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Tobacco smoke exposure and the risk of childhood acute lymphoblastic leukemia and acute myeloid leukemia

A meta-analysis

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Abstract

Objective: Tobacco smoke contains carcinogens known to damage somatic and germ cells. In this study, we investigated the effect of tobacco smoking on the risk of childhood acute lymphoblastic leukemia (ALL) and myeloid leukemia (AML).

Methods: Information about tobacco smoking exposures of the mother before, during, and after pregnancy was collected via PubMed, Embase, and Web of Science databases through November 5, 2018. We performed to evaluate the association between smoking exposure and the risk of childhood ALL and AML. Study selection, data abstraction, and quality assessment were performed by 2 independent reviewers. Random effects models were used to obtain summary odds ratios (ORs) and 95% confidence intervals (CIs).

Results: Nineteen case–control studies of childhood leukemia (age < 15 years) conducted in 9 countries from 1974 to 2018. Maternal smoking exposures did not a significant association with childhood ALL (OR = 1.004, 95% CI 0.953–1.058, $P = .881$) and AML (OR = 0.92, 95% CI 0.815–1.038, $P = .177$) during exposure time windows. However, there was an association with paternal smoking and ALL (OR = 1.15, 95% CI 1.038–1.275, $P = .007$). Paternal smoking in AML showed there was no association with smoking exposures and childhood AML (OR = 1.133, 95% CI 0.943–1.362, $P = .181$). Next, maternal daily cigarettes consumption showed no associations with ALL (OR = 1.08, 95% CI 1.000–1.168, $P = .051$) during pregnancy. No association with maternal daily smoking and AML (OR = 0.909, 95% CI 0.682–1.211, $P = .514$). Paternal daily cigarettes consumption was associated with increased risks of childhood ALL (OR = 1.200, 95% CI 1.112–1.302, $P = .000$). The higher consumption of paternal smoking (more than 10 per day) was significantly related to childhood ALL. Paternal daily smoking consumption also was related to AML (OR = 1.242, 95% CI 1.031–1.496, $P = .022$).

Conclusion: Maternal smoking before, during, or after pregnancy was not associated with childhood ALL or AML. However, paternal smoking was related to a significantly elevated risk of childhood ALL during pregnancy, but not for AML. Maternal daily smoking consumption was not associated with ALL or AML during pregnancy. The higher consumption of paternal smoking were, the higher the risk of childhood ALL or AML.

Abbreviations: ALL = acute lymphoblastic leukemia, AML = acute myeloid leukemia, AnLL = acute nonlymphocytic leukemia, OR = odd risks.

Keywords: childhood acute lymphoblastic leukemia/acute myeloid leukemia, tobacco smoke exposure

1. Introduction

Acute leukemia is the most common childhood cancer, acute lymphoblastic leukemia (ALL) accounts for 75% to 80% of total cases of childhood leukemia, acute nonlymphocytic leukemia (AnLL) for about 20%.[1] Many studies have examined the potential precipitating factors of acute leukemia. For instance, benzene is known to damage cells of myeloid lineage and pluripotent hematopoietic stem cells,[2] which potentially playing a role in the development of both childhood ALL and acute myeloid leukemia (AML). Meanwhile, there also are other risk factors including: car exhaust fumes, pesticides, antiepileptic drugs, chemical contamination in drinking water, both viral and bacterial infections, and parental cigarette smoking, and so on.[3] Many studies have proven carcinogens are present in tobacco,[4] which is known to increase the risk of various adult cancers.[5] The cause lies in smoking is associated with oxidative damage and aneuploidy of sperm.[6] Tobacco smoke has increased frequencies of chromosomal abnormalities.[7] Tobacco-related contaminants can damage DNA in human somatic cells, and there is growing evidence that tobacco affects germ cells not only in animals, but in humans.[8]

There are strong reasons for considering parental smoking behavior as a risk factor for childhood cancer. Many studies

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showed that active tobacco smoking is an established risk for adult myeloid leukemia.[9] A case–control investigation of childhood ALL was conducted showed that maternal smoking was associated significantly with childhood ALL.[10] However, a study from the French demonstrated there was no effect of maternal smoking on the childhood acute lymphoblastic risk.[11] Although the association may be biologically plausible, it is less clear whether tobacco smoke exposure was related with acute leukemia. Many studies contradict and increase people's confusion.

We conducted a systematic review and meta-analysis to investigate risk factor between tobacco smoke exposures and childhood leukemia during critical exposure time windows (preconception, pregnancy, and childhood).

2. Methods

Sine this study is a meta-analysis of previously published studies, the ethical approval and patient consent are not required. This study was conducted and reported in adherence to Preferred Reporting Items for Systematic Reviews and Meta-analysis.

2.1. Literature search

The PubMed, Embase, and Web of Science databases were systematically searched for relevant studies until November 5, 2018. The following keywords were used individually and in combination: "acute lymphoblastic leukemia," "acute myeloid leukemia," and "tobacco smoke exposure."

2.2. Inclusion and exclusion criteria

We choose original epidemiologic studies of childhood leukemia using a case–control study design with an assessment of smoking exposure and childhood ALL or AML. The following studies were excluded: letters, reviews, case reports, conference abstracts, or expert opinions; and articles with insufficient information on smoking exposure variables.

2.3. Data extraction and assessment of study quality

Two investigators independently extracted data that met our inclusion and exclusion criteria. The Newcastle–Ottawa scale was used to evaluate the methodologic quality of all included case–control studies.[12]

2.4. Statistical analysis

Pooled estimates of odds ratios (ORs) with 95% confidence intervals (CIs) were used to evaluate the associations between tobacco smoking exposures and childhood acute leukemia. To stratify the data for analysis, (maternal or paternal smoking in ALL/AML, paternal or maternal daily cigarettes in ALL/AML). Based on the Chi-squared statistic Q, inter-study heterogeneity was assumed[13] in cases in which $I^2 > 50\%$, and ORs were pooled according to random-effects models. Alternatively, fixed-effects models were used. All statistical analyses were performed using Stata 13.0 (Stata Corporation, College Station, TX). A P-value $<.05$ were considered statistically significant.

3. Results

3.1. Study selection and characteristics

The literature search was conducted on November 5, 2018. The detailed steps of the systematic search and selection process are given as a flow diagram (Fig. 1). The searches yielded 227 potentially eligible titles. After removing duplicate articles and reviewing the abstracts, the full text of 29 articles were obtained and compared to the inclusion criteria. Ten articles were excluded (Fig. 1). This resulted in 19 eligible articles (Table 1). These were all case–control studies for smoking mother research. The main characteristics of the included studies are presented in Table 1. Nineteen case–control studies of childhood leukemia (age <15 years) conducted in 9 countries from 1974 to 2018. The following data were extracted: author's name, research year, country, case recruitment, control selection, matching, and sample sizes. Data were available for the pooled analyses.

3.2. Correlating tobacco smoke exposure with childhood acute lymphoblastic during exposure time windows (preconception, pregnancy, and postnatal)

We examined the relationship between parental smoking exposure and childhood acute leukemia during exposure time windows (Figs. 2 and 3 and Table 2). As showed in the Figure 2A and Table 2, in childhood ALL maternal smoking, there was no significant heterogeneity was found ($I^2 = 0.0\%$, $P = .803$). Our results showed that maternal smoking exposure were not associated with childhood ALL (OR = 1.004, 95% CI 0.953–1.058, $P = .881$). In subgroups, maternal preconception smoking subgroup were OR = 1.046, 95% CI (0.972–1.125), $P = .23$. And pregnancy subgroup were OR = 0.973, 95% CI (0.898–1.054) $P = .500$, and postnatal subgroup were OR = 1.004, 95% CI (0.953–1.058), $P = .317$. In these maternal smoking subgroups, there was no evidence of a general tendency for increased the ALL risk.

When maternal smoking were in childhood AML in the Figure 2B and Table 3, our data also showed that no heterogeneity was found ($I^2 = 15.1\%$, $P = .27$). There was no significant association with maternal smoking exposures and childhood AML during exposure time windows (OR = 0.92, 95% CI 0.815–1.038, $P = .177$). At the same time, for the maternal preconception, pregnancy, and postnatal subgroup, the results were respectively (OR = 0.951, 95% CI 0.790–1.144, $P = .592$) in preconception; (OR = 0.916, 95% CI 0.722–1.163, $P = .472$) in pregnancy; and (OR = 0.865, 95% CI 0.654–1.144, $P = .309$) in postnatal subgroup. All subgroups were no significant with childhood AML.

Next, paternal smoking in ALL was showed in the Figure 3A and Table 2. We found there was an association with paternal smoking and ALL (OR = 1.15, 95% CI 1.038–1.275, $P = .007$). For paternal smoking preconception subgroup was also associated with an increased ALL risk (OR = 1.146, 95% CI 1.009–1.302, $P = .036$). The result was significant. But paternal pregnancy and postnatal subgroup were, respectively, no significance: OR = 1.23, 95% CI (0.989–1.530), $P = .063$, pregnancy, OR = 0.98, 95% CI (0.789–1.218), $P = .855$, postnatal.

Paternal smoking in AML was showed in the Figure 3B and Table 2. Our results showed there was no association with paternal smoking and childhood AML (OR = 1.133, 95% CI 0.943–1.362, $P = .181$). In subgroups, the results also were no

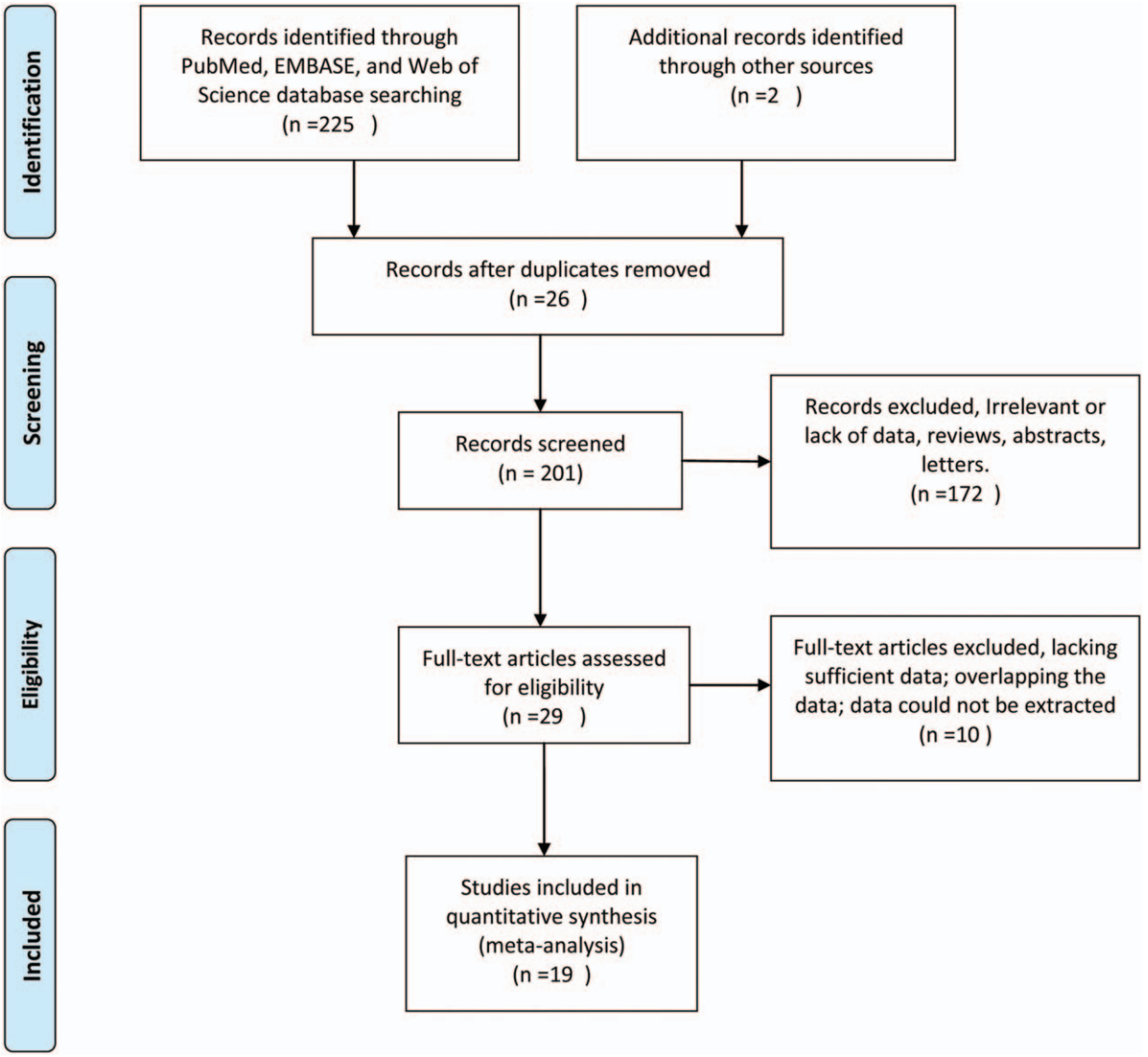


Figure 1. Flow chart of study selection process.

significant. They were respectively OR = 1.178, 95% CI (0.896–1.547), $P = .240$, preconception, OR = 1.155, 95% CI (0.792–1.683), $P = .455$, pregnancy, and OR = 0.940, 95% CI (0.680–1.300), $P = .708$, postnatal.

Overall, maternal smoking before, during, or after pregnancy was not associated with childhood ALL and AML. However, paternal smoking, particularly before pregnancy, was significantly related to an elevated risk of childhood ALL. But not for AML, which was no significance.

3.3. Childhood ALL with parental daily consumption of cigarettes during pregnancy

As showed in the Figure 4A and Table 3 for maternal daily cigarettes consumption in ALL, which show childhood ALL have no associations with maternal daily consumption cigarettes during pregnancy (OR = 1.08, 95% CI 1.000–1.168, $P = .051$). However, there were slightly an increased risks for ALL (OR = 1.12, 95% CI 0.996–1.252, $P = .059$) in <10 maternal cigarettes consumption subgroup, but not statistically significant. While, 10 to 20 subgroup and >10 subgroup showed no associations with childhood ALL during pregnancy. Their results were OR = 1.07, 95% CI (0.938–1.226), $P = .308$, 10 to 20 cigarettes/day and OR = 1.01, 95% CI (0.850–1.209), $P = .881$, >20 cigarettes/day). Both were not associated with increased risks of childhood ALL in pooled analyses.

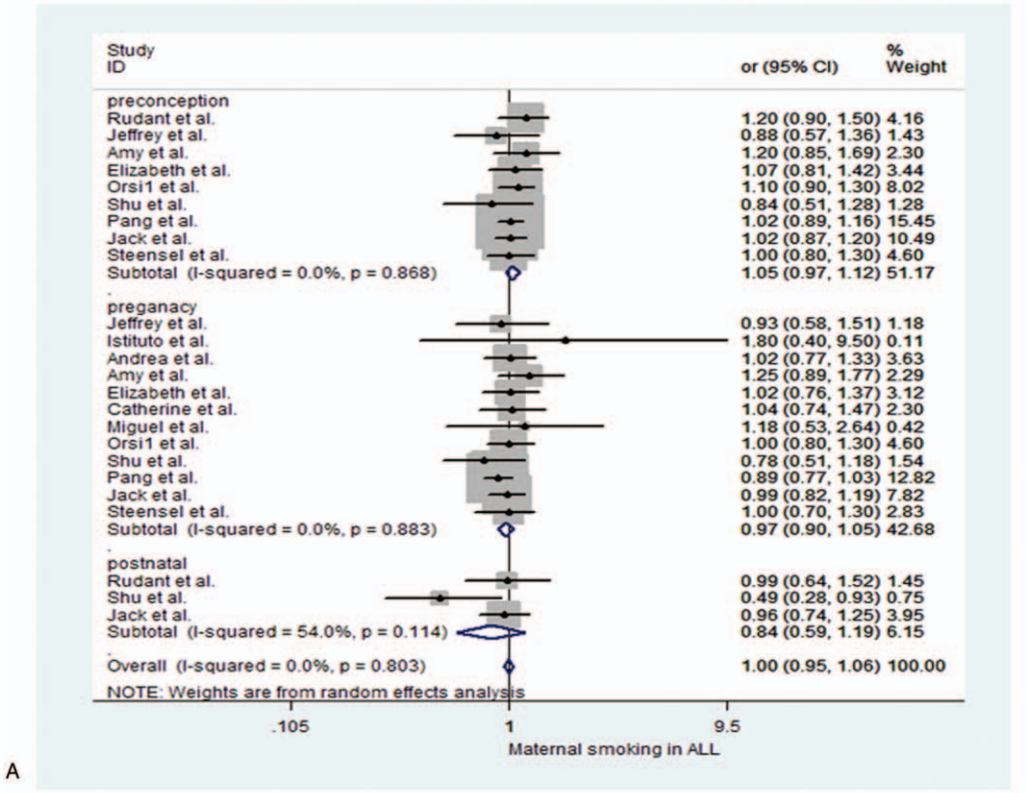
Paternal daily cigarette consumption in ALL was showed in the Figure 4B and Table 3. The paternal daily cigarette consumption was associated with the increased risks of childhood ALL (OR = 1.200, 95% CI 1.112–1.302, $P = .000$). In subgroups, paternal smoking <10 subgroup showed an associations with childhood ALL during pregnancy (OR = 1.190, 95% CI 1.017–1.384, $P = .030$, <10 subgroup). Moreover, the higher consumption of paternal smoking (more than 10 per day) was also significantly related to childhood ALL. Paternal smoking 10 to 20 cigarettes per day was OR = 1.150, 95% CI (1.023–1.287), $P = .019$; >20 was OR = 1.300, 95% CI (1.072–1.586), $P = .008$, during pregnancy. Both were

Table 1

Characteristics of included studies.

Study	Year	Sources	Country	Cases /controls	Case definition	Age	Case recruitment	Control selection	Matching
Rudant et al[14]	2003–2004	the ESCALE study	France	1316 (938 ALL, 171 HL, 207 NHL)/1681	ALL,HL, and NHL	<15	French pediatric oncology hospital department	Randomly selected from the French population, using a quota sampling method	Age, region, sex, ethnic origin
Chang et al[15]	1994–2002	A case–control study	USA	327 (281 AL, 46 (AML)/416	ALL,ANLL	<15	Local 7 hospitals	A set of 4 birth certificates meeting the matching criteria was randomly generated.	Age, sex, hispanic ethnicity, and maternal race
van Duijn et al[16]	1973–1979	A case–control study	The Netherlands	597 (80 ANLL, 517 ALL)/240	ALL,ANLL	<15	The national morbidity registration of the Dutch Childhood Leukemia Study Group	Noncancer inpatients in same or related hospital	Age, region, sex, ethnic origin
Cocco et al[10]	1980–1989	A case–control study	Italy	80/241	ALL	<22	Patients from local hospitals of Cagliari province	Their respective residences	Age, region, sex, ethnic origin
Farioli et al[17]	1998–2003	The SETIL case–control study	Italy	557/580	ALL	0–10	Italian Association of Pediatric Hematology and Oncology	14 Italian Regions	Age, region, sex
Mattioli et al[18]	1998-2001	The SETIL study	Italy	80/1044	ANLL	<18	Italian Association of Pediatric Hematology and Oncology	Randomly drawn from Local Health Authority	Age, sex, provenience, birth order, breastfeeding, parental educational level age, birth year, occupational exposure to benzene
MacArthur et al[19]	1990–1994	A case–control study	Canada	399/399	ALL,NHL	0–14	The provincial government health insurance rolls	5 regions across Canada	Age, region, sex
Milne et al[20]	2003–2006	An Australian population-based case–control study	Australia	393/1249	ALL	<15	Diagnosed at the 10 pediatric oncology centers	National random digit dialing and frequency	Age, sex, state of residence
Metayer et al[21]	2000–2008	A case–control study	USA	767/1139 (ALL), 135/1139 (AML)	ALL,ANLL	<15	The Northern California Childhood Leukemia Study	Randomly selected using birth certificates obtained through the California Office of Vital Records	Birth, sex, hispanic ethnicity
Schuz et al[22]	1992–1997	A case–control study	Germany	2358/2588	ALL,ANLL NHL	<20	Cases from the nationwide German childhood cancer registry in Mainz	Randomly selected from complete files of local offices for registration of residents	Age, region, sex
Castro-Jimenez et al[23]	2000–2005	A case–control study	Colombia	85/85	ALL	<15	Bucaramanga, Bogotá, Tunja, and their closest municipalities	From a house-to-house search; recruited for the healthy and living in the same neighborhood	Age, sex
Orsi et al[24]	2010–2011	The ESTELLE study	France	747/1421	ALL, ANLL	<15	France in 2010 and 2011 using a quota sampling method		Age, sex
Sorahan et al[25]	1980–1983	A case–control study	UK	555/555	ALL	<16	Inter-Regional Epidemiological Study of Childhood Cancer	GP lists	Age, region, sex
Shu et al[26]	1983–1988	A Children's Cancer Group (CCG) case–control study	United States, Canada, and Australia	302/558	ALL, AML	<1.5	The registration files of the CCG	Random-digit-dialing procedure	Age, region, sex
Pang et al[27]	1991–1994	A case–control study	UK	3838/7629	ALL,AML	<15	United Kingdom Childhood Cancer Study	Family Health Services Authorities lists	Sex, date of birth, and geographical area of residence
Greaves and Alexander[28]	1973–1980	A case–control study	The Netherlands	519/507	ALL,AML	<15	Dutch Childhood Leukaemia Study Group	The Netherlands census lists	Age, sex
Menegaux et al[11]	1995–1998	A French population-based case–control study	French	472/567	ALL	<15	The National Registry of Childhood Blood Malignancies	The French population with respect to region of residence and municipality population category	Gender, age, region of residence
Brondum et al[29]	1989–1993	A case–control study	French–American–British	638 AML/771, 2079 ALL/2597	ALL,AML	<17	CCG	Digit dialing procedure	Age, region, sex
Lee et al[30]	2003–2005	A hospital-based case–control	Korea	164/298	ALL	<18	Seoul National University Hospital, Asian Medical Center and Samsung Medical Center	The patients admitted to the Department of Pediatrics, Seoul National University	Age, region, sex

ALL = acute lymphoblastic leukemia, AML = acute myeloid leukemia.



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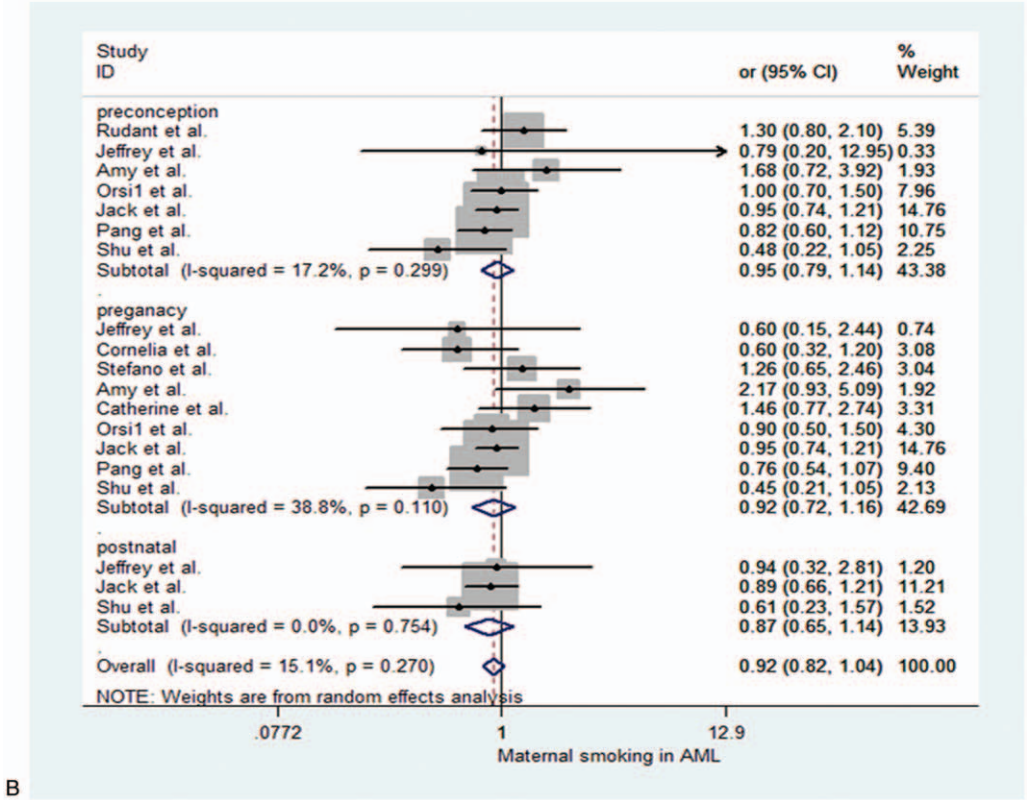

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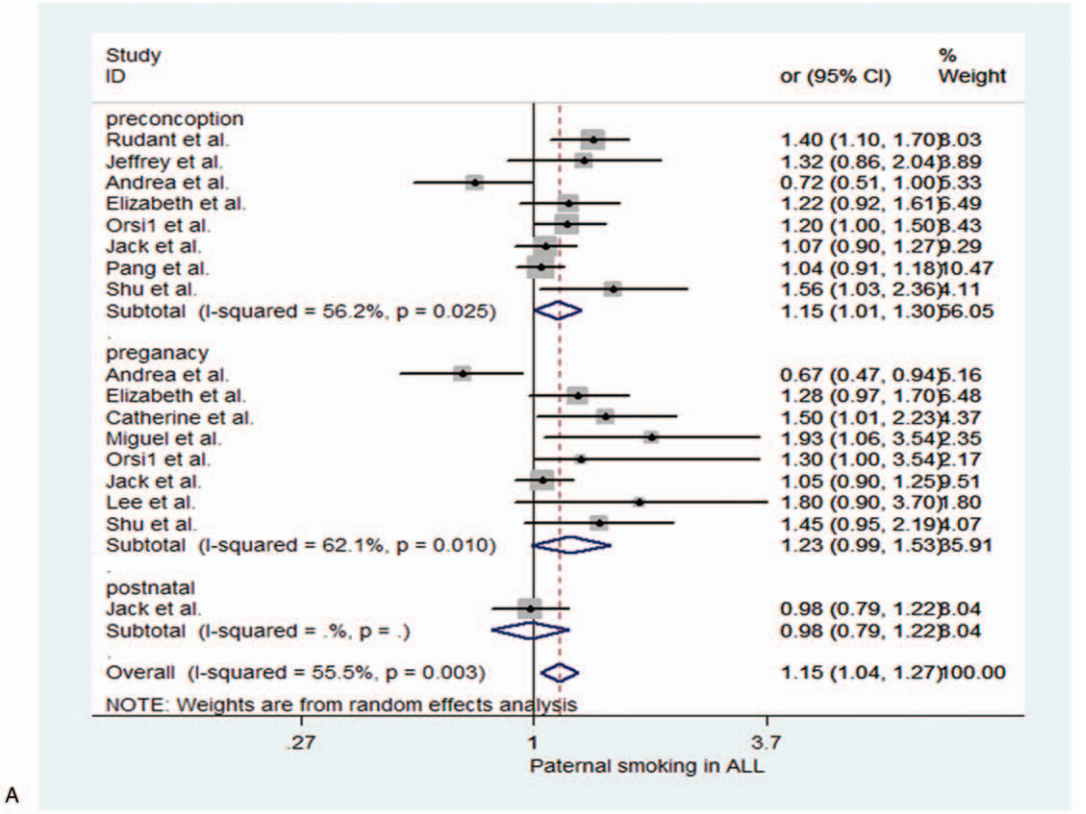
Figure 2. Forest plot depict parental smoking and odds ratios (ORs) for parental smoking in childhood acute lymphoblastic during exposure time windows. (A) Maternal smoking in acute lymphoblastic leukemia. (B) Maternal smoking in acute myeloid leukemia.



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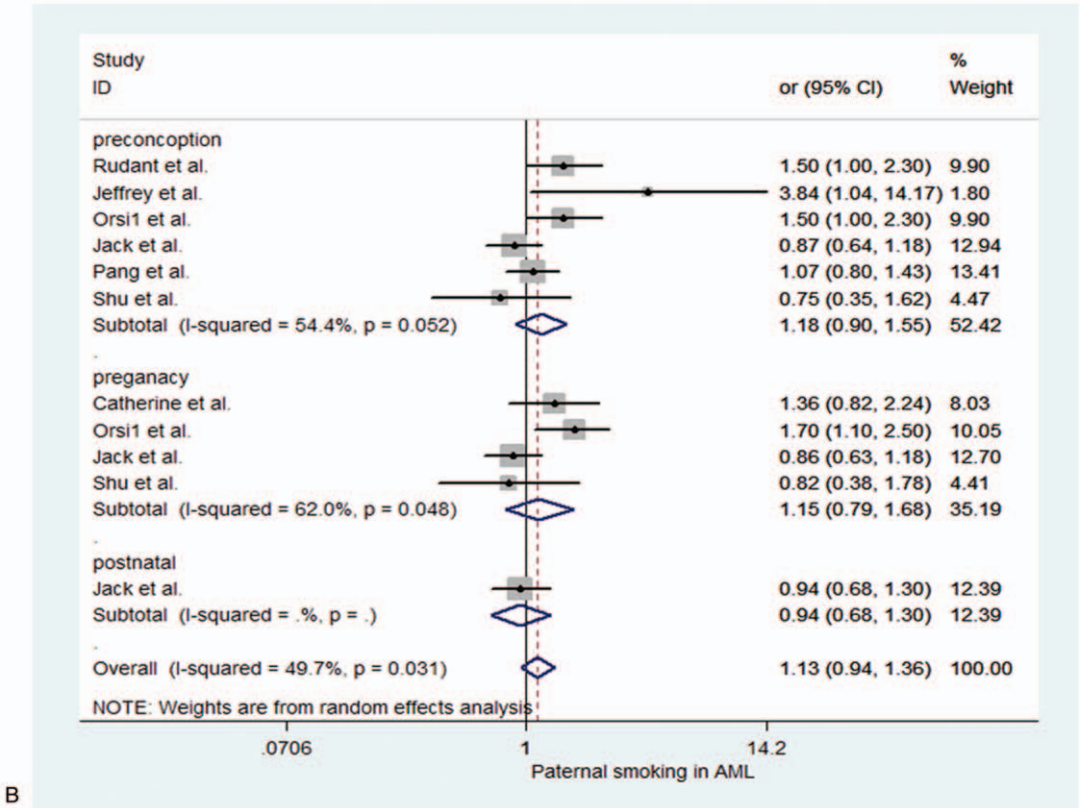

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Figure 3. Forest plot depict parental smoking and odds ratios (ORs) for parental smoking in childhood acute lymphoblastic during exposure time windows. (A) Paternal smoking in acute myeloid leukemia (AML). (B) Paternal smoking in AML.

Table 2

Odd risks (OR) of childhood ALL associated with tobacco smoke during exposure time windows.

	ALL						AML					
		Pooled data (fixed)			Heterogeneity test			Pooled data (fixed)			Heterogeneity test	
Stage	No. of studies	OR	95% CI	*P*-value	I^2	*P*-value	No. of studies	OR	95% CI	*P*-value	I^2	*P*-value
Maternal smoking												
Preconception	9	1.046	0.972–1.125	.23	0	.868	7	0.951	0.790–1.144	.592	0.172	.299
pregnancy	12	0.973	0.898–1.054	.5	0	.883	9	0.916	0.722–1.163	.472	0.388	.11
postnatal	3	0.836	0.588–1.188	.317	0.54	.114	3	0.865	0.654–1.144	.309	0	.754
Overall	24	1.004	0.953–1.058	.881	0	.803	19	0.92	0.815–1.038	.177	0.151	.27
Paternal smoking												
Preconception	8	1.146	1.009 -1.302	.036	0.562	.025	6	1.178	0.896–1.547	.24	0.544	.052
pregnancy	8	1.23	0.989–1.530	.063	0.621	.01	4	1.155	0.792–1.683	.455	0.62	.048
postnatal	1	0.98	0.789–1.218	.855	–	–	1	0.94	0.680–1.300	.708	–	–
Overall	17	1.15	1.038–1.275	.007	0.555	.003	11	1.133	0.943–1.362	.181	0.497	.031

ALL = acute lymphoblastic leukemia, AML = acute myeloid leukemia, CI = confidence interval.

statistically significant increased risks of childhood ALL for father smoking during pregnancy.

As showed in the Figure 5A and Table 3 for maternal cigarettes daily consumption in AML during pregnancy. No association with maternal cigarettes consumption per day and AML was found (OR = 0.909, 95% CI 0.682–1.211, *P* = .514). In the subgroups, neither <10, 10 to 20, or >20 was association with AML. The results were, respectively, OR = 0.991, 95% CI (0.621–1.583), *P* = .971, <10 cigarettes per day; cigarettes per day OR = 0.95, 95% CI (0.574–1.572), *P* = .841, 10 to 20 cigarettes per day; and OR = 0.635, 95% CI (0.371–1.085), *P* = .096, >20 cigarettes per day. Meanwhile, there also were no heterogeneity (I^2 = 46.1%, 0.026).

Interestingly, as showed in the Figure 5B and Table 3, we found that paternal cigarettes consumption daily was related to childhood AML (OR = 1.242, 95%CI 1.031–1.496, *P* = .022). In the subgroups, paternal cigarettes consumption <10 per day during pregnancy, there was a slightly trend for the risk of childhood AML (OR = 1.365, 95% CI 0.958–1.943, *P* = .085), but not statistically significant. Moreover, 10 to 20 or >20 subgroup was no association with childhood AML. The results were respectively 10 to 20 subgroup (OR = 1.136, 95% CI 0.881–1.464, *P* = .327), >20 cigarettes per day (OR = 1.289, 95% CI 0.829–2.006, *P* = .260). Meanwhile, there were no heterogeneity (I^2 = 23.7%, *P* = .18).

Overall, the interaction between maternal daily cigarettes consumption during pregnancy and childhood ALL, AML was not significant. While a significant association between paternal cigarettes consumption and childhood ALL, AML was observed during pregnancy (Table 3).

When maternal passive smoking during pregnancy in ALL (Fig. 6 and Table 4), our results were (summary OR = 1.383, 95% CI 0.755–2.533). The *P*-value was .294. It showed maternal passive smoking was no associated with an increased risk of childhood ALL.

4. Discussion

Previous studies suggested that tumor in children may be caused by noxious substance exposures early in life.[31] Tobacco contains several mutagenic and carcinogenic compounds to cause human germ cell mutations during spermatogenesis.[10,32] Some studies displayed smoking can have adverse effects on the health of the baby during pregnancy.[33,34] Several lines of evidence support the potential role of tobacco in the pathogenesis of cancer.[35] In this study, we investigate the relationship of parental smoking exposure and the risk of ALL and AML during exposure time windows (preconception, pregnancy, postnatal).

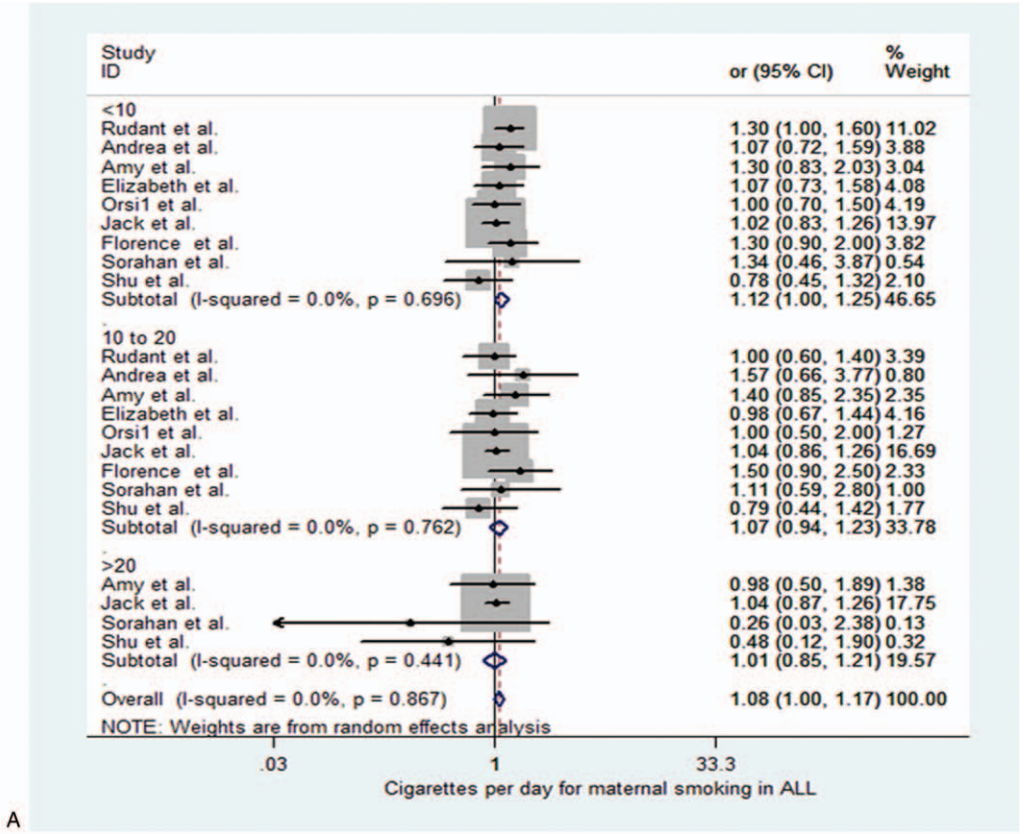
Previous case–control studies have tended to show weak associations between maternal smoking and childhood ALL.[20,36,37] A study from the French demonstrated no effect of maternal smoking during the index pregnancy on the childhood acute lymphoblastic risk.[11] Greaves and Alexander also showed no association between childhood leukemia and

Table 3

Odd risks (OR) of childhood ALL associated with parental daily consumption of cigarettes during pregnancy.

		Pooled data (fixed)			Heterogeneity test				Pooled data (fixed)			Heterogeneity test	
Stage	No. of studies	OR	95% CI	*P*-valve	I^2 (%)	*P*-valve		No. of studies	OR	95% CI	*P*-valve	I^2 (%)	*P*-valve
Maternal smoking in ALL							Maternal smoking in AML						
<10	9	1.12	0.996–1.252	.059	0	.696	<10	6	0.991	0.621–1.583	.971	0.556	.046
10–20	9	1.07	0.938–1.226	.308	0	.762	10–20	6	0.95	0.574–1.572	.841	0.472	.092
>20	4	1.01	0.850–1.209	.881		.441	>20	3	0.635	0.371–1.085	.096	0	.658
Overall	22	1.08	1.000–1.168	.051	0	.867	Overall	15	0.909	0.682–1.211	.514	0.461	.026
Paternal smoking in ALL							Paternal smoking in AML						
<10	8	1.19	1.017–1.384	.03	0.1	.354	<10	6	1.365	0.958–1.943	.085	0.122	.337
10–20	8	1.15	1.023–1.287	.019	0	.8	10–20	6	1.136	0.881–1.464	.327	0	.566
>20	6	1.3	1.072–1.586	.008	0.57	.04	>20	5	1.289	0.829–2.006	.26	0.624	.031
Overall	22	1.2	1.112–1.302	0	0.14	.271	Overall	17	1.242	1.031–1.496	.022	0.237	.18

ALL = acute lymphoblastic leukemia, AML = acute myeloid leukemia, CI = confidence interval.



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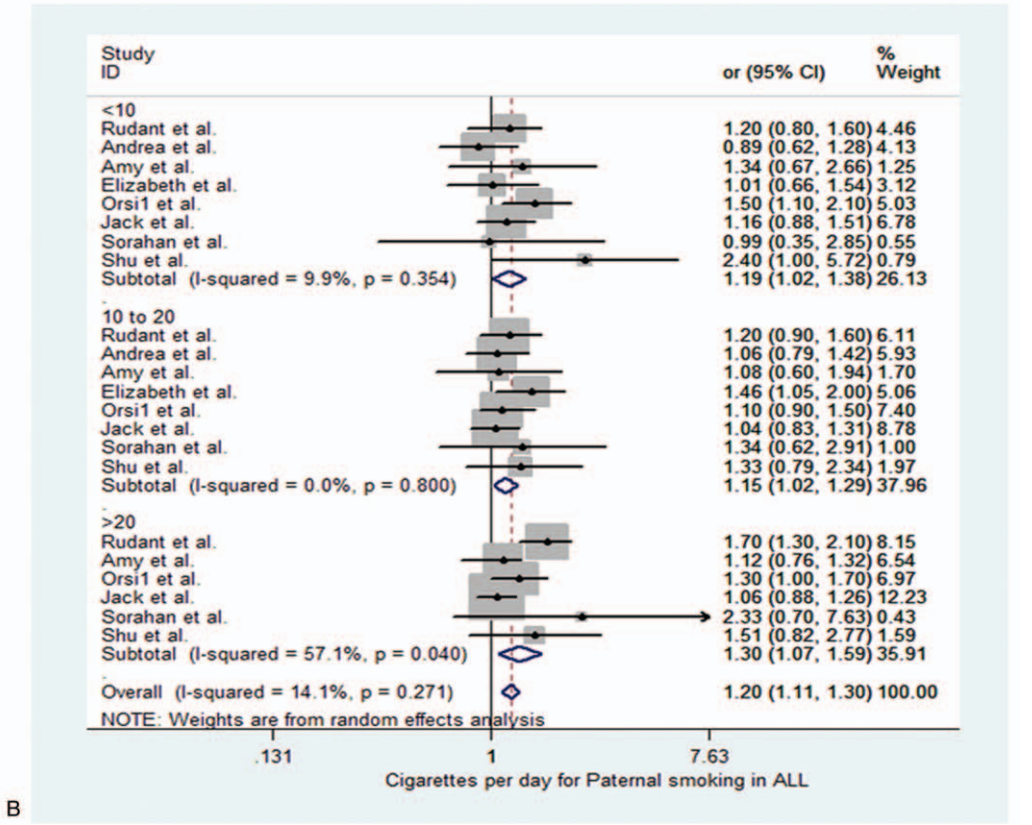

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Figure 4. Forest plot depict childhood acute lymphoblastic leukemia (ALL) with parental cigarettes daily consumption during pregnancy. (A) Cigarettes per day for maternal smoking in ALL. (B) Cigarettes per day for paternal smoking in ALL.

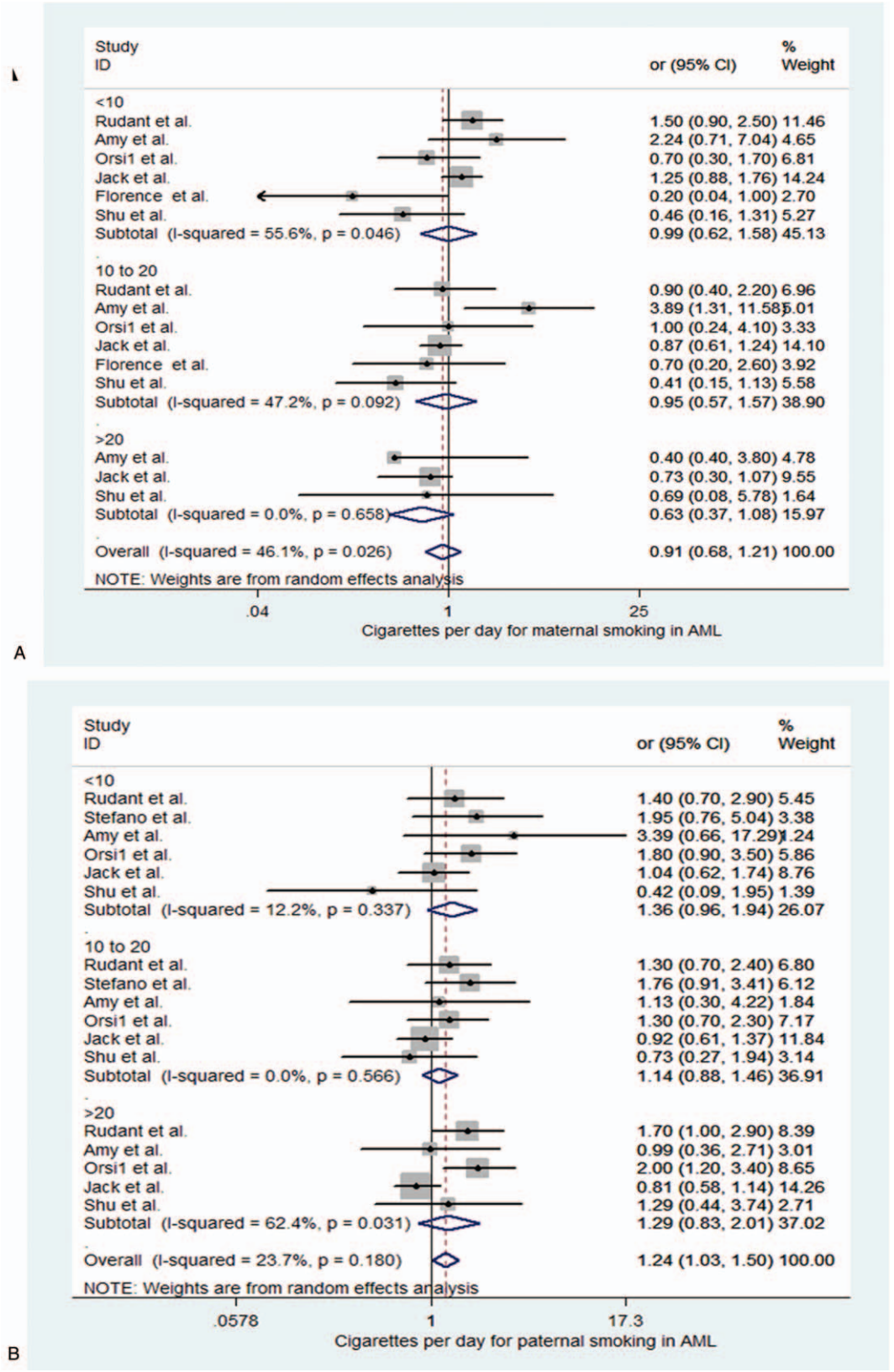

Figure 5. Forest plot depict childhood acute lymphoblastic leukemia with parental cigarettes daily consumption during pregnancy. (A) Cigarettes per day for maternal smoking in acute myeloid leukemia (AML). (B) Cigarettes per day for paternal smoking in AML.

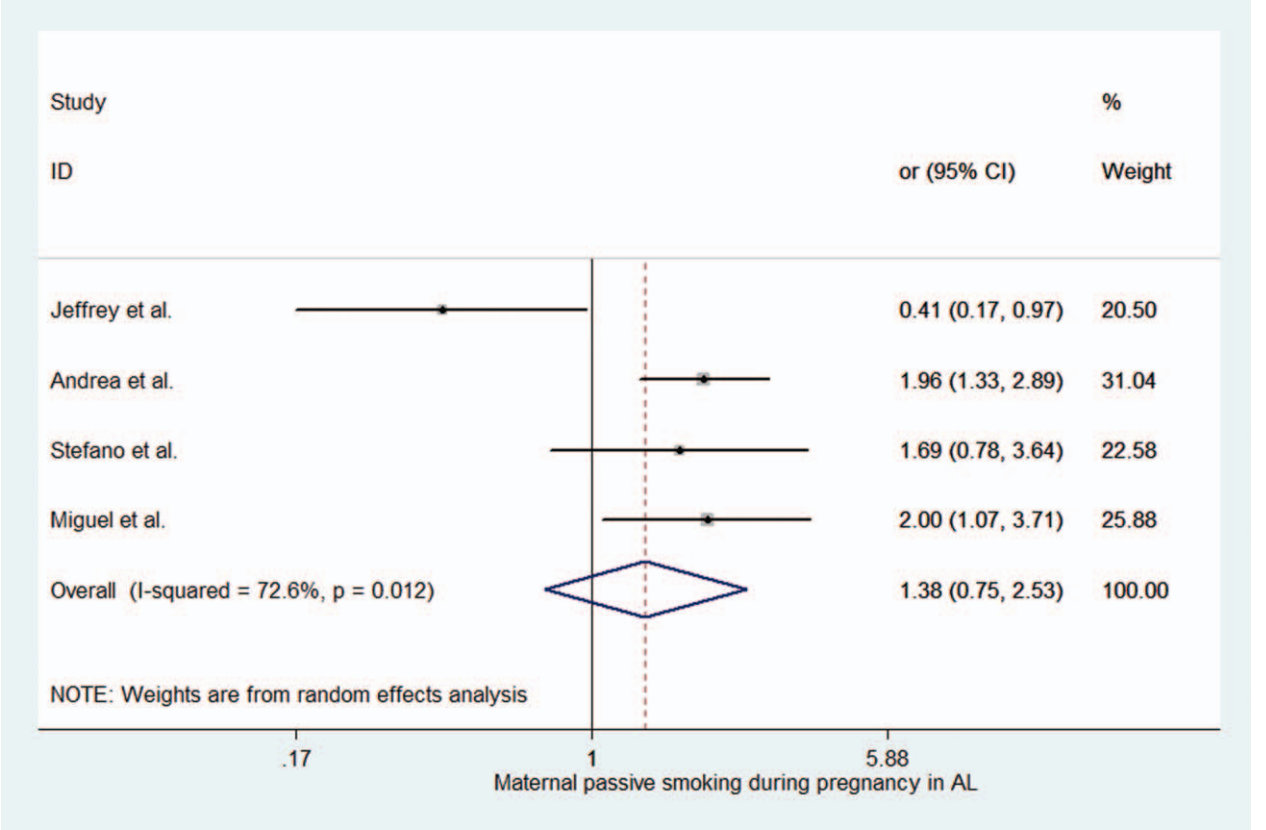

Figure 6. Forest plot depiction of maternal passive smoking during pregnancy in acute lymphoblastic leukemia.

maternal smoking exposure.[28] Milne et al demonstrated that maternal smoking was not increased the risk of childhood ALL.[20] Our data showed that maternal smoking before, during, or after pregnancy was not associated with childhood ALL.

Several studies examined the potential association between childhood leukemia and tobacco. Active maternal smoking during pregnancy has been associated with a higher risk of behavior disorders in children.[34] An United Kingdom Childhood Cancer Study showed that a statistically significant increased risk of developing hepatoblastoma was found in children whose mothers smoked preconceptionally (OR = 2.68, $P = .02$) and strongest for both parents smoking (OR = 4.74, $P = .003$).[27] Our findings suggested only maternal preconception subgroups was a slightly trend with childhood ALL.

In AML, a study showed that maternal smoking during pregnancy was negatively associated with infant leukemia AML risk (OR = 0.45, 95% CI = 0.21–0.96).[26] Brondum et al showed that maternal smoking was no significant risk of AML (OR = 0.95, 95% CI 0.74–1.22).[29] Our data showed that maternal smoking before, during, or after pregnancy was not associated with childhood AML, by which did not elevate risk for either AML.

Next, Menegaux et al demonstrated that no association with parental smoking, either maternal or paternal, was observed with ALL.[11] However, a national registry-based case–control study ESCALE was carried out in France, which was paternal smoking significantly associated with childhood ALL (OR = 1.4, 95% CI 1.1–1.7), AML (OR = 1.5, 95% CI 1.0–2.3),[14] by which it was related to an elevated risk of ALL.[27] Our results showed that paternal smoking was related to a significantly elevated risk of childhood ALL, but for AML, in which was no significance.

Interestingly, Milne et al demonstrated that the OR for paternal smoking of 15 cigarettes per day around the time of the child's conception was 1.35 (95% CI 0.98–1.86).[20] Orsi et al study showed that preconception paternal daily smoking consumption was significantly associated with ALL (OR = 1.2, CI 1.1–1.5) and AML (OR = 1.5, CI 1.0–2.3).[24] Our data showed that paternal daily smoking consumption during pregnancy was observed a significant association with ALL and AML.

Table 4

Maternal passive smoking during pregnancy in childhood ALL.

		Pooled data (fixed)			Heterogeneity test	
Stage	**No. of studies**	**OR**	**95% CI**	***P*-value**	**I^2 (%)**	***P*-value**
Maternal passive smoking	4	1.383	0.755–2.533	.294	72.60%	.012

ALL = acute lymphoblastic leukemia, CI = confidence interval, OR = odds ratio.

An Australian Study of Causes of ALL study showed that a heavier paternal smoking around the time of conception is a risk factor for childhood ALL (OR = 1.15, 95% CI 1.06–1.24) for any paternal smoking around the time of the child's conception and for smoking 20 cigarettes per day at that time (OR = 1.44, 95% CI 1.24–1.68).[20] Results were broadly in line with those of previous studies. Our analysis did supported a productive evidence that the higher paternal tobacco daily consumption, the higher was the risk of childhood ALL. A heavier smoking does appear to increase this risk. At the same time, the high correlation paternal daily smoking consumption was related with ALL between pregnancy and postnatal paternal smoking. Our findings indicate that both the timing and dose of paternal smoking are important in influencing risk of childhood ALL and AML.

Consistent with most previous studies,[38] there were no association between maternal daily smoking consumption and risk of childhood ALL or AML during pregnancy. Maternal daily smoking consumption during pregnancy was negatively associated with childhood AML or ALL. Meanwhile, in most past studies on passive smoke exposure of children and risk of AnLL, most findings were negative.[39] Our results for maternal passive smoke also suggested a negative association with ALL.

Our study also have several limitations: the present study is more likely to be subject to reporting bias because of increased public awareness of adverse effects of smoking and blinding parents with respect to the study hypothesis regarding smoking was impracticable. These data were collected at a time when there was little pressure on mothers to stop smoking during pregnancy and therefore less liability to bias. More importantly, since smoking is such a well-known risk factor for cancer and for unfavorable pregnancy outcomes, the possibility of guilt feelings leading to underreporting, especially in case mother, must be considered. Next, childhood leukemia is a heterogeneous disease and epidemiologic studies of childhood leukemia can be greatly improved by grouping childhood leukemia into more homogeneous groups by molecular techniques and assess gene–environment interaction.

5. Conclusion

Our study supports that paternal smoking is associated with the risk of childhood ALL and AML during pregnancy, but not for maternal smoking. Further studies are needed to confirm the association of paternal smoking with increased risk of childhood ALL in offspring.

Author contributions

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