studies of childhood leukemia (age <15 years) conducted in 10 countries from 1974 to 2012 and participating in CLIC (28) contributed data to the pooled analyses (Web Table 1 available at <http://aje.oxfordjournals.org/>). This included 9 studies with published data: Brazil (limited to infants <24 months of age) (29), the United Kingdom (United Kingdom Childhood Cancer Study) (19),

Table 1. Continued

Variable	Controls (n = 13,169)		Cases (n = 1,330)	
	No.	%	No.	%
Child's ethnicity ^d				
Non-Hispanic white	10,363	79	860	65
Hispanic	1,711	13	372	28
Non-Hispanic other	1,018	8	90	7
Missing	77	1	8	1
Mother's age at child's birth, years				
<25	3,688	28	414	31
25–29	4,555	35	448	34
30–34	3,319	25	305	23
≥35	1,575	12	158	12
Missing	32	0	5	0
Father's age at child's birth, years				
<25	1,785	14	247	19
25–29	3,762	29	360	27
30–34	3,868	29	350	26
≥35	3,297	25	331	25
Missing	457	4	42	3

Abbreviations and designations: FAB, French-American-British; M0, acute myeloblastic leukemia, minimally differentiated; M1, acute myeloblastic leukemia, without maturation; M2, acute myeloblastic leukemia, with granulocytic maturation; M3, acute promyelocytic leukemia; M4, acute myelomonocytic leukemia; M5, acute monoblastic/monocytic leukemia; M6, acute erythroid leukemia; M7, acute megaloblastic leukemia.

^a Percentages may not sum to 100 because of rounding.

^b Child's age at diagnosis for cases and recruitment for controls.

^c Does not include missing values for Washington State.

^d Studies that did not provide ethnicity data were automatically assigned the most common ethnicity based on population-based data.

France (Adele; Epidemiologic Study on Childhood Cancer and Leukemia) (20, 21), Germany (German Childhood Cancer Registry) (22), Greece (Nationwide Registration for Childhood Hematological Malignancies) (30), Italy (Study on the Etiology of Childhood Lymphohematopoietic Malignancies) (25), and the United States (Northern California Childhood Leukemia Study (18) and linked registry data from Washington State (31)), as well as 3 studies with unpublished data at the time of this report from Costa Rica, Mexico (Mexican Interinstitutional Group for the Identification of the Causes of Childhood Leukemia), and New Zealand (New Zealand Childhood Cancer Study). Study characteristics are presented in Web Table 2 (28). Data for 1,330 newly diagnosed de novo AML cases and 13,169 controls were available for the pooled analyses.

Data collection and standardization

CLIC studies provided original data on self-reported maternal and paternal tobacco (cigarette) smoking for “ever/never smoking,” smoking during specific time windows (preconception, during pregnancy as a whole and/or by

Table 2. Pooled Risk of Childhood Acute Myeloid Leukemia Associated With Maternal Smoking Across Time Periods, Childhood Leukemia International Consortium, 1974–2012

Window of Exposure	Total Controls, no.	Total Cases, no.	Exposed, %		OR ^a	95% CI
			Controls	Cases		
Ever-smoking	5,929	563	42	42	1.01	0.84, 1.22
Smoking during prenatal period ^b	12,631	1,266	29	26	0.93	0.81, 1.07
Smoking during preconception period ^b	10,137	1,012	31	27	0.89	0.76, 1.04
Smoking during pregnancy ^b	12,621	1,266	19	15	0.95	0.81, 1.13
Smoking after birth	10,229	1,028	28	26	0.96	0.82, 1.12

Abbreviations: CI, confidence interval; OR, odds ratio.

^a Odds ratios were adjusted for age, sex, ethnicity, highest parental education, and study center.^b Odds ratios were computed by using imputed values of education.

trimester, and after birth), and duration (Web Table 1). Data on maternal tobacco smoking during pregnancy were the most complete (12 studies), compared with other smoking-related data (6–9 studies) (Web Table 1). Information on parental smoking was collected from interviews with mothers and/or fathers (Northern California Childhood Leukemia Study, German Childhood Cancer Registry, Nationwide Registration for Childhood Hematological Malignancies,

United Kingdom Childhood Cancer Study, Costa Rica, Study on the Etiology of Childhood Lymphohematopoietic Malignancies, the Mexican Interinstitutional Group for the Identification of the Causes of Childhood Leukemia), mothers only (Adele; Epidemiologic Study on Childhood Cancer and Leukemia, New Zealand Childhood Cancer Registry, Brazil), or via maternal self-report or medical/prenatal record review (United States-Washington State). We also obtained

Table 3. Risk of Acute Myeloid Leukemia Associated With Maternal Smoking During Pregnancy, by Selected Characteristics, Childhood Leukemia International Consortium, 1974–2012

Variable	Total Controls, no.	Total Cases, no.	Exposed, %		OR ^{a,b}	95% CI	P Value for Interaction ^c
			Controls	Cases			
Child's ethnicity							<0.01
Non-Hispanic white	7,732	644	23	19	0.82	0.66, 1.01	
Hispanic	1,130	332	5	7	2.08	1.20, 3.61	
Non-Hispanic other	1,013	89	13	16	1.08	0.56, 2.07	
Highest parental education							0.98
None/primary	2,605	284	27	23	0.85	0.58, 1.24	
Secondary	4,851	464	23	17	0.93	0.69, 1.24	
Tertiary	5,493	553	12	10	0.99	0.71, 1.39	
Child's birth weight, g							0.53
Low birth weight (<2,500)	1,039	108	25	16	0.58	0.29, 1.17	
Normal birth weight (2,500–4,000)	10,831	1,091	19	15	0.95	0.77, 1.17	
High birth weight (>4,000)	1,219	121	12	16	1.20	0.65, 2.19	
Child's age, years							0.93
Age <1	1,169	175	17	17	1.08	0.66, 1.78	
Age 1–4	5,725	472	20	15	0.97	0.72, 1.32	
Age 5–9	3,542	327	19	17	0.83	0.55, 1.25	
Age 10–14	2,653	346	18	14	0.83	0.57, 1.20	

Abbreviations: CI, confidence interval; OR, odds ratio.

^a Odds ratios were adjusted for age, sex, ethnicity, highest parental education, and study center, except when it was the variable of interest.^b Odds ratios were computed by using imputed values of education.^c P value for interaction derived from the Woolf test.

Table 4. Pooled Risk of Childhood Acute Myeloid Leukemia Associated With Paternal Smoking Across Time Periods, Childhood Leukemia International Consortium, 1974–2012

Window of Exposure	Total Controls, no.	Total Cases, no.	Exposed, %		OR ^a	95% CI
			Controls	Cases		
Ever-smoking	5,538	528	53	60	1.34	1.11, 1.62
Smoking during prenatal period	11,080	1,094	45	51	1.24	1.08, 1.42
Smoking during preconception period	7,699	860	46	50	1.18	1.01, 1.38
Smoking during pregnancy	7,337	810	44	48	1.24	1.06, 1.46
Smoking after birth	11,199	1,035	42	50	1.27	1.11, 1.45

Abbreviations: CI, confidence interval; OR, odds ratio.

^a Odds ratios were adjusted for age, sex, ethnicity, highest parental education, and study center.

data on child's race/ethnicity, sex, age (at diagnosis for cases and corresponding age for matched controls or age at enrollment/interview), birth weight, parental ages at the time of the child's birth, maternal consumption of alcohol during pregnancy, home exposure to paints and solvents, and parental educational level (highest level achieved by mother or father at the time of the child's birth). The Washington State study

provided imputed values for missing data on parental education, using methods previously described (32). All studies, except those in Brazil, Costa Rica, and Germany (German Childhood Cancer Registry), provided data on AML subtype according to the French-American-British (FAB) classification (Table 1). Four studies (United Kingdom Childhood Cancer Study, Adele, Epidemiologic Study on Childhood

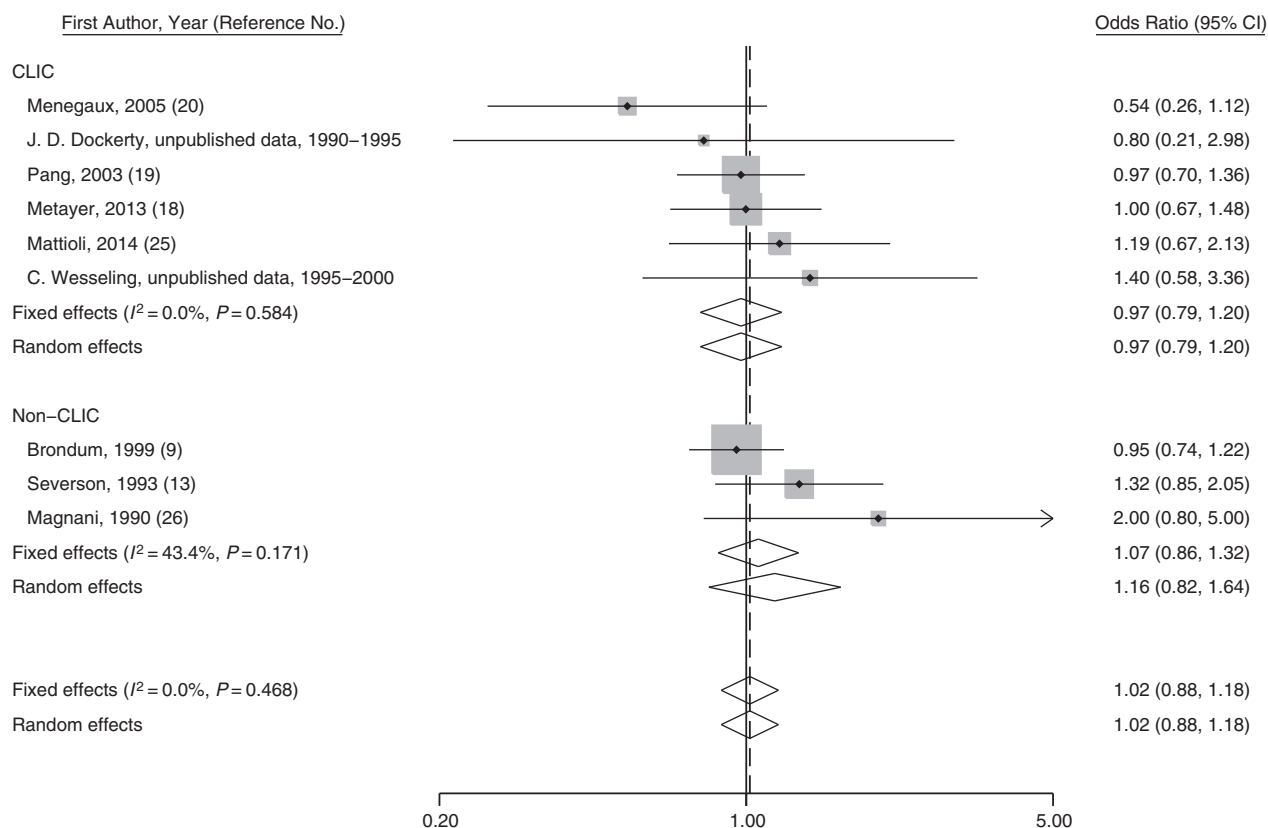
**Figure 1.** Study-specific odds ratios and fixed- and random-effects meta-analysis odds ratios for maternal ever-smoking and risk of acute myeloid leukemia in selected Childhood Leukemia International Consortium (CLIC) and non-CLIC studies between 1990–2014. Odds ratios for CLIC studies were generated by using original data. The P value for heterogeneity between groups is 0.552. The vertical solid line represents the reference for “no association,” and the dashed line represents the risk estimate from the fixed-effect meta-analysis. CI, confidence interval.

Table 5. Risk of Acute Myeloid Leukemia Associated With Paternal Ever-Smoking, by Selected Characteristics, Childhood Leukemia International Consortium, 1974–2012

Variable	Total Controls, no.	Total Cases, no.	Exposed, %		OR ^a	95% CI	P Value for Interaction ^b
			Controls	Cases			
Child's ethnicity							0.08
Non-Hispanic white	3,951	307	54	58	1.10	0.87, 1.41	
Hispanic	506	61	42	52	1.45	0.84, 2.50	
Non-Hispanic other	475	47	47	64	1.81	0.94, 3.49	
Highest parental education							0.26
None/primary	815	116	66	78	1.71	0.87, 3.39	
Secondary	2,242	215	58	60	1.09	0.79, 1.50	
Tertiary	2,487	197	44	50	1.25	0.92, 1.70	
Child's birth weight, g							0.96
Low birth weight (<2,500)	479	41	56	71	1.39	0.58, 3.32	
Normal birth weight (2,500–4,000)	4,482	426	53	61	1.21	0.96, 1.53	
High birth weight (>4,000)	599	64	49	55	1.32	0.76, 2.29	
Child's age, years							0.74
Age <1	247	56	52	50	1.04	0.55, 1.96	
Age 1–4	2,574	187	49	58	1.36	0.96, 1.94	
Age 5–9	1,583	141	55	66	1.35	0.86, 2.12	
Age 10–14	1,156	147	58	63	1.11	0.74, 1.65	

Abbreviations: CI, confidence interval; OR, odds ratio.

^a Odds ratios were adjusted for age, sex, ethnicity, highest parental education level, and study center, except when it was the variable of interest.

^b P value for interaction was derived from the –2 log likelihood estimate from multivariate analyses.

Cancer and Leukemia, and Northern California Childhood Leukemia Study) provided information on the presence of the mixed lineage leukemia gene (*MLL*) translocation (11q23) detected by fluorescence in situ hybridization.

Data were reviewed by CLIC principal investigators and harmonized for pooling. Variables with heterogeneous definitions across studies were categorized for periods of smoking (Web Table 3), highest levels of parental education (none/primary, secondary, and tertiary), and ethnicity (Hispanic, non-Hispanic white/Caucasian/European, later referred to as non-Hispanic white, and non-Hispanic other) (Web Table 4). Studies from Germany, Italy, and Costa Rica did not collect data on subject-specific ethnicity; on the basis of population-based data, all subjects in Germany and Italy were considered non-Hispanic white, and all subjects in Costa Rica were considered Hispanic.

Statistical analyses

Study-specific and pooled odds ratios and 95% confidence intervals were estimated by using unconditional logistic regression models. Parents' and child's age and birth weight were treated as continuous variables. The amount of smoking was analyzed by using data as reported and categorical variables based on the observed frequency distribution among controls (nonsmokers, moderate smokers (1–15 cigarettes per day), and heavy smokers (≥ 16 cigarettes per day)). Models were adjusted for child's age, sex, and ethnicity, because

these variables were used as matching factors in the individual studies. We also adjusted for parental educational level (a surrogate for socioeconomic status found to be a confounder and/or indicator of selection bias in individual studies) and study center. Other potential confounders (parental age at delivery, maternal alcohol intake, birth weight, and home exposure to paints and solvents) were not retained in the final additive models because their inclusion did not alter the odds ratio by more than 10%, and none were effect modifiers in the multiplicative models. In stratified analyses, $P < 0.20$ was used as a threshold for the statistical significance of heterogeneity between strata, using likelihood ratio techniques or Woolf's test. We conducted sensitivity analyses to assess the robustness of our results by systematically excluding 2 studies at a time (Web Figure 1).

To further assess study heterogeneity, we conducted meta-analyses for CLIC studies and non-CLIC studies. For CLIC studies, we computed the study-specific odds ratios using the original study design and corresponding unconditional or conditional regression models adjusted for study-specific confounders. A systematic search in PubMed, Embase, and Web of Science identified 24 studies of childhood AML and parental smoking, including 13 CLIC and 11 non-CLIC studies (details in Web Figure 2, based on Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines) (33). The following search terms were used: “(pediatric OR childhood) AND leukemia AND (tobacco OR smok*) AND (parent* OR maternal OR paternal)” in PubMed,

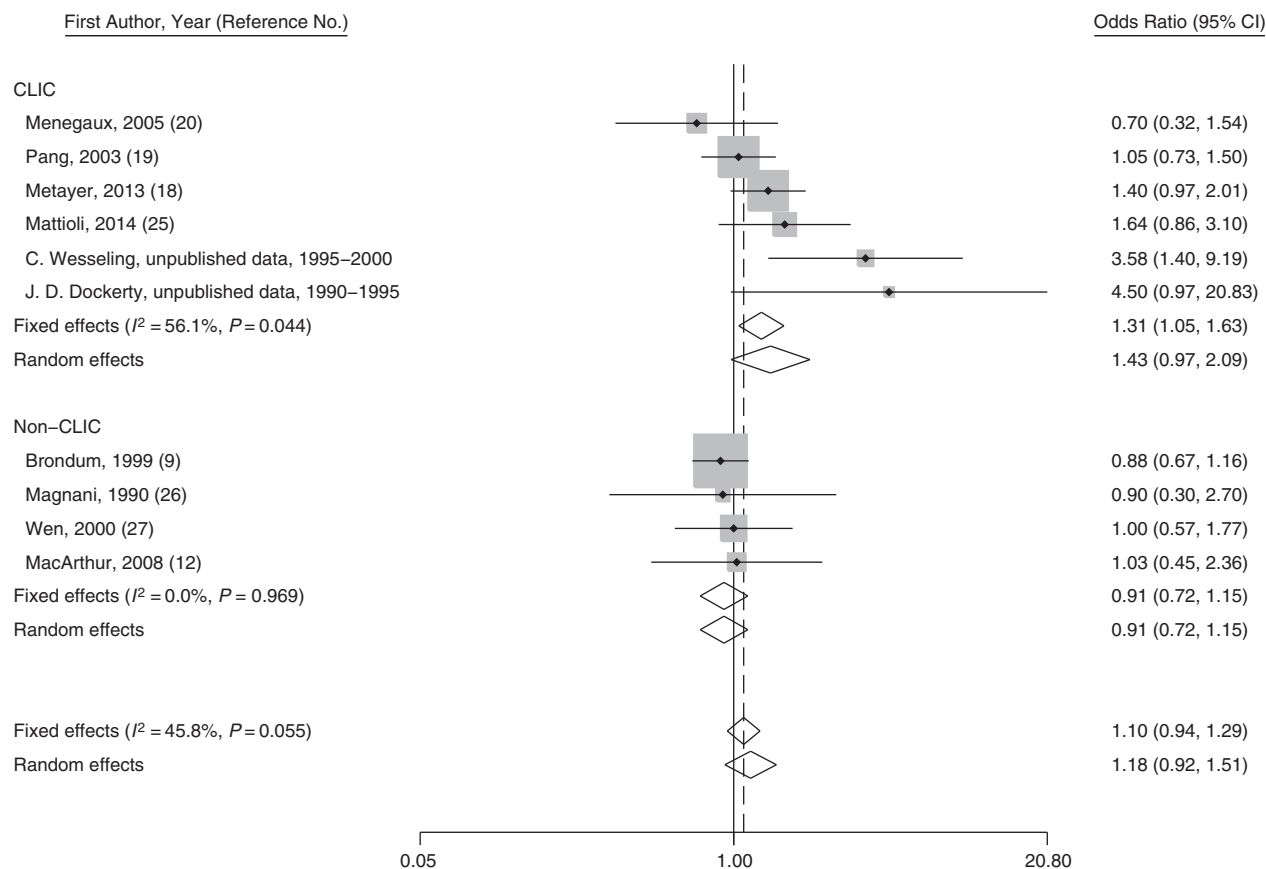


Figure 2. Study-specific odds ratios and fixed- and random-effects meta-analysis odds ratios for paternal ever-smoking and risk of acute myeloid leukemia in Childhood Leukemia International Consortium (CLIC) and non-CLIC studies between 1990 and 2014. Odds ratios for CLIC studies were generated by using original data. The P value for heterogeneity between groups is 0.026. The solid line represents the reference for “no association,” and the dashed line represents the risk estimate from the fixed-effect meta-analysis. CI, confidence interval.

Embase and Web of Science; reference lists of a published review paper (16) and a meta-analysis (30) were also screened. The search resulted in 268 papers, and 23 passed the 6 exclusion criteria (Web Figure 2). For those, the following information was extracted: author's name, publication year, country where the study was conducted, case-control design (individually or frequency matched), sample size (cases and controls), and any measure of association for parental smoking. The search and data abstraction were conducted by 1 investigator, and quality control was performed by an independent investigator. Funnel plots were generated and showed no indication of publication biases (data not shown). Meta odds ratios for yes/no smoking at various times were estimated for CLIC and non-CLIC studies and all studies combined using random and fixed effect models; the I^2 statistics were used as a measure of heterogeneity (34).

RESULTS

Sociodemographic characteristics were similar for cases and controls with the exception of ethnicity, likely because of the inclusion of a large number of controls from Europe

(Table 1). Overall, paternal tobacco smoking was least prevalent in the United States, and fathers smoked more than mothers in all countries (Tables 2–4). The ϕ correlation coefficients between maternal and paternal smoking ranged from 0.26 to 0.32 for various periods (data not shown). The ϕ correlation coefficients between periods were greater than 0.68 for mothers and 0.91 for fathers. Among smokers, 91% of fathers and 49% of mothers smoked from preconception to after birth, and 37% of mothers stopped smoking during pregnancy.

Overall, maternal smoking during any time period was not associated with increased risks of childhood AML in pooled analyses (Table 2) or in meta-analyses of CLIC and non-CLIC studies (Figure 1 and Web Figures 3–5). However, in pooled analyses restricted to Hispanic children, maternal smoking during pregnancy was associated with a 2-fold increased risk of AML (95% CI: 1.20, 3.61), whereas no increased risks were observed for other ethnic groups (P for interaction < 0.01) (Table 3). Data on Hispanics were from studies in Mexico (257 cases and 520 controls; odds ratio (OR) = 1.68, 95% CI: 0.77, 3.66); Costa Rica (34 cases and 558 controls; OR = 2.42, 95% CI: 0.43, 13.62); California (64 cases and 517 controls; OR = 2.02, 95% CI: 0.84, 4.89);

Table 6. Risk of Acute Myeloid Leukemia Associated With Number of Cigarettes Smoked per Day by the Mother and Father, by Period of Exposure, Childhood Leukemia International Consortium, 1974–2012

Window of Exposure and Smoking Status	No. of Studies	Controls, no.	Cases, no.	OR ^a	95% CI
<i>Mother</i>					
Prenatal	11				
Nonsmokers		6,037	512	1.00	Referent
Moderate smokers ^b		2,074	130	0.82	0.66, 1.00
Heavy smokers ^c		4,321	404	0.74	0.50, 1.11
Per 5 cigarettes/day ^d		12,432	1,046	0.99	0.98, 1.00
Preconception	6				
Nonsmokers		5,569	461	1.00	Referent
Moderate smokers ^b		1,576	99	0.82	0.65, 1.04
Heavy smokers ^c		854	54	0.83	0.61, 1.13
Per 5 cigarettes/day ^d		7,999	614	0.95	0.89, 1.01
Pregnancy	9				
Nonsmokers		8,448	723	1.00	Referent
Moderate smokers ^b		1,812	139	0.96	0.79, 1.17
Heavy smokers ^c		383	23	0.68	0.44, 1.07
Per 5 cigarettes/day ^d		10,643	885	0.96	0.89, 1.03
Postnatal	4				
Nonsmokers		3,544	301	1.00	Referent
Moderate smokers ^b		570	41	0.87	0.61, 1.23
Heavy smokers ^c		206	10	0.54	0.28, 1.04
Per 5 cigarettes/day ^d		4,320	352	0.92	0.82, 1.04
<i>Father</i>					
Prenatal	7				
Nonsmokers		5,296	375	1.00	Referent
Moderate smokers ^b		1,726	141	1.18	0.96, 1.45
Heavy smokers ^c		1,949	174	1.31	1.08, 1.60
Per 5 cigarettes/day ^d		8,971	690	1.06	1.02, 1.10
Preconception	5				
Nonsmokers		3,252	254	1.00	Referent
Moderate smokers ^b		1,113	85	1.04	0.79, 1.35
Heavy smokers ^c		1,217	117	1.37	1.07, 1.77
Per 5 cigarettes/day ^d		5,582	456	1.06	1.02, 1.11
Pregnancy	3				
Nonsmokers		2,283	149	1.00	Referent
Moderate smokers ^b		884	58	1.03	0.74, 1.44
Heavy smokers ^c		997	89	1.41	1.06, 1.89
Per 5 cigarettes/day ^d		4,164	296	1.06	1.01, 1.12
Postnatal	3				
Nonsmokers		2,546	139	1.00	Referent
Moderate smokers ^b		779	43	0.93	0.65, 1.33
Heavy smokers ^c		937	68	1.27	0.93, 1.73
Per 5 cigarettes/day ^d		4,262	250	1.03	0.97, 1.10

Abbreviations: CI, confidence interval; OR, odds ratio.

^a Odds ratios were adjusted for age, sex, ethnicity, highest parental education (using imputed values for mothers when needed), and study center.^b Moderate smokers are defined as smoking 1–15 cigarettes per day.^c Heavy smokers are defined as smoking 16 or more cigarettes per day.^d Odds ratios were computed with the continuous variable provided, divided by 5.

Table 7. Risk of Acute Myeloid Leukemia FAB Subtype and *MLL* Rearrangement Status in Relation to Paternal Ever-Smoking, Childhood Leukemia International Consortium, 1974–2012

FAB Subtype	Total Cases, no.	Exposed Cases, %	OR ^a	95% CI
M0	23	65	1.33	0.54, 3.24
M1	43	51	0.83	0.45, 1.55
M2	116	62	1.35	0.91, 2.01
M3	45	62	1.55	0.83, 2.91
M4	60	65	1.87	1.08, 3.25
M5	80	48	0.76	0.48, 1.21
M6	10	40	0.59	0.16, 2.20
M7	42	55	1.25	0.66, 2.36
<i>MLL</i> rearrangement				
Negative	338	57	1.19	0.95, 1.50
Positive	41	51	1.08	0.57, 2.03

Abbreviations and designations: CI, confidence interval; FAB, French-American-British (classification); M0, acute myeloblastic leukemia, minimally differentiated; M1, acute myeloblastic leukemia, without maturation; M2, acute myeloblastic leukemia, with granulocytic maturation; M3, acute promyelocytic leukemia; M4, acute myelomonocytic leukemia; M5, acute monoblastic/monocytic leukemia; M6, acute erythroid leukemia; M7, acute megaloblastic leukemia; *MLL*, mixed lineage leukemia gene; OR, odds ratio.

^a Odds ratios were adjusted for age, sex, ethnicity, highest parental education, and study center.

and Washington State (12 cases and 95 controls; OR = 6.30, 95% CI: 0.39, 101.1; data not shown). Analyses stratified by age, birth weight, and highest parental education led to inconclusive findings (Table 3).

Paternal smoking during any period was associated with increased risks of childhood AML with pooled odds ratios ranging from 1.18 to 1.34 (Table 4). Similar results were observed when analyses were restricted to households with non-smoking mothers (~25%) and for analyses of concurrent paternal and maternal ever-smoking versus nonsmoking parents (data not shown). Sensitivity analyses indicated that the mean odds ratio for childhood AML associated with paternal ever-smoking remained >1 for all 15 possible combinations of studies (Web Figure 1). The magnitude of the association with paternal ever-smoking was lower among non-Hispanic whites, compared with other ethnicities (*P* for interaction = 0.08) (Table 5). Despite heterogeneity among CLIC studies, the fixed- and random-effects meta odds ratios were similar to the pooled odds ratios, ranging from 1.2 to 1.4 depending on the time period (Figure 2 and Web Figures 6–8). For non-CLIC studies, the study-specific odds ratios for paternal smoking were below or close to 1 for all periods, resulting in overall meta odds ratios of smaller magnitude, yet above 1 (Figure 2 and Web Figures 6–8).

Among non-Hispanic white controls, 36% and 17% of smoking mothers smoked 16 cigarettes or more per day before conception and during pregnancy, respectively, suggesting that heavy smoking among smokers was not rare. However, fewer Hispanic mothers reported smoking 16 cigarettes or more per

day before conception (7%) and during pregnancy (3%). Overall, the odds ratios did not increase with increasing amount of maternal smoking (Table 6), except for Hispanic mothers during pregnancy (for an increase of 5 cigarettes per day, OR = 1.81, 95% CI: 1.11, 2.96). The highest level of paternal smoking (≥16 cigarettes per day) in all time periods was associated with the greatest risk of AML (Table 6); however, dose-response relationships were statistically significant only for the prenatal periods. The mean duration of paternal smoking in the prenatal period was similar between cases and controls (16.2 and 17.2 years, respectively; *P* for *t* test = 0.21), and the odds ratio for every year of smoking was 1.01 (95% CI: 0.98, 1.03). About 80% of fathers continued to smoke after the child's birth, and the mean duration of smoking did not vary between cases and controls (*P* for *t* test = 0.60).

Although modestly increased odds ratios were observed for some AML subtypes, only the association between paternal ever-smoking and acute myelomonocytic leukemia (designated M4 in the French-American-British (FAB) classification) was statistically significant (OR = 1.87, 95% CI: 1.08, 3.25) (Table 7). Maternal ever-smoking was also associated with an increased risk of M4 (OR = 1.80, 95% CI: 1.09, 2.97), but this association weakened after adjustment for paternal smoking (OR = 1.49, 95% CI: 0.87, 2.53). There were no statistically significant increased risks of AML with *MLL* fusion in relation to paternal or maternal ever-smoking.

DISCUSSION

The current study, based on individual data from 12 case-control studies in Europe, the Americas, and Oceania, is the largest to date to investigate the role of parental smoking in the etiology of childhood AML. Our pooled analyses support the association between paternal smoking and childhood AML; however, the high correlation between pre- and postnatal paternal smoking limited our ability to identify specific windows of exposure. Overall, no associations were detected between maternal smoking and childhood AML. Meta-analyses including both CLIC and non-CLIC case-control studies (9–15, 35–39) led to similar findings for maternal smoking, although the magnitude of the associations was decreased for paternal smoking.

There was a suggestion that the increased risk of AML associated with maternal smoking during pregnancy was observed in Hispanic children. The findings for Hispanics were based on studies in Costa Rica and Mexico, as well as 2 US studies in California and Washington states that accounted for 42% and 11% of Hispanics, respectively (including 83%–88% from Mexican origin on the basis of census data from 2011 (40, 41) and self-report in the California study). This is the first study to examine the risk of tobacco smoking and childhood AML in Hispanics, an ethnic group that has experienced a rising incidence of childhood leukemia (3), as well as rising prevalence of smoking among women (42–44). Our findings may be due to population heterogeneity, study-specific biases, or chance. Alternatively, differences by ethnic group may be explained by variation in types of tobacco used (black or blond) (45–49) and, consequently, differences in concentrations of carcinogens, such as *N*-nitroso compounds. Also, genes involved in transport and metabolism of

tobacco-related chemicals have been found to differ in non-Hispanics versus Hispanics (50, 51).

Similar to our findings, those of previous studies have suggested a positive dose-response relationship with paternal smoking, although based on unstable estimates. A study from China reported a 2.3-fold (95% CI: 0.4, 14.8) increase in risk of childhood AML with preconception paternal smoking of 5 or more pack-years, whereas no associations were seen for lesser amounts (35). In a US study of 88 infants with AML (15), higher risk of childhood leukemia was observed among fathers' smoking more than 20 cigarettes per day (OR = 1.29, 95% CI: 0.44, 3.74). A study conducted in the United Kingdom reported a positive dose-response relationship with lifetime paternal smoking and childhood AML, using death as a surrogate for leukemia diagnosis ($n = 190$ from 1971 to 1976) (39), although a later study did not ($n = 145$ from 1977 to 1981) (37). A larger case-control study conducted in the United States failed to support an association with paternal ever-smoking or during any time period, and no evidence of a dose-response relationship was found ($n = 517$ from 1989 to 1993) (9). Duration of smoking was not associated with an increased risk of childhood AML in our study. Brondum et al. (9) reported a decreased risk with increasing smoking duration (P for trend = 0.06), whereas no other childhood AML studies have published data.

Few fathers changed their smoking habits over time, limiting our ability to assess the independent contribution of pre-versus. postnatal exposure to tobacco. Under the assumption that maternal smoking before birth (for non-Hispanic children) and after birth does not induce AML in the index child, it is possible that preconception paternal smoking contributes to AML risk, either solely, or in combination with postnatal smoking. Such associations have also been reported for risk of childhood acute lymphoblastic leukemia (18, 30, 52). These epidemiologic observations are supported by laboratory studies showing that tobacco smoke is a germ-cell mutagen in rodents, and likely in humans (53), and can induce germ cell epigenetic changes (54). A child's exposure to secondhand smoking, however, may also contribute to the development of AML (18). The CLIC study from Italy reported an increased risk of AML associated with preconception paternal smoking only among mothers less than 30 years of age at delivery (25), but we did not reproduce this finding in our pooled analyses (data not shown).

We observed increased risks of M4 in children of smoking fathers and, possibly, smoking mothers. Nonstatistically significant odds ratios were also observed between paternal smoking and acute myeloblastic leukemia, minimally differentiated (FAB subtype M0), acute myeloblastic leukemia, with granulocytic maturation (FAB subtype M2), and acute promyelocytic leukemia (FAB subtype M3). However, the interpretation of our subtype analyses is limited by small sample sizes. Another case-control study also reported associations of larger magnitude between childhood M4 leukemia and maternal ever-smoking ($n = 37$ cases) (13). Studies conducted in adults have reported a higher frequency of M2, M4, acute monoblastic/monocytic leukemia (FAB subtype M5), and acute erythroid leukemia (FAB subtype M6) among smokers, whereas acute myeloblastic leukemia without maturation (FAB subtype M1) and M3 were more frequent in nonsmokers (16, 39, 55). Treatment-related M2 frequently occurs in patients

treated with alkylating agents and radiation, and FAB subtypes M3, M4, and M5 occur after exposure to topoisomerase II inhibitors (56, 57), suggesting that some metabolic pathways may be shared between tobacco- and treatment-induced AML. We observed no difference in risk for children classified as *MLL* positive and *MLL* negative. The *MLL* fusion is more frequent among infants with leukemia (58), and a study of 88 infant AMLs reported no association with parental smoking (15). In contrast, a recent case-case study found that maternal smoking during pregnancy resulted in a 3-fold increased risk of AML with *MLL* rearrangement ($n = 57$) compared with *MLL* negative ($n = 59$) (59). The occurrence of AML with *MLL* fusion proteins may be further modulated by inherited genetic susceptibility factors (60, 61).

Our analyses have some limitations. Selection bias may occur in case-control studies if parents' participation is dependent on the exposure of interest, here smoking habit, and is correlated with sociodemographic factors or race/ethnicity. The distribution of educational levels varied among participating CLIC studies (i.e., lower education in cases vs. controls in 4 studies, lower education in controls vs. cases in 1 study, and no difference between cases and controls in 7 studies). As a result, it is difficult to assess the magnitude of selection bias and the influence on the overall pooled risk estimates. However, the observation of both positive and negative findings in our analyses argues against strong selection bias. There is a concern, especially among pregnant women, that recall of smoking history may be inaccurate (62). Studies have reported a lack of concordance between self-reported smoking during pregnancy and cotinine blood level in mothers and newborns (63, 64). Also, compared with nonpregnant women, pregnant women are more likely to underreport smoking (63) or exhibit unstable smoking habits (65). In most studies, mothers provided information for paternal smoking, and it has been shown that spouses of cases and controls usually report paternal smoking accurately (18, 66, 67). We compared smoking prevalence in CLIC studies with population-based data, and for CLIC studies conducted in the United Kingdom, Greece, Italy, Mexico, and Brazil, the prevalence of smoking for mothers and fathers (among controls) was higher by approximately 6%–8%, compared with population-based data (68–72) that were available for the corresponding study periods and the corresponding age groups; the population-based data for Germany, France, Costa Rica, and California were available after the corresponding CLIC study period and suggested the same trend (73–76). In contrast, the prevalence of smoking among controls in the birth registry-based study conducted in Washington State was lower than the prevalence reported in the general population (77), and it is possible that mothers underreported smoking at the interviews conducted by hospital staff soon after the child's birth. Overall, this may indicate that subjects participating in the CLIC case-control studies overreported smoking habits or represent a selected group not representative of the general population. However, our data indicated that maternal smoking was correlated with low birth weight in both cases and controls (data not shown), consistent with the well-established observation that maternal smoking induces intrauterine growth retardation (78). This observation indirectly suggests that recall

bias may not fully explain the negative findings for maternal smoking (among non-Hispanics). Alternatively, maternal smoking during pregnancy is associated with stillbirth and miscarriage (79), which could represent a competing outcome preventing our evaluation of childhood leukemia risk.

Although alcohol consumption during pregnancy has been associated with a 1.5-fold increased risk of childhood AML (17, 80), there was no evidence of confounding (or effect modification) with alcohol use in our analyses. No other factors affected the observed associations, but residual confounding from unmeasured factors is possible. In previous CLIC pooled analyses on prenatal folate and vitamin supplementation, we observed that adjustment for study site accounted for confounding by measured and unmeasured study characteristics, even when the heterogeneity between studies is large (81). Meta-analyses indicated some heterogeneity for paternal smoking, and to a lesser extent for maternal smoking. Nevertheless, exclusion of studies resulted in relatively stable estimates, indicating that results were not largely driven by specific studies. Finally, it is possible that multiple comparisons may have led to false positive findings. Despite limitations, the strengths of the CLIC pooled analyses are the inclusion of published and unpublished original data, large sample size for a rare disease like childhood AML, inclusion of Hispanic children, and the ability to conduct subgroup and dose-response analyses, as well as adjustment for confounders.

In conclusion, we observed an association between paternal smoking and childhood AML. Findings for maternal smoking remained mostly null, except possibly for Hispanic children exposed in utero. Until associations with maternal smoking are further elucidated, and given the many health risks associated with smoking, it is important to educate families and health professionals on preventing fathers, mothers, and children from being exposed to tobacco smoke before and after the child's birth.

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