Environmental Science and Pollution Research (2021) 28:35376–35391
https://doi.org/10.1007/s11356-021-14053-8

REVIEW ARTICLE

Exposure to outdoor air pollution at different periods and the risk of leukemia: a meta-analysis

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Received: 5 January 2021 / Accepted: 19 April 2021 / Published online: 19 May 2021

Abstract

The causes of leukemia remain largely unknown; our aims were to examine the association between the exposure to outdoor air pollution and leukemia risk and to explore the effect of this exposure during different periods of pregnancy and early life. We searched for all case–control and cohort studies published before February 20, 2021, which measured the risk of leukemia in relation to exposure to the air pollutants: particulate matter, benzene, nitrogen dioxide (NO_2), and nitrogen oxides (NO_x). We then carried out a meta-analysis and calculated the summary relative risks (RRs) of leukemia by using a random-effects model. The potential dose–response relationship was further explored. The results showed that the highest exposure to benzene (RR: 1.20, 95%CI: 1.06–1.35) and NO_2 (RR: 1.04, 95%CI; 1.02–1.08) were positively correlated with leukemia risk when compared to the lowest exposure categories for each air pollutant. During pregnancy, exposure to benzene in the third trimester, as well as exposure to NO_2 in the second trimester and entire pregnancy, could also increase the risk of leukemia. In the dose–response analysis, benzene exposure and NO_2 exposure were linearly associated with the risk of leukemia. Other air pollutants did not have a statistical correlation with leukemia risk. There was a certain degree of publication bias in studies on benzene. Overall, our results support a link between outdoor air pollution and leukemia risk, particularly due to benzene and NO_2. Prospero Registration Number: PROSPERO CRD42020207025.

Keywords Leukemia · Outdoor air pollution · Meta-analysis · Cancer · Epidemiology · Systematic review

Introduction

Leukemia is a common cancer not only among adults (Rosenberg et al. 2012) but also among children and adolescents. In the recent years, the incidence of leukemia and the number of patients seeking medical advice showed an upward trend (Barrington-Trimis et al. 2017; Isaevska et al. 2017). Although the causes of leukemia remain largely unknown, some studies have suggested that exposure to outdoor air pollution is one of the risk factors for leukemia (Konstantinoudis et al. 2020; Metayer et al. 2016; Schraufnagel et al. 2019). Additionally, according to WHO's report, air pollution is a major environmental health problem affecting low-, middle-, and high-income countries. Recently published studies have inconsistent results; a case–control study suggested that their results did not support the relationship between outdoor air pollution and leukemia (Peckham-Gregory et al. 2019). The effects of different exposure periods on leukemia are different. Two meta-analyses showed that the risk estimates were generally higher for exposures that happened during the postnatal period compared to the prenatal period (Filippini et al. 2019; Filippini et al. 2015). However, a cohort study showed different results which suggested that postnatal exposure was not associated with leukemia, whereas prenatal exposure could lead to leukemia (Lavigne et al. 2017). The prenatal period was further divided into three exposure windows, such as the first trimester, second trimester, and third trimester. One study showed that only exposure to air pollution in the second trimester could increase the risk of leukemia (Ghosh et al. 2013), and another study suggested that only exposure to air pollution in the first trimester was associated with the risk of leukemia (Lavigne

Responsible Editor: Lotfi Aleya

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et al. 2017). In addition, a study showed that exposure to air pollutants could initiate leukemia in utero by causing chromosomal rearrangements and mutations that are on the causal pathway to these malignancies in fetal hematopoietic stem cells (Carlos-Wallace et al. 2016). Given that a number of the most recent studies assessed more time windows of exposure, an updated review and meta-analysis are warranted.

Methods

Search strategy

We performed a systematic search in the PubMed and Web of Science databases from inception to February 20, 2021. Keywords included air pollution, traffic-related pollution, particulate matter, benzene, nitrogen dioxide, nitrogen oxides, outdoor air pollution, air pollutants, outdoor air pollutants, leukemia, childhood leukemia, adult leukemia, acute lymphoblastic leukemia, acute myeloid leukemia, chronic leukemia, chronic myeloid leukemia, and chronic lymphoblastic leukemia. Full details on the related database search strings are reported in Supplementary Table S1. We also searched the reference lists of eligible studies and checked which other articles cited the eligible studies. The protocol for this meta-analysis can be found in the International Prospective Register of Systematic Reviews (PROSPERO), the registration number is CRD42020207025.

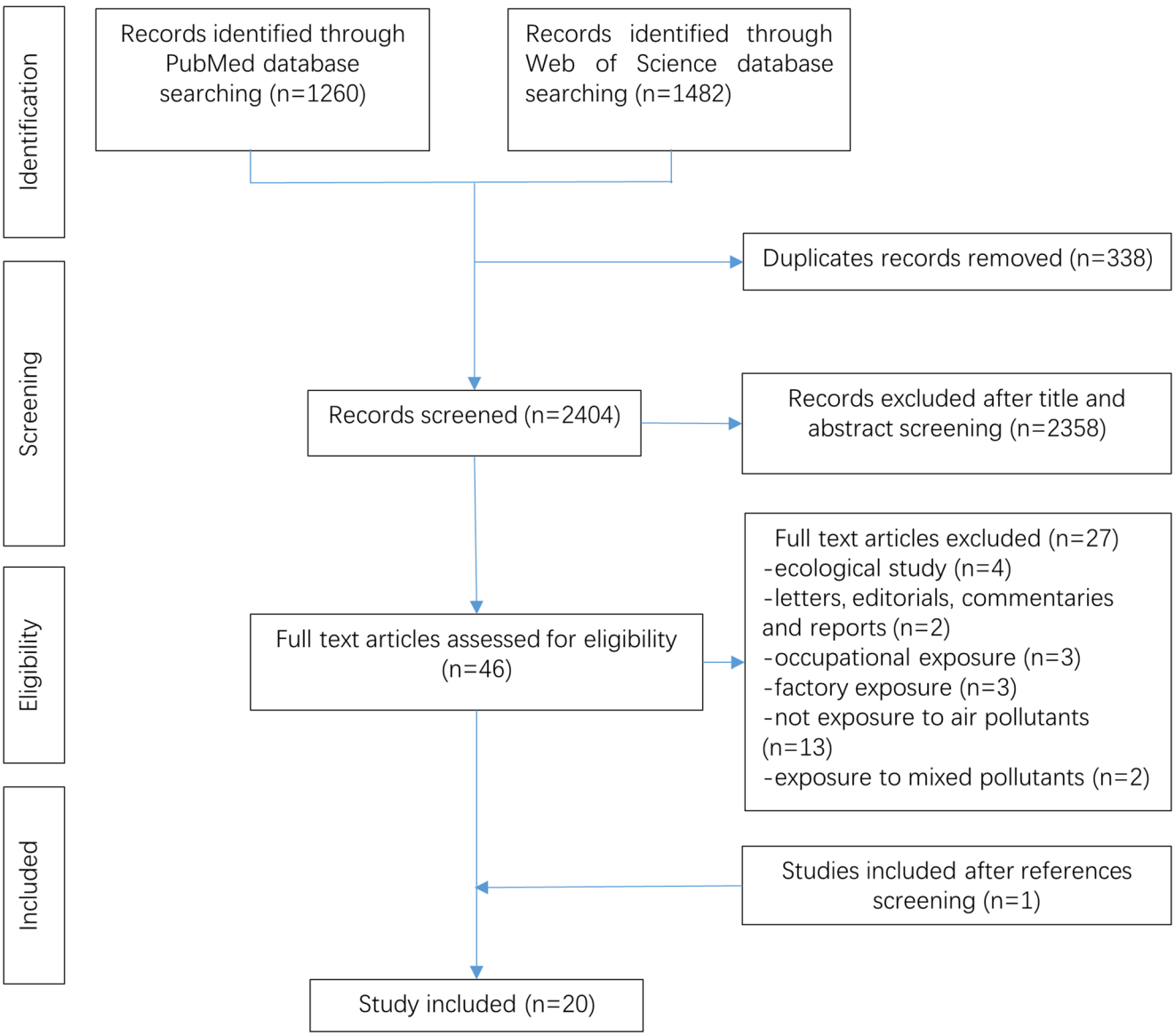


Fig. 1 Flowchart of study selection

Table 1 Characteristics of the included studies

Reference	Country	Study period	Study design	Cases/controls	Age (y)	Type of air pollutant	Type of cancer	Exposure period	Statistical analysis	Matching variables	NOS stars
Hvidtfeldt et al. (2020)	Denmark	1981–2013	Case–control study	1295(1030LL+193AML)	<20	$PM_{2.}$ NO_2	Leukemia (LL+AML)	Residence at diagnosis	Conditional logistic regression	Sex, birth month and year	9
Puett et al. (2020)	Denmark	1989–2014	Case–control study	13602(547ALL+7402CLL+4220AML+1433CML) / 51624	≥20	$PM_{2.5}$ NO_2	Leukemia (ALL+CLL+AML+CML)	Residence at diagnosis	Conditional logistic regression	Sex, birth month and year	9
Taj et al. (2020)	Denmark	1989–2014	Case–control study	13590(545ALL+7398CLL+4216AML+1431CML) / 46992	≥20	$PM_{2.5}$	Leukemia (ALL+CLL+AML+CML)	Residence at diagnosis	Conditional logistic regression	Sex, birth month and year	9
Raaschou-Nielsen et al. (2018)	Denmark	1968–1991	Case–control study	852 (727ALL+125AML) / 5428	0–14	Benzene	ALL+AML	Entire pregnancy, residence at diagnosis	Conditional logistic regression	Age, sex and calendar time	9
Lavigne et al. (2017)	Canada	1988–2012	Cohort study	941 (849ALL+92AML) / 2350898 (total cohort)	0–5	$PM_{2.5}$ NO_2	ALL+AML	1st trimester, 2nd trimester, 3rd trimester, entire pregnancy, child's 1st year	Cox proportional hazards models	None	9
Janitz et al. (2017)	USA	1997–2012	Case–control study	307 (228ALL+79AML) / 1013	0–19	Benzene	Leukemia (ALL+AML)	Residence at birth	Conditional logistic regression	Week of birth	8
Symanski et al. (2016)	USA	1995–2011	Case–control study	1248 / 12172	0–4	Benzene	ALL	Residence at birth	Mixed-effects logistic regression model	Birth year and month	9
Raaschou-Nielsen et al. (2016)	Denmark	1992–2010	Case–control study	1967 / 3381	30–84	NO_2 NO_x	ALL+AML+CML	Residence at diagnosis	Conditional logistic regression	Sex and year of birth	9
Janitz et al. (2016)	USA	1997–2012	Case–control study	307 / 1013	0–19	NO_2	Leukemia (ALL+AML)	Residence at birth	Conditional logistic regression	Week of birth	8
Houot et al. (2015)	France	2002–2007	Case–control study	517 (425ALL+92AML) / 6147	0–14	NO_2 Benzene	ALL+AML	Residence at diagnosis	Unconditional logistic regression	None	8
Heck et al. (2014)	USA	1990–2007	Case–control study	115 (69ALL+46AML) / 19209	0–5	Benzene	ALL+AML	1st trimester, 2nd trimester, 3rd trimester, entire pregnancy, child's first year	Unconditional logistic regression	Year of birth	8
Badaloni et al. (2013)	Italy	1998–2001	Case–control study	747 / 1509	0–10	NO_2 PM_{10} $PM_{2.5}$	Leukemia	Residence at birth	Unconditional logistic regression	Birth date, sex and region of residence	6

Table 1 (continued)

Reference	Country	Study period	Study design	Cases/controls	Age (y)	Type of air pollutant	Type of cancer	Exposure period	Statistical analysis	Matching variables	NOS stars
Ghosh et al. (2013)	USA	1998–2008	Case–control study	1563 (1346ALL+ 217AML) / 80658	0–5	NO_2 NO_x	ALL+AML	1st trimester, 2nd trimester, 3rd trimester, entire pregnancy	Unconditional logistic regression	Year of birth	9
Heck et al. (2013)	USA	1998–2007	Case–control study	1509 (1280ALL+ 229AML) / 80224	0–5	$PM_{2.5}$	ALL+AML	Entire pregnancy	Unconditional logistic regression	Year of birth	8
Vinceti et al. (2012)	Italy	1998–2009	Case–control study	83 / 332	0–14	PM_{10} Benzene	Leukemia (ALL+ AML)	Residence at diagnosis	Conditional logistic regression	Sex, year of birth and residence province	9
Amigou et al. (2011)	France	2003–2004	Case–control study	763 (645ALL+ 118AML) / 1681	0–14	NO_2	Leukemia (ALL+ AML)	Residence at diagnosis	Unconditional logistic regression	Sex and age	8
Weng et al. (2008)	China	1995–2005	Case–control study	308 / 308	0–14	NO_2	Leukemia	Residence at diagnosis	Conditional logistic regression	Sex, year of birth and year of death	8
Crosignani et al. (2004)	Italy	1978–1997	Case–control study	120/480	0–14	Benzene	Leukemia	Residence at diagnosis	Conditional logistic regression	Sex and date of birth	9
Raaschou-Nielsen et al. (2001)	Denmark	1968–1991	Case–control study	955 / 1891	0–14	Benzene NO_2	Leukemia	Entire pregnancy	Conditional logistic regression	Age, sex and calendar time	9
Feychting et al. (1998)	Sweden	1960–1985	Case–control study	23 / 91	0–15	NO_2	Leukemia	Residence at diagnosis	Conditional logistic regression	Year of birth, lived in the same parish during the year of diagnosis	8

ALL, acute lymphoblastic leukemia; *AML*, acute myeloid leukemia; *CLL*, chronic lymphoblastic leukemia; *CML*, chronic myeloid leukemia; *NO_2*, nitrogen dioxide ; *NOx*, nitrogen oxides; *PM*, particulate matter; *LL*, lymphoblastic leukemia

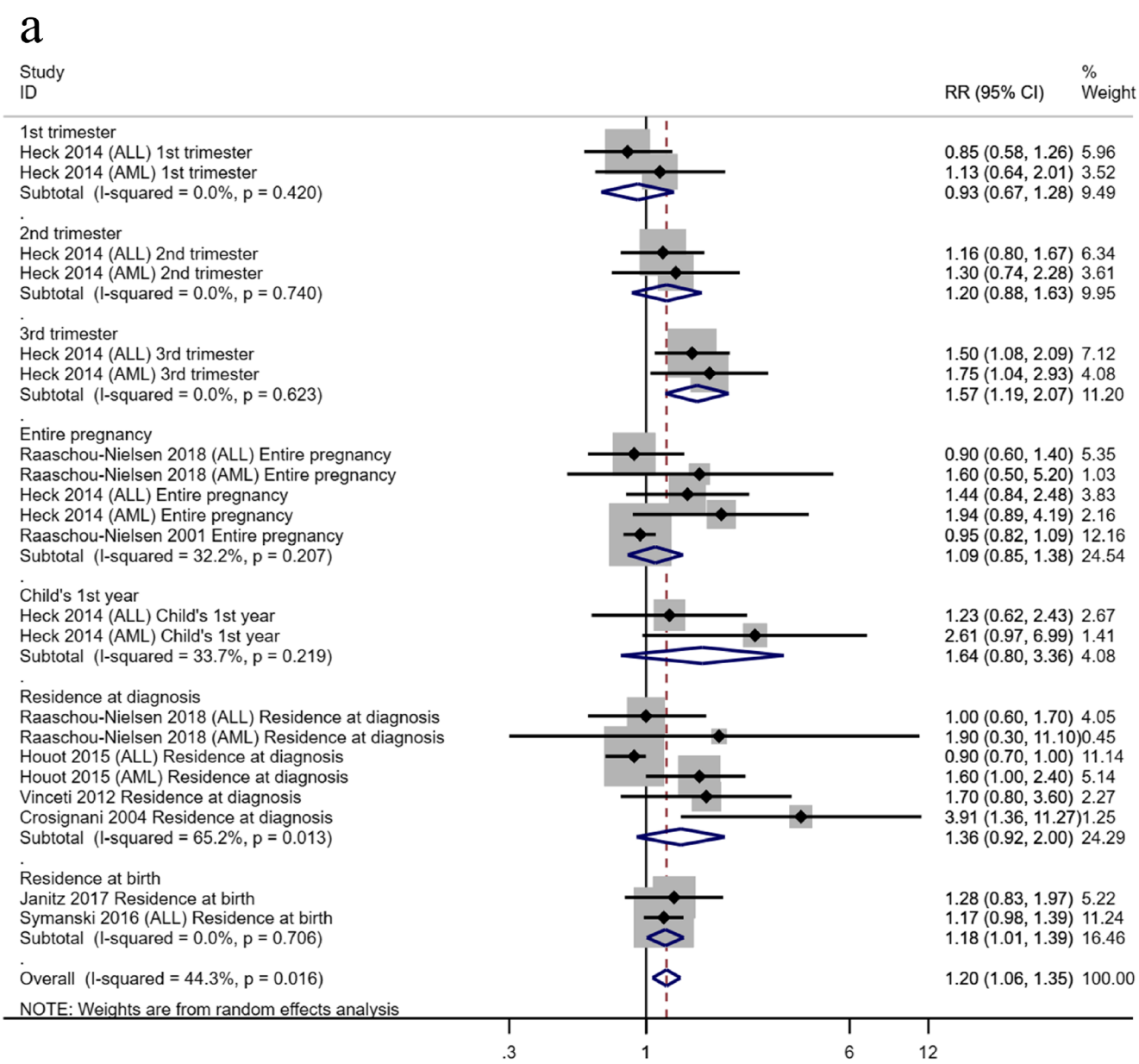


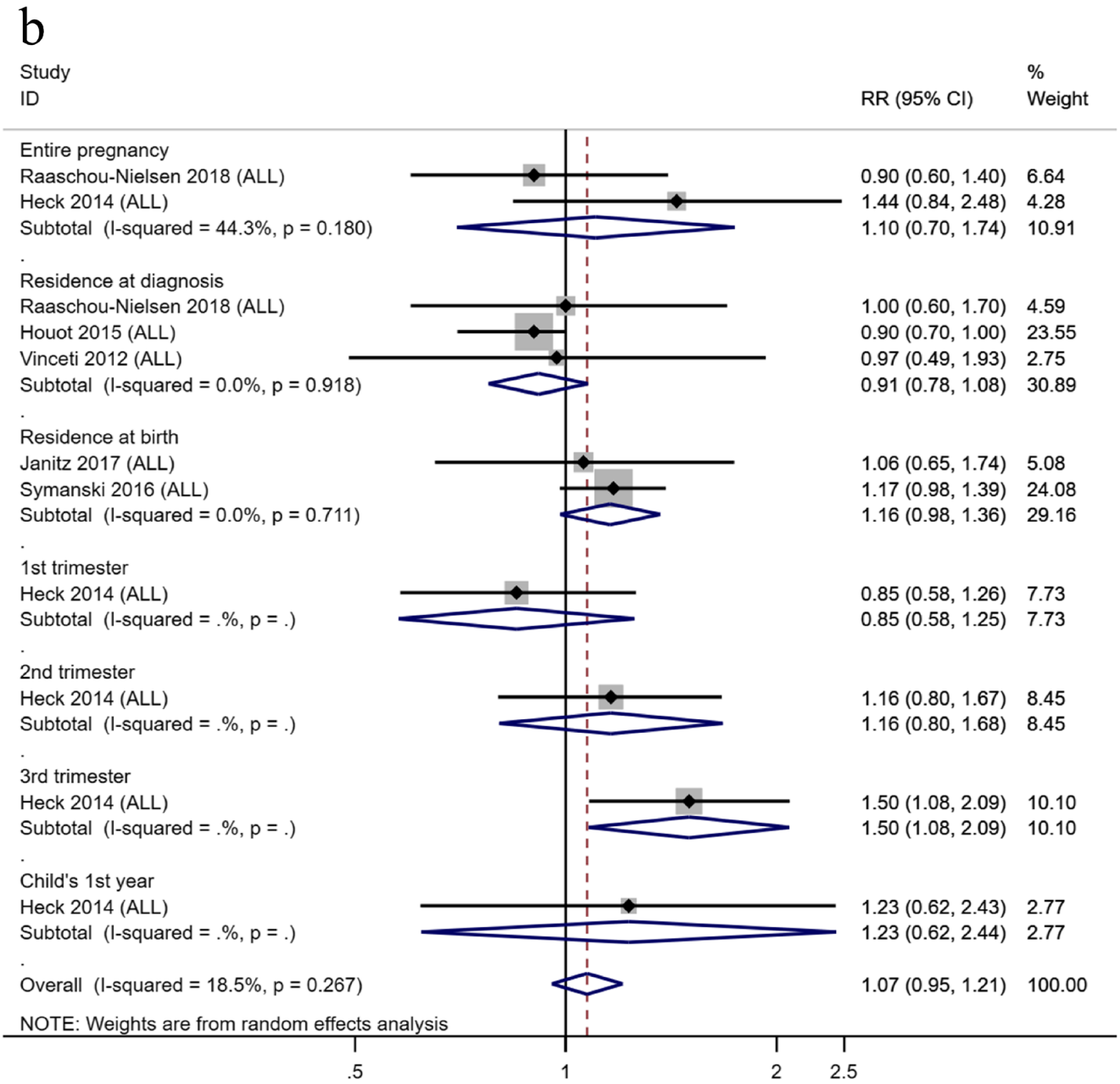
Fig. 2 Forest plot of included studies of benzene exposure and leukemia. **a** All studies of benzene exposure; **b** studies of benzene exposure and acute lymphoblastic leukemia; and **c** studies of benzene exposure and acute myeloid leukemia

Study selection

Inclusion criteria were (a) epidemiologic case–control or cohort studies, (b) any type of assessment of exposure to outdoor air pollutants, and (c) reporting of risk estimates or ability to compute them from the reported data. Exclusion criteria included (a) ecologic study design, (b) exposure assessment limited to only occupational activities, (c) exposure assessment limited to only factory emissions, and (e) editorials, letters, commentaries, and reports.

Data extraction and quality assessment

Two authors independently extracted the data. Any disagreement was resolved through discussion until a consensus was reached or by consulting a third author. We extracted information on author, year of publication, country, study period, sample size, study design, age, air pollutant, type of leukemia, exposure window, matching variables, and statistical methods. We categorized these exposure periods into 7 time frames: first trimester, second trimester,



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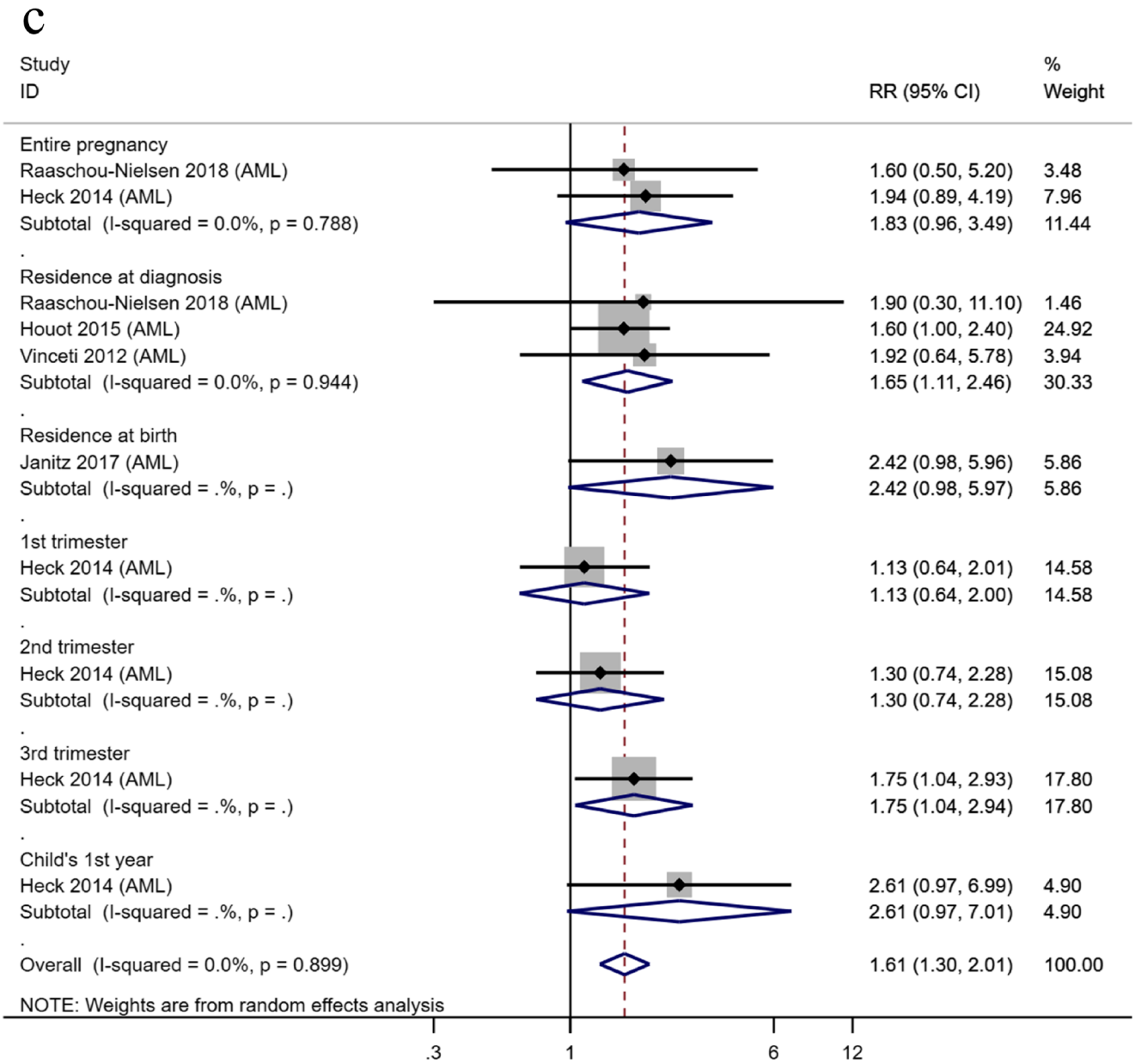
third trimester, entire pregnancy, child's first year, residence at birth, and residence at diagnosis. The Newcastle-Ottawa Scale (NOS) was used to assess the quality of each included study. Each study was judged based on three broad perspectives: the selection of the study groups; the comparability of the groups; and the ascertainment of the outcome of interest for case–control or cohort studies, respectively. A higher score indicates that the study is of a higher quality GA Wells et al. (2019).

Exposure assessment methods

In our meta-analysis, the ranges of exposure levels for most studies were roughly comparable, although cut-points for the highest level of exposure identification differed across the various studies to some extent. We extracted relative risks (RRs) for each category of air pollutant exposure from all studies, by abstracting the odds ratios (ORs) from 15 studies (Hvidtfeldt et al. 2020; Puett et al. 2020; Taj et al. 2020; Janitz et al. 2017;



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Symanski et al. 2016; Raaschou-Nielsen et al. 2016; Janitz et al. 2016; Houot et al. 2015; Heck et al. 2014; Heck et al. 2013; Ghosh et al. 2013; Badaloni et al. 2013; Vinceti et al. 2012; Amigou et al. 2011; Weng et al. 2008) and hazard ratios (HRs) or rate ratios (RRs) from 5 studies (Raaschou-Nielsen et al. 2018; Lavigne et al. 2017; Crosignani et al. 2004; Raaschou-Nielsen et al. 2001; Feychting et al. 1998), as also used in previous review (Filippini et al. 2019). For the dose–response analysis, except for the above information, the median or mean exposure level was also abstracted. When the mean (or median) of an exposure strata was not directly reported, we calculated the midpoint of reported upper and lower boundaries. If the category of exposure had an open interval, we entered a value that was 20% higher or lower than the closest cut point (Filippini et al. 2019).

Statistical analysis

We used a random-effects model to calculate the summary RR and 95% confidence intervals (CIs) to provide an overall estimate of the strength of the association between air pollution and the leukemia outcome during different exposure periods, comparing the highest and lowest exposure categories for each metric of interest. Furthermore, we conducted stratified analyses by leukemia subtype (ALL and AML).

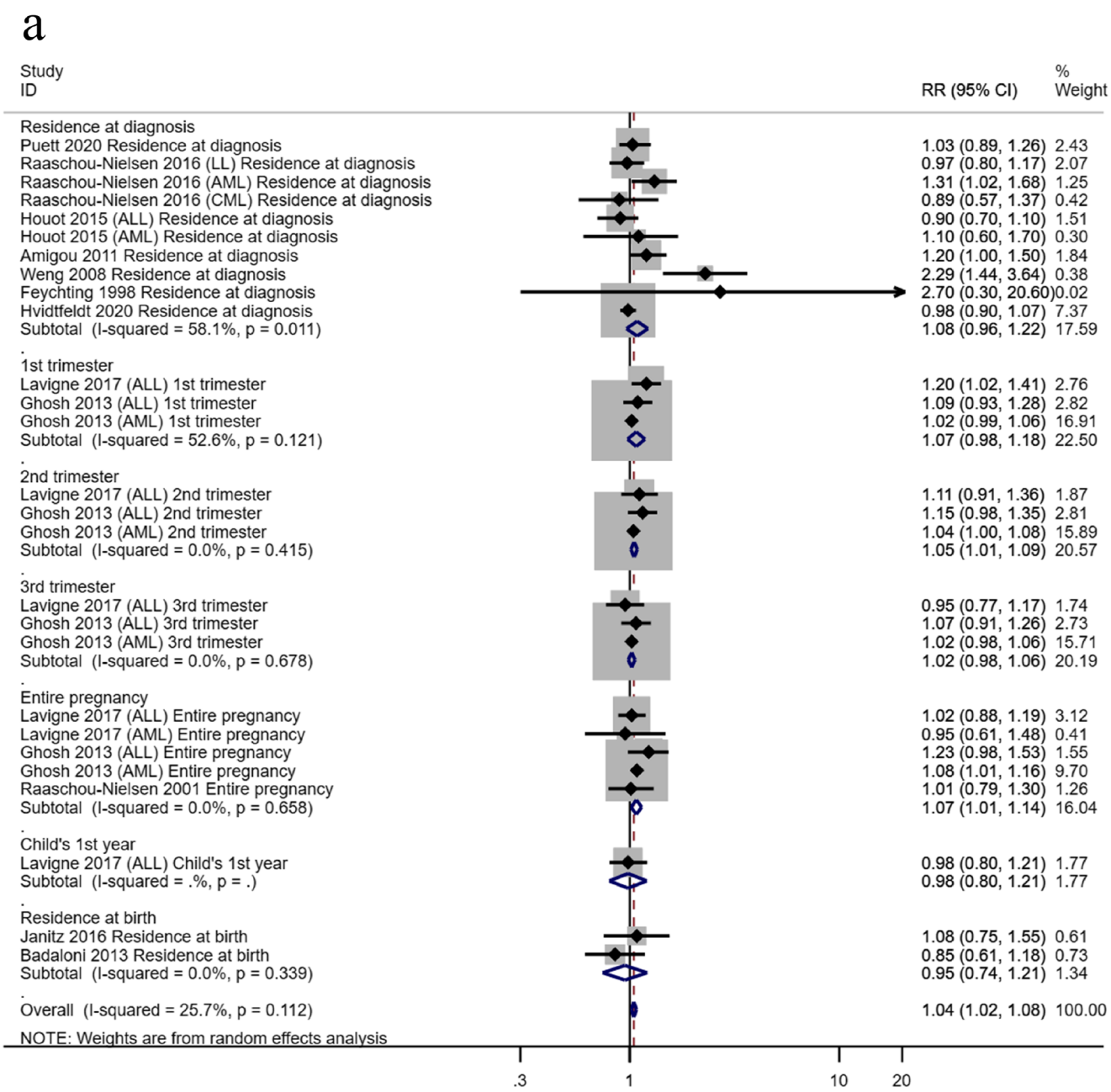
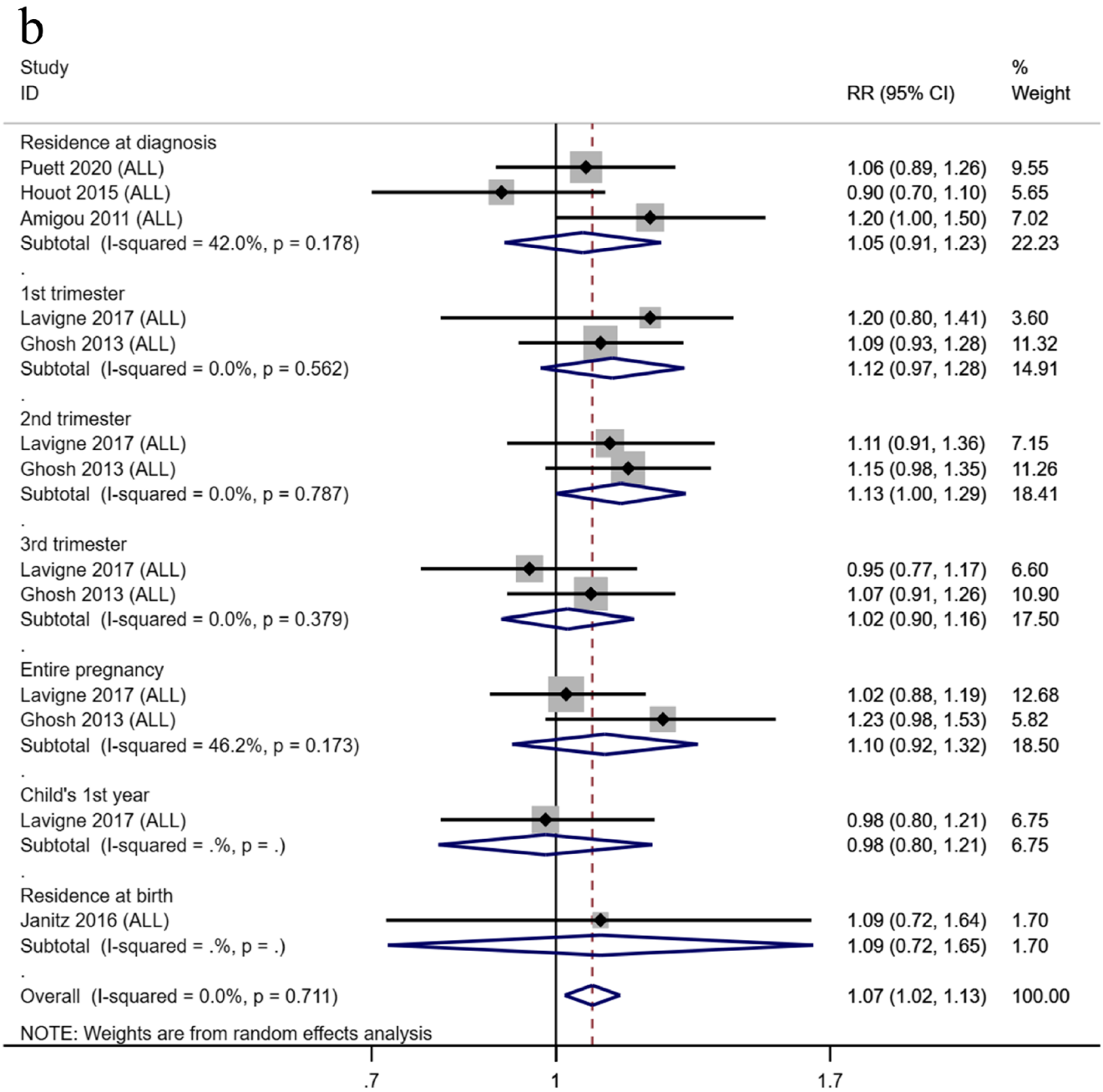


Fig. 3 Forest plot of included studies of NO_2 exposure and leukemia. **a** All studies of NO_2 exposure; **b** studies of NO_2 exposure and acute lymphoblastic leukemia; and **c** studies of NO_2 exposure and acute myeloid leukemia

For dose–response analysis, we performed a two-stage random-effects dose–response meta-analysis (Orsini et al. 2012). In the first stage, a restricted cubic spline model with three knots at the 25th, 50th, and 75th centiles of the exposure distribution was estimated using generalized least square regression. Then the study-specific estimates were combined using the restricted maximum likelihood method in a multivariate random-effects meta-analysis (Sun et al. 2018; Orsini et al. 2012). The *P* value for nonlinearity was assessed by testing the null hypothesis that the coefficient of the second spline equals to zero (Zhang et al. 2020). Initially, a nonlinear model was applied if model verification indicated significance ($P < 0.05$), otherwise, a linear model was adopted (Lu et al. 2016).

We used the Q test and I^2 statistic to assess the heterogeneity. Furthermore, we used Egger's test to assess publication bias. If there had the publication bias, we would use the trim and fill method to test whether the publication bias affected the results (Duval and Tweedie 2000). All data analyses were conducted using the STATA/SE software, version 15, and *P* values were two-sided. $P<0.05$ indicated a statistically significant result.



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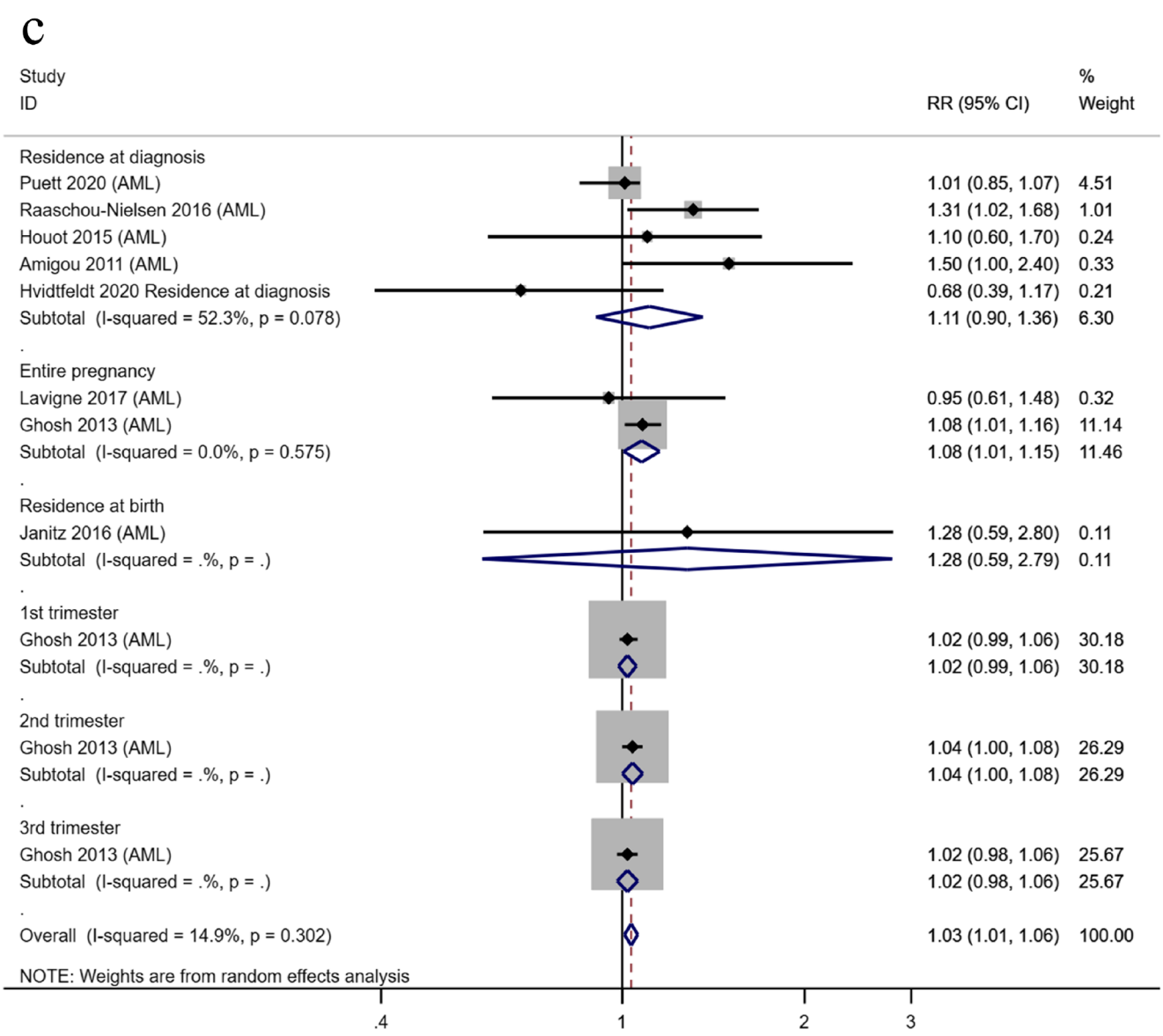
Results

We identified 2742 studies from the PubMed and Web of Science databases. Three hundred and thirty-eight studies were duplicates, leaving 2404 studies for title and abstract screening. After screening, forty-six studies needed to be assessed for their eligibility. Twenty-seven studies were excluded with reasons, and the remaining nineteen articles. After screening the reference lists of eligible studies and checked the articles cited the eligible studies, 1 study was included. Finally, 20 studies were included in our meta-analysis. Figure 1 shows the flowchart of study selection.

Table 1 shows the characteristics of the included studies, 19 studies were case–control studies, and 1 study was a cohort study. The study period ranged from 1968 to 2014. Seventeen studies included children aged under 20 years at diagnosis. Air pollutants included in these studies were the following: nitrogen dioxide (NO_2) (n=12), benzene (n=8), fine particulate matter ($PM_{2.5}$) (n=6), inhalable particles (PM_{10}) (n=2), and nitrogen oxides (NO_X) (n=2). Twelve studies were conducted in Europe, six studies in the USA,



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one in Canada, and one in Taiwan, China. Twelve studies used conditional logistic regression, six studies used unconditional logistic regression, one study used the mixed-effects logistic regression model, and the cohort study used the Cox proportional hazards models. The total score of the NOS scale was 9. For included studies, the median value of the NOS scale was 8, which meant that these studies were of good quality and had a low risk of bias. The detail of NOS scale scores of included studies were reported in Supplementary Table S2.

Figure 2a shows that exposure to benzene was a risk factor for leukemia, (RR: 1.20, 95%CI: 1.06–1.35). Additionally, in subgroup analysis, when the exposure period was taken into account, exposure in the 3rd trimester and exposure associated with the residence at birth was correlated with leukemia risk. Figure 3a demonstrates the exposure period subgroup meta-analysis for leukemia, which indicates that there was a positive correlation between NO_2 and leukemia risk (RR: 1.04, 95%CI; 1.02–1.08), especially in the 2nd trimester and entire pregnancy. There was no significant correlation between the $PM_{2.5}$, NO_X, and leukemia risk (Figs. 4a and 5). For PM_{10}, there were insufficient results to conduct a meta-analysis (n=2). Heterogeneity between studies on benzene, NO_2, NO_X, and $PM_{2.5}$ were 44.3%, 25.7%, 43.2%, and 30.9%, respectively. Both studies on the relationship between PM_{10} and leukemia showed that there was no significant correlation between exposure to PM_{10} and leukemia risk, either at the birth address or at the diagnosis address (Badaloni et al. 2013; Vinceti et al. 2012).

In the stratified analyses results of disease subtypes, we found that summary RR estimates differ markedly for benzene

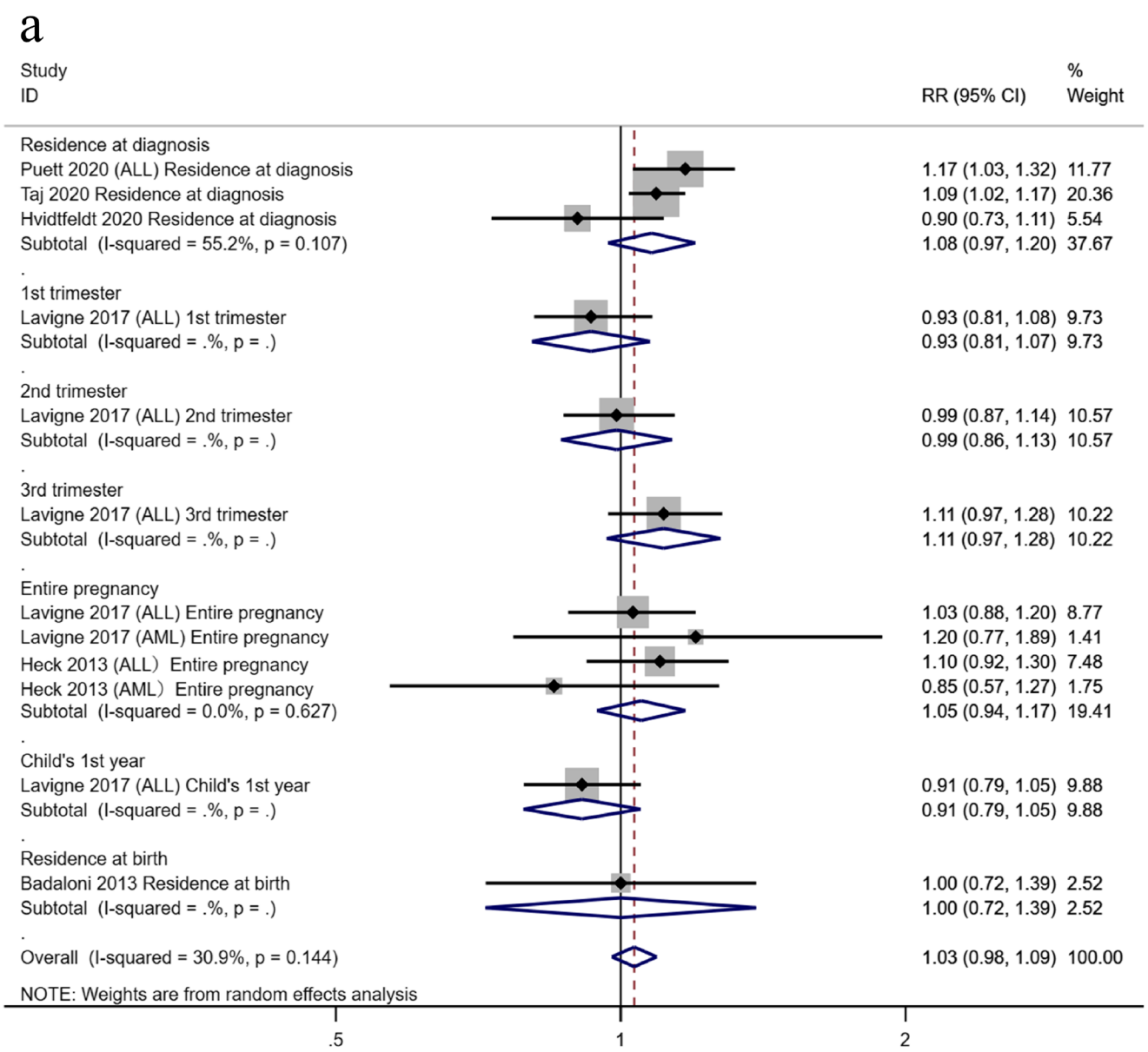
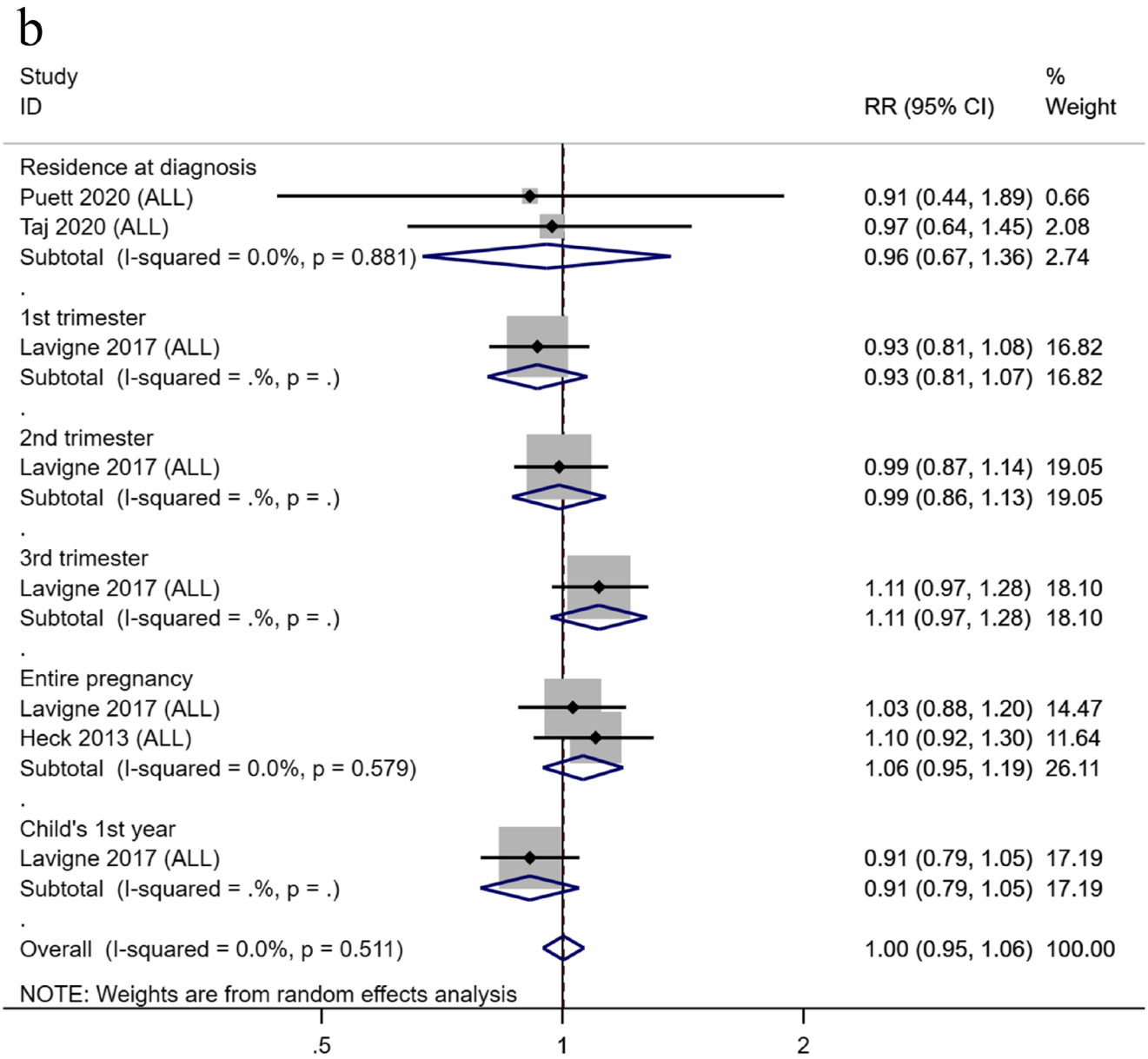


Fig. 4 Forest plot of included studies of $PM_{2.5}$ exposure and leukemia. **a** All studies of $PM_{2.5}$ exposure; **b** studies of $PM_{2.5}$ exposure and acute lymphoblastic leukemia; and **c** studies of $PM_{2.5}$ exposure and acute myeloid leukemia

and $PM_{2.5}$ exposures. For benzene, when we limited the studies enrolling only the ALL subtype, we estimated a summary RR of 1.07 (95% CI: 0.97–1.17) with I^2=18.5% (Fig. 2b) while for the AML subtype, a summary RR of 1.61 (95% CI: 1.30–2.01) with I^2=0.0% (Fig. 2c) was observed. No such change in RR according to leukemia subtype was found for NO_2 and $PM_{2.5}$.

In the dose–response meta-analysis, for benzene (Raaschou-Nielsen et al. 2018; Janitz et al. 2017; Vinceti et al. 2012; Crosignani et al. 2004), there was a linear increase in estimated risk (P for nonlinearity=0.654). The RR of leukemia was 1.02 (95%CI: 0.99–1.05) for every 1 μg/m^3 increment in benzene exposure (Fig. 6). A linear relationship was also found between NO_2 exposure (Janitz et al. 2016; Amigou et al., 2011; Weng et al. 2008; Feychting et al. 1998) and the risk of leukemia (P for nonlinearity=0.598). The RR of leukemia was 1.19 (95%CI: 1.07–1.32) for per 10 μg/m^3 increment in NO_2 exposure (Fig. 7).

Publication bias was found in studies which estimated the risk of exposure to benzene by Egger's test (P=0.001, Supplementary Table S3). We then used the trim and fill method to test the effect of publication bias on the results (Supplementary Fig. S1). The results of the trim and fill analysis indicated that the summary effects of benzene showed a change to RR=1.11 (95%CI: 0.98–1.26). Publication bias was not observed in studies on NO_2, NO_X, $PM_{2.5}$, and PM_{10} (Supplementary Table S3).



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Discussion

Our meta-analysis indicated that outdoor air pollution could increase the risk of leukemia, especially with exposure to benzene and NO_2. When the exposure time window was divided into 7 periods, we found that exposure at different periods might cause different outcomes. An exposure to benzene in the 3rd trimester of pregnancy, residence at birth exposure, as well as exposure to NO_2 in the 2nd trimester and entire pregnancy, might increase the risk of leukemia. The results from our subgroup studies suggested benzene exposure has different effects on the two subtypes of leukemia which could increase the risk of AML, not ALL. The dose–response analyses showed that there was a linear correlation between benzene exposure and leukemia risk. And NO_2 exposure was also linearly associated with risk of leukemia. We found that increase of NO_2 exposure contributed to elevated leukemia risk significantly.

In the meta-analyses, Egger's test and the trim and fill method showed that studies which focused on benzene had a publication bias. The occurrence and potential influence of publication bias is very difficult to assess (Filippini et al. 2015). The heterogeneity between studies and the number of studies could influence the asymmetry of the funnel plot (Sterne et al. 2011). Exposure time windows, leukemia types (ALL or AML), and cutoffs for exposure categories are used in different studies to some extent are the causes of

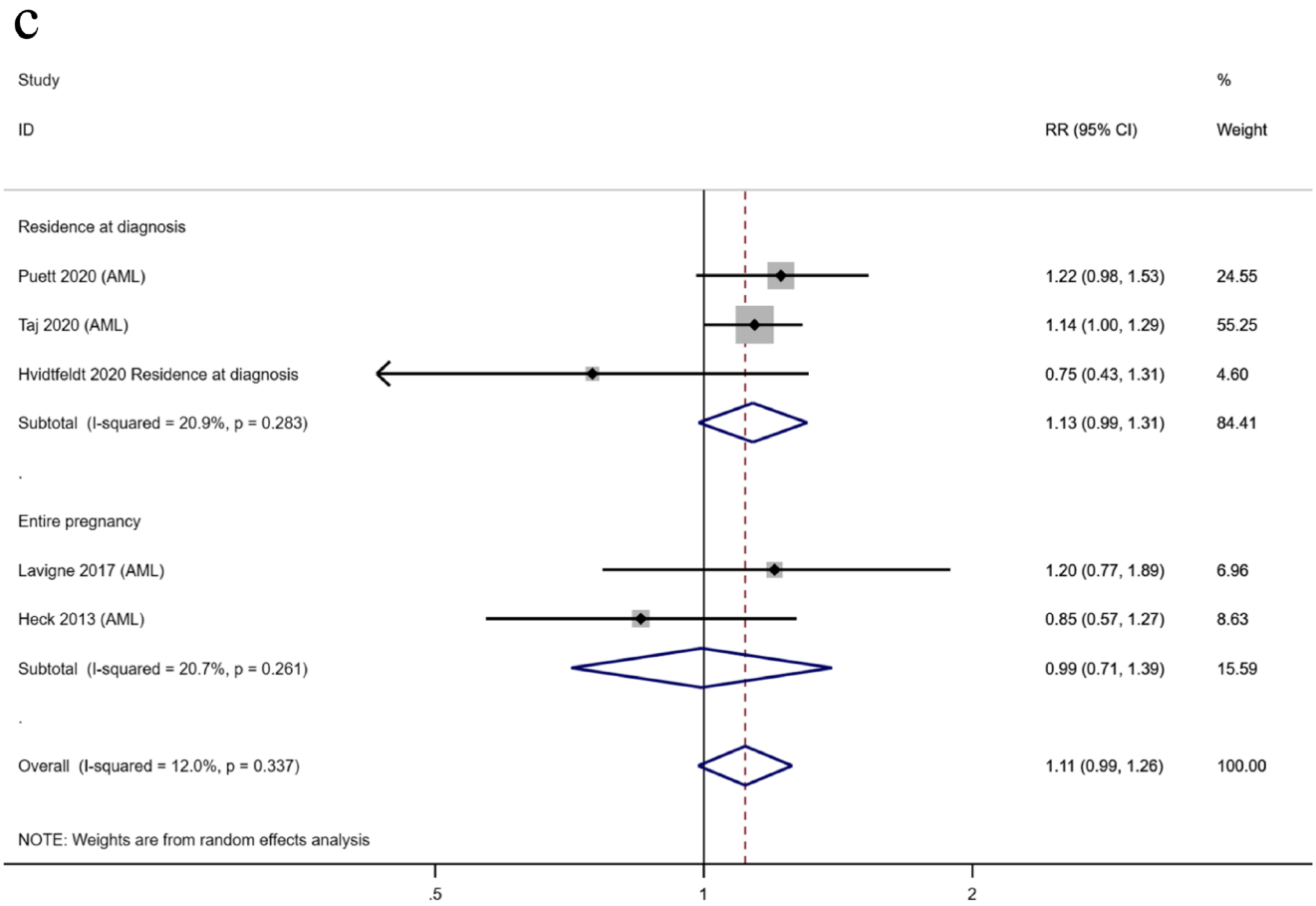

Fig. 4 continued.

heterogeneity among included studies. The results of the trim and fill analysis indicated that the summary effects of benzene showed a slightly changed. The main goal of the trim and fill analysis should be seen as providing methods for sensitivity analyses, and does seem to give good indications of which meta-analyses do not suffer from publication bias and which need to be evaluated much more carefully (Duval and Tweedie 2000). In our meta-analysis, the single RR estimates (1.20/1.11) generated by pooling all studies independently of the metrics adopted, the timing of the exposure assessment and the disease subtype (ALL or AML), a choice that considerably decreases the ability to detect and assess associations that can be seen (and likely exist) only in stratified analyses.

Although there was an inconsistency in conclusions on the correlation between air pollution and leukemia (Schüz and Erdmann 2016), the following mentioned studies, meta-analyses (Carlos-Wallace et al. 2016; Gong et al. 2019) and reviews (Pourvakhshoori et al. 2020; Schraufnagel et al. 2019) tended to support that outdoor air pollution was the risk factor for leukemia. These studies divided the exposure window into postnatal and prenatal (Boothe et al. 2014) or residence at diagnosis and residence at birth (Filippini et al. 2015), which showed that the risk of postnatal exposure was higher than that of prenatal exposure. Our meta-analysis divided the exposure window into seven periods which obtained similar results. Meanwhile, although some exposure period subgroups included fewer studies, we also found that the risk was different at different periods of pregnancy which was not mentioned in previous meta-analyses.

Laboratory studies comparing benzene exposed children after refinery emitted and unexposed children confirmed that exposure to outdoor air pollution could decrease hemoglobin levels (D'Andrea and Reddy 2016), and a review also discussed that the children lived near petrochemical estate region more likely to suffer from bone marrow injury resulting in hematologic toxicity leading to changes in blood cell formation than unexposed children (D'Andrea and Reddy 2018). The studies in mice showed that air pollution could increase the expression levels of inflammatory factors, IL-2, IL-10, IL-17A, and TNFα mRNA in leukemia cells which indicated that air pollution might lead to the occurrence of leukemia by affecting cytokine expression (Chen et al. 2018; Jin et al. 2016). One article mentioned that air pollution had toxic effects through inducing DNA-single strand breaks and DNA modifications to cause cancer (Gong et al. 2019). A review based on human studies concluded that air pollution caused leukemia via proinflammatory cytokine production and impaired immunosurveillance (Guo et al. 2020). During

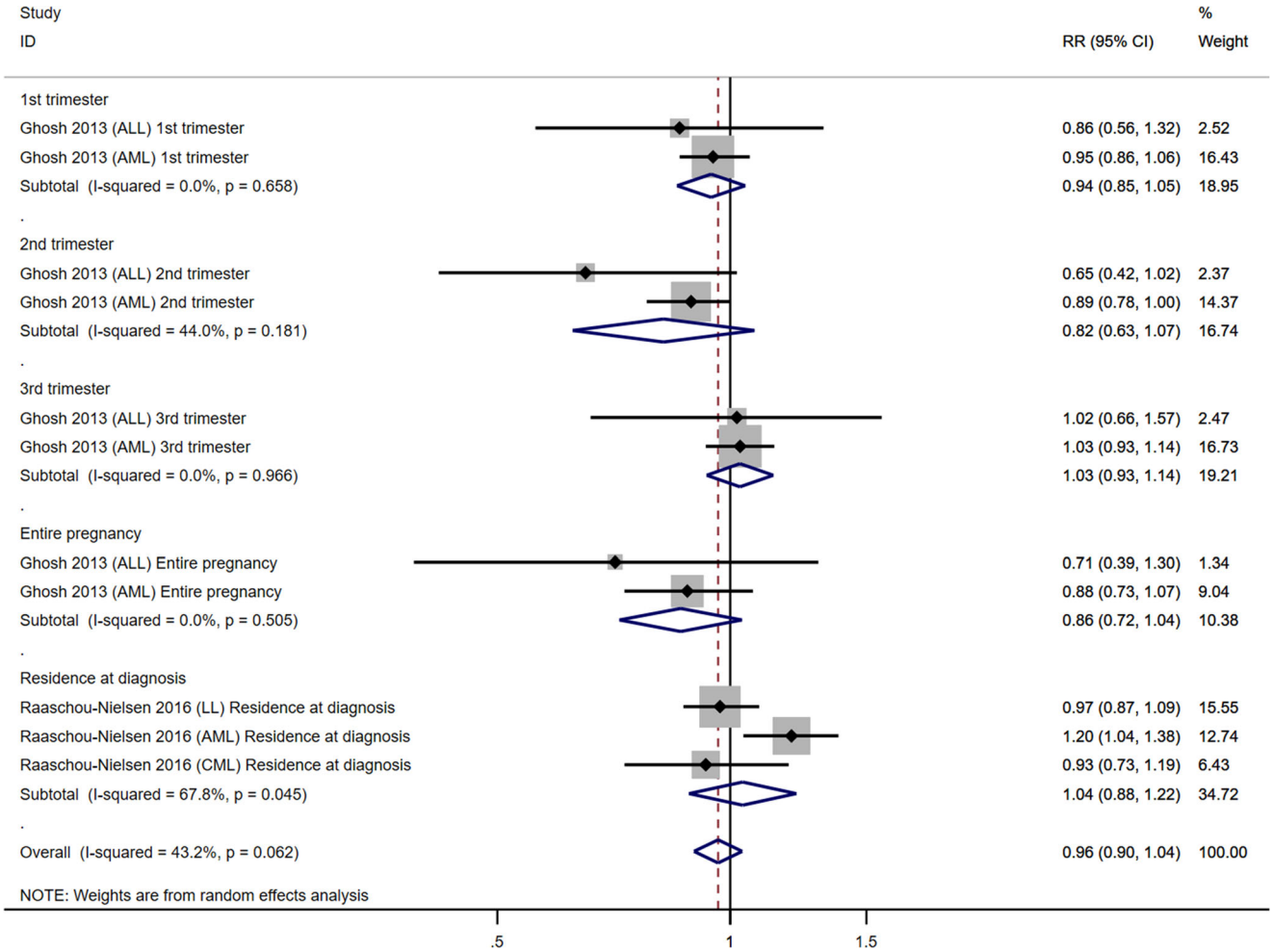

Fig. 5 Forest plot of included studies of NO_x exposure and leukemia

pregnancy, air pollution can cross the placenta (Dowty et al. 1976), leading to the increase of reactive oxygen species (ROS) which might play an important role in the development of childhood leukemia through disruption of hematopoietic cell signaling pathways (Badham and Winn 2010). And the mice experiment confirmed that the air pollution exposure in

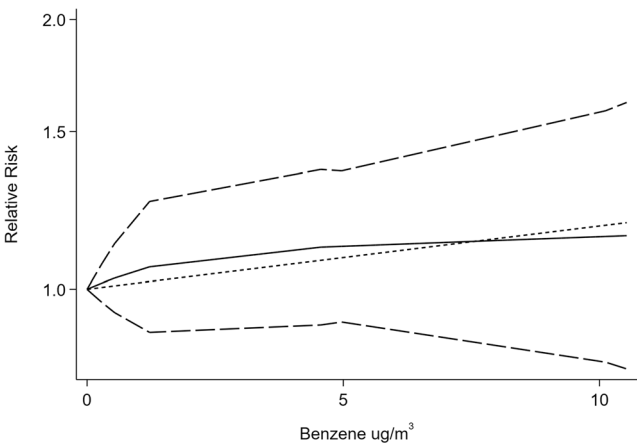

Fig. 6 The dose–response analysis between benzene exposure and the risk of leukemia. The solid line and the long dash line represent the estimated relative risks and its 95% CIs. Short dash line represents the linear relationship

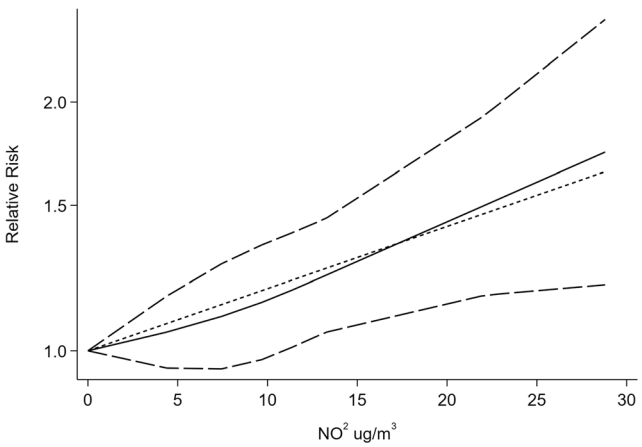

Fig. 7 The dose–response analysis between NO_2 exposure and the risk of leukemia. The solid line and the long dash line represent the estimated relative risks and its 95% CIs. Short dash line represents the linear relationship

utero could also increase the frequency of micronuclei and DNA recombination events that lead to childhood leukemia (Lau et al. 2009).

There are some limitations in our meta-analysis that need to be declared. First, some included studies were old; second, some air pollutants and subgroups included fewer studies which might have affected the credibility of our results; and last, we could not entirely rule out the occurrence of publication bias. Nevertheless, as far as we know, this is the first meta-analysis to assess air pollution and leukemia by dividing the exposure window into detailed periods.

Overall, outdoor air pollution could increase the risk of leukemia, especially exposure to benzene and NO_2. Exposure at different periods and different leukemia subtypes had different effects. It is therefore necessary to formulate policies that aim at reducing air pollution exposure and protect people from leukemia. Furthermore, there existed a linear relationship between benzene and NO_2 exposure and leukemia risk. More epidemiological studies are needed to confirm our findings.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s11356-021-14053-8.

Author contribution TW and FL designed this study. TW and RJ selected studies. TW, RJ, and FL extracted data and assessed the quality of included studies. TW, RN, RJ, ZZ, YS2, YS1, CN, LZ, and XR analyzed the data. TW draft the manuscript. FL revised and made the decision to submit for publication. All authors contributed to manuscript revision and read and approved the submitted version.

Declarations

Ethics approval and consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and materials Not applicable.

Competing interests The authors declare that they have no competing interests.

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