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Review

Association between Outdoor Air Pollution and Childhood Leukemia: A Systematic Review and Dose–Response Meta-Analysis

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BACKGROUND: A causal link between outdoor air pollution and childhood leukemia has been proposed, but some older studies suffer from methodological drawbacks. To the best of our knowledge, no systematic reviews have summarized the most recently published evidence and no analyses have examined the dose–response relation.

OBJECTIVE: We investigated the extent to which outdoor air pollution, especially as resulting from traffic-related contaminants, affects the risk of childhood leukemia.

METHODS: We searched all case–control and cohort studies that have investigated the risk of childhood leukemia in relation to exposure either to motorized traffic and related contaminants, based on various traffic-related metrics (number of vehicles in the closest roads, road density, and distance from major roads), or to measured or modeled levels of air contaminants such as benzene, nitrogen dioxide, 1,3-butadiene, and particulate matter. We carried out a meta-analysis of all eligible studies, including nine studies published since the last systematic review and, when possible, we fit a dose–response curve using a restricted cubic spline regression model.

RESULTS: We found 29 studies eligible to be included in our review. In the dose–response analysis, we found little association between disease risk and traffic indicators near the child's residence for most of the exposure range, with an indication of a possible excess risk only at the highest levels. In contrast, benzene exposure was positively and approximately linearly associated with risk of childhood leukemia, particularly for acute myeloid leukemia, among children under 6 y of age, and when exposure assessment at the time of diagnosis was used. Exposure to nitrogen dioxide showed little association with leukemia risk except at the highest levels.

DISCUSSION: Overall, the epidemiologic literature appears to support an association between benzene and childhood leukemia risk, with no indication of any threshold effect. A role for other measured and unmeasured pollutants from motorized traffic is also possible. https://doi.org/10.1289/EHP4381

Introduction

Acute leukemia is the most frequent childhood cancer (Kehm et al. 2018a; Siegel et al. 2016). Its age-standardized incidence has been increasing by 0.6% per year from 1975 through most recent years (Isaevska et al. 2017; Noone et al. 2018), up to about five cases per 100,000 population in the United States and other high-income countries (Barrington-Trimis et al. 2017; Isaevska et al. 2017; Noone et al. 2018). The etiology of childhood leukemia is largely unknown, although there is increasing evidence that environmental determinants may play a major role (Metayer et al. 2016a). In addition to established and putative environmental risk factors such as ionizing and nonionizing radiation (Amoon et al. 2018; Bartley et al. 2010), infections (Kreis et al. 2019; Marcotte et al. 2014), pesticides (Malagoli et al. 2016), parental smoking (Heck et al. 2016), diet (Henshaw and Suk 2015), and occupation (Spycher et al. 2017), there is concern about outdoor air pollution and, in particular, exposure to contaminants released by motorized traffic, a nearly ubiquitous exposure (De Donno et al. 2018; Landrigan et al. 2018; Montero-Montoya et al. 2018; Suk et al. 2016). In recent years, five systematic reviews have evaluated the association between traffic-related air pollution and acute childhood leukemia (Boothe et al. 2014; Carlos-Wallace et al. 2016; Filippini et al. 2015; IARC 2016; Sun et al. 2014) and one has evaluated the association between benzene exposure and disease (IARC 2018). All but one (Sun et al. 2014) indicated some association. For instance, the 2016 IARC-WHO review of air pollution noted that weak associations with childhood leukemia (especially acute lymphoblastic leukemia) could not be ruled out based on epidemiological studies. Such associations were defined as "suggestive" but "inconsistent" (IARC 2016). However, most of these reviews relied on simple metrics of traffic density, and none addressed the dose–response relation between pollutants and leukemia. Furthermore, several recently published studies were not included in those reviews. In the present review, we include nine additional studies (Houot et al. 2015; Janitz et al. 2016, 2017; Lavigne et al. 2017; Magnani et al. 2016; Raaschou-Nielsen et al. 2018; Spycher et al. 2015; Symanski et al. 2016; Tamayo-Uria et al. 2018). In addition to analyses comparing highest versus lowest categories of exposure, we conducted a dose–response meta-analysis. The dose–response analysis incorporated several proxies to assess exposure to air pollutants besides modeling levels of air contaminants.

Methods

Search Strategy

We performed a systematic PubMed, Web of Science, and Embase literature database search formatting the research question according to the PECOS statement (Population, Exposure, Comparator(s),

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Outcomes, and Study design) ([Morgan et al. 2018](#)). Full details of the definition of the research question and related database search strings are reported in Table S1. In our latest database search, we looked at all papers up to 20 March 2019, without limiting the literature search to specific languages. We also used extensive search techniques to identify additional references of potential interest, including "snowballing" methods, that is, screening the reference lists of eligible or key articles (backward citations), checking which other articles have cited the eligible or key articles (forward citations), and using the "similar articles" function of online databases, which identifies articles similar to a selected paper [[Booth 2008](#); [European network for Health Technology Assessment (EUnetHTA) 2017](#); [Vinceti et al. 2017](#)].

Study Selection and Review

All titles and abstracts were screened by two authors (TF and MV). When there was disagreement or when the abstract was missing, both authors reviewed the full texts to determine eligibility for inclusion. Full-text evaluation of all potentially eligible studies was performed in duplicate, with controversies discussed by the two authors (TF and MV). Inclusion criteria were *a*) epidemiologic case–control or cohort studies, *b*) childhood population, *c*) any type of assessment of exposure to traffic from motorized vehicles, *d*) reporting of risk estimates or ability to compute them from the reported data. Exclusion criteria included *a*) ecologic study design, *b*) studies on only adult populations, *c*) exposure assessment limited to only occupational activities, and *d*) a lack of reporting of risk estimates for childhood leukemia.

We then examined all retrieved studies assessing outdoor air pollutant exposure through traffic density, air monitoring data, and dispersion air pollutant models based on motorized traffic. Traffic density included metrics such as traffic count (the estimated number of vehicles per day in the roads within a defined distance from the residence), road density (the sum of the length of roads within a defined area around the residence), and residential distance (the distance between the residence and a major road). We evaluated both maternal exposure during pregnancy and child's exposure at birth, time of diagnosis, and average exposure during the child's lifetime, based on residential addresses during pregnancy, at birth, or at the time of diagnosis. The effect of these different exposure windows was compared in analyses stratified into peri- and postnatal periods. We (TF and AC) also extracted other details of interest such as study size and characteristics, age at diagnosis, and leukemia subtype, that is, acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML). We (TF and MV) assessed the characteristics and quality of included studies through the Newcastle-Ottawa Scale (NOS). Briefly, the NOS scale is based on a "star" system in which a study is assessed on three broad perspectives: the "selection" of the study groups, the "comparability" of the groups, and the ascertainment of either the "exposure" or "outcome" of interest for case–control or cohort studies, respectively ([Wells et al. 2019](#)). High-quality answers to each NOS scale question are identified with an asterisk/star. In Table S2, we reported details used for the evaluation. Total score is the sum of the score for each answer to the NOS scale. A high score indicates that the study is of high quality.

Statistical Analysis

In our meta-analysis, the ranges of exposure levels for most studies were roughly comparable, although cut points for exposure category identification differed across studies to some extent. We extracted from all studies the risk ratio (RR) in each exposure category, by abstracting the odds ratios in case–control studies and hazard ratios or rate ratios in cohort studies, as well as the number of cases or events and controls or person-years in each exposure category. We used a random-effects model to estimate a summary RR for childhood leukemia, comparing the highest and lowest exposure categories for each metric of interest.

We also performed a dose–response meta-analysis to understand the shape of the curve relating air pollution and disease risk. To do that, we used methodology developed by Greenland and Longnecker ([1992](#)) and Orsini et al. ([2012](#)) that has been applied in other contexts ([Crippa et al. 2018b](#); [Vinceti et al. 2016](#)) to estimate the trend from the RRs across categories of pollutant exposure levels and their approximate pointwise 95% confidence intervals (CIs) based on asymptotic normality. For each of the exposure strata, we abstracted the mean or, if means were unavailable, the median. If neither mean nor median were stated, we used the midpoint. When the highest and lowest exposure categories were "open," that is, mean or median or extreme values were not presented, we entered a value that was 20% higher or lower than the closest cut point. We based this decision on the studies reporting both cut point values and median/mean values for the extreme categories and which found a difference ranging between 15% and 20%. We excluded from this dose–response meta-analysis the studies not reporting any exposure category cut points for the investigated pollutant and the studies providing only RR estimates based on 1-unit increment in exposure based on a linear model because these studies could not contribute to the assessment of departure from linearity. However, all those studies were included in the analysis of overall studies comparing highest versus lowest exposure. We then investigated the shape of the relation between traffic or pollutant exposures and childhood leukemia risk with either one-stage and two-stage dose–response meta-analysis, using restricted cubic splines with 3 knots at fixed percentiles (10, 50, and 90%) of the exposure distribution ([Crippa et al. 2018a](#); [Orsini et al. 2012](#)). The restricted cubic spline model was fit with a generalized least-squares regression taking into account the correlation within each set of published RRs, and combining the study-specific estimates using the restricted maximum likelihood method in a multivariable random-effects meta-analysis ([Greenland and Longnecker 1992](#); [Jackson et al. 2010](#); [Orsini et al. 2006](#), [2012](#)). This dose–response meta-analysis was applied to three traffic-related metrics (traffic count, road density, and residential distance from a major road) and to the only two pollutants for which enough data for measured or monitored air levels were available [benzene and nitrogen dioxide (NO_2)]. For one study ([Heck et al. 2014](#)), some data needed for the meta-analysis were not reported in the publication but were provided by two coauthors (JEH and ASP). In these analyses, estimates for benzene were adjusted for 1,3-butadiene (and vice versa).

Heterogeneity was taken into consideration in the estimation of the random-effects model in the highest versus lowest analysis. We reported the I^2 and τ^2 measures for each analysis. In order to explore the source of heterogeneity, we conducted stratified analyses, by leukemia subtype (ALL and AML), age at diagnosis (<6 and ≥6 y of age), exposure time window (residence during pregnancy, at birth, and/or diagnosis), and continent. Because the fixed effect (average regression coefficients across studies) and variance/covariance structure of the random effects in spline models are not easily interpreted, we provided a graphical overlay of the marginal and conditional (best linear unbiased prediction of study-specific) dose–response trends we computed for each study ([Crippa et al. 2018a](#)). We also re-ran the analyses repeatedly, each time without one of the studies, to assess the missing study's influence and to characterize the source and magnitude of any heterogeneity of results.

Finally, we checked for the possible presence of publication bias using funnel plots for studies reporting highest versus lowest exposure. We used Stata software (release 15.1; Stata Corp.) for all data analyses and specifically the "metan," "metaninf," "metafunnel," "mkspline," and "drmeta" routines.

Results

Description of Included Studies

Figure 1 reports the flowchart of the literature search. We retrieved 29 papers eligible for this review, including 26 case–control and three cohort studies. Detailed characteristics of included studies are summarized in Table 1. Overall, they included over 13,000 cases and (for the case–control studies) 145,000 controls worldwide. The year of diagnosis of the cases ranged from 1960 to 2012. Seven studies limited their study population to children <6 y of age (Ghosh et al. 2013; Heck et al. 2013, 2014; Lavigne et al. 2017; Reynolds et al. 2001, 2004; Symanski et al. 2016), and seven presented age-stratified analyses (Badaloni et al. 2013; Houot et al. 2015; Janitz et al. 2016, 2017; Savitz and Feingold 1989; Spycher et al. 2015; Vinceti et al. 2012).

The various methods used in these studies for the assessment of exposure to traffic exhaust contaminants are summarized in Figure 2. Traffic density was assessed in 20 studies: as traffic count ($n = 6$), road density ($n = 6$), residential distance from a major road ($n = 7$), or a combination of them ($n = 6$). Another 16 studies utilized measured or modeled levels of traffic-related air contaminants, mainly benzene ($n = 8$), 1,3-butadiene ($n = 2$), NO_2 ($n = 10$), and particulate matter (PM) ($n = 4$). Other pollutants considered in these studies were ozone, other nitrogen oxides, carbon monoxide, and polycyclic organic matter. These pollutants were generally included in a multivariate model with other pollutants. Sixteen studies utilized only one method of exposure assessment, whereas the remaining 13 studies used two or more methods. NOS scale scores of included studies are reported in Table S3. The median value of the total score was 9 for both case–control and cohort studies, the highest level of this scale, indicating a generally very good quality and a substantially low risk of bias. Most studies had a population-based design, with 2 being hospital-based. Among the 27 population-based studies overall, 19 (including all those assessing benzene exposure) did not depend on voluntary participation of children and their families. These studies performed an exposure assessment, without contacting the participants, based on modeling applied to location information for the residence of study participants.

To assess exposure, most studies used either the residential address at the time of diagnosis or the address retrieved from the
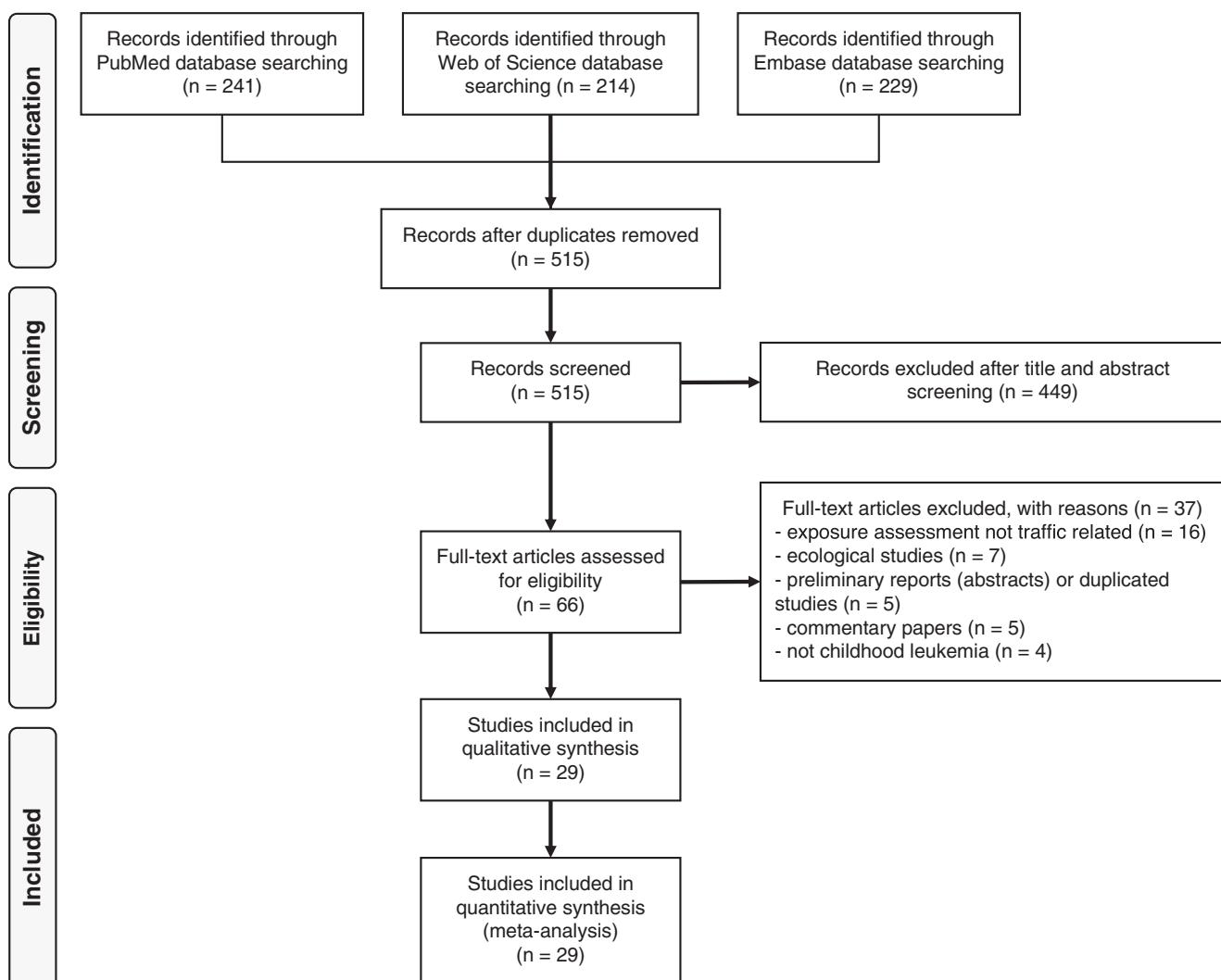

Figure 1. Flowchart of literature search and identification through 20 March 2019.

Table 1. Main characteristics of case–control and cohort studies on air pollution from motorized traffic and risk of childhood leukemia.

Reference	Region	Study period	Type of cancer	Cases/controls	Age (y)	Exposure assessment	Methods	Type of residence	Case selection	Control selection	Matching variables	Adjustment factors
Abdul Rahman et al. 2008	Malaysia	2001–2007	All leukemias	128/128	0–14	Traffic density	Traffic density using distance from main road ($\leq$100, >100 m)	Residence at diagnosis	Histological confirmed diagnosis of acute leukemia in two Malaysian hospitals	Hospital selection from children received treatment in one of the two hospitals	None	Family income, paternal social contact, number of elder siblings, maternal age, paternal age, family history of cancer, paternal smoking, distance to main road, and distance to power line
Amigou et al. 2011	France	2003–2004	All leukemias (ALL + ANLL)	763 (645 + 118)//1,681	0–14	Traffic density estimated using three models and a composite of them, including NO_2 estimated levels	Traffic density through proximity to main roads within area of 500 m using Navteq software function to characterize road classes on the basis of their importance and through density of heavy traffic roads within 500 m from the residence. Traffic-related NO_2 levels	Residence at diagnosis	French National Cancer Registry of Childhood Hematopoietic Malignancies	Community recruitment with telephone interviews. Response rates for case/controls of 91% and 71%	Sex and age	Sex, age, and socioeconomic status
Badaloni et al. 2013	Italy	1998–2001	All leukemias	747/1,509	0–10 (0–4)	Traffic density using two models and pollutants exposure (NO_2, PM_{10}, O_3, and $PM_{2.5}$)	Traffic density using distance from main roads ($\leq$50, 50–150, $\geq$150 m) and main roads' length within area of 100 m. Pollutant exposures estimated using LUR model for NO_2, PM_{10}, O_3, and $PM_{2.5}$ divided into quartiles	Residence at birth	Italian Association of Pediatric Hematology and Oncology Registry	Community selection with face-to-face not-blinded interview. Response rates for case/controls of 91.4% and 69.2%	Sex and age	Sex, age, region of residence and parental education level
Crosignani et al. 2004	Italy	1978–1997	All leukemias and ALL	120/480	0–14	Traffic density using distance from major roads and benzene exposure	Distance from major roads (>150, 20–150, <20 m). Benzene estimated exposure in three categories (<0.1, 0.1–10, >10 µg/m³)	Residence at diagnosis	Lombardy Cancer Registry	Community selection by Health Services archives of Varese	Sex and birth year	Sex, age, and socioeconomic status
Feychting et al. 1998	Sweden	1960–1985	All leukemias	39/151	0–15	NO_2 exposure using continuous values and in two categorical models	NO_2 estimated levels through continuous scale (1 µg/m³) and three categories, using 50th ($\leq$39, 40–49, $\geq$50 µg/m³) and 75th percentiles ($\leq$49, 50–79, $\geq$80 µg/m³) as referent respectively	Residence for at least 1 y within 300 meters from power lines	Swedish Cancer Registry linking medical records to verify diagnoses	Community selection from same area	Age, municipality and residence near the same high voltage power lines	Magnetic fields and socioeconomic status

Note: Metric conversion factors: 1 foot = 0.3048 meter; 1 mile = 1,609.34 meter. ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; ANLL, acute non-lymphoblastic leukemia; CALINE, California line source dispersion model; CO, carbon monoxide; LUR, land-use regression; NATA, National-Scale Air to Toxics Assessment; NO, nitric oxide; NO_2, nitrogen dioxide, NO_x, nitrogen oxides; O_3, ozone; PAH, polycyclic aromatic hydrocarbons; PM, particulate matter; POM, polycyclic organic matter.

Table 1. (Continued.)

Reference	Region	Study period	Type of cancer	Cases/controls	Age (y)	Exposure assessment	Methods	Type of residence	Case selection	Control selection	Matching variables	Adjustment factors
Ghosh et al. 2013	California	1988–2008	ALL + AML	1,346 + 216/80,658	0–5	NO, NO_2, and NO_x exposure	Pollutant exposures estimated using LUR, unseasonalized, and seasonalized models	Residence at birth	California Cancer Registry	Community selection from birth certificates from mothers living in Los Angeles County	Sex and birth year	Sex, birth year, race/ethnicity, maternal education level, parity, prenatal care insurance type, and neighborhood socioeconomic index
Harrison et al. 1999	United Kingdom	1990–1994	All leukemias	130/251	0–15	Traffic density as measured by weighted distance from major roads	Addresses within 100 m of major roads, using Geographic Information System	Residence at diagnosis	West Midland Cancer Intelligence Units, using ICD-9	Solid tumor cases from the same register as the cases	None	None
Heck et al. 2013	California	1998–2007	ALL + AML	1,280 + 229/80,224	0–5	Traffic density, CO, and $PM_{2.5}$ exposure estimated levels	Traffic density in vehicles per day within 500 m of the residence. Pollutant exposures estimated using CALINE dispersion model for CO; $PM_{2.5}$ using measures from community air monitors	Residence at birth	California Cancer Registry	Community selection from birth certificates	Birth year	Birth year, maternal race/ethnicity, mother's birth place, and neighborhood socioeconomic index
Heck et al. 2014	California	1990–2007	ALL + AML	69 + 46/2,994	0–6	Air toxic exposure	Pollutant exposures (total PAHs, benzene, ethylbenzene, 1,3-butadiene) taken from air monitors within 2 or 6 km of residence	Residence at birth	California Cancer Registry	Community selection from birth certificates	Birth year	Birth year, maternal race/ethnicity, mother's birth place, and neighborhood socioeconomic index
Houot et al. 2015	France	2002–2007	All leukemias (ALL + AML)	2,760 (2,275 + 418/30,000, overall 517 (425 + 92)/6,147, Île-de-France Region	0–14 (0–4, 5–9, 10–14)	Traffic density estimated using two models, NO_2 and benzene estimated levels	Traffic density through proximity to major roads within area of 500 m of residence and length of major roads within 150 m of residence using Navteq software function to characterize road classes on the basis of their importance. Traffic-related NO_2 and benzene levels	Residence at diagnosis	French National Cancer Registry of Childhood Hematopoietic Malignancies	Community selection from National Institute for Statistics and Economic Studies	None	Age (and deprivation index only in road length analysis)
Janitz et al. 2016	Oklahoma	1997–2012	All leukemias (ALL + AML)	307 (228 + 79)/1,013	0–19 (0–4, 5–9, 10–14, 15–19)	Traffic density using two models and NO_2 exposure	Traffic density through proximity to major roads within area of 750 or 500 m of residence. Traffic-related NO_2 levels using a satellite-based LUR model	Residence at birth	Oklahoma Central Cancer Registry	Community selection from birth certificates	Birth week	Age, maternal education (and urbanization)

Table 1. (*Continued.*)

Reference	Region	Study period	Type of cancer	Cases/controls	Age (y)	Exposure assessment	Methods	Type of residence	Case selection	Control selection	Matching variables	Adjustment factors
Janitz et al. 2017, 2018	Oklahoma	1997–2012	All leukemias (ALL+AML)	307 (228+79)/1,013	0–19 (0–4, 5–9, 10–14, 15–19)	Benzene exposure	Benzene exposure levels based on National-Scale Air to Toxics Assessment (NATA) 2005 models	Residence at birth	Oklahoma Central Cancer Registry	Community selection from birth certificates	Birth week	Age, maternal education and urbanization
Langholz et al. 2002	California	1978–1984	All leukemias	212/202	0–10	Traffic density as vehicles per day estimated in two models	Traffic density at the longest-lived residence for all streets within 1,500-ft radius, divided into three categories (<500, 500–9,999 ≥10,000) or in quintiles as cut points (<2,301, 2,301 – <5,997, 5,997 – <13,264, 13,264–28,497, ≥28,497)	Residence of longest duration	Los Angeles Country Cancer Registry	Community selection by not-blinded telephone interviews with random digit dialing method	Sex and age	Wire-code
Lavigne et al. 2017	Ontario, Canada	1988–2012	All leukemias (ALL+AML)	941 (849+92/2,350,898 (total cohort)	0–5	NO_2 and $PM_{2.5}$ exposure	Land-use regression model estimates of NO_2 and temporally varying satellite-derived estimates of $PM_{2.5}$	Residence at birth	Pediatric Oncology Group of Ontario Networked Information System	Mother–baby Linked database of hospital admission records of deliveries across Ontario	Not applicable	Age at delivery, infant sex, parity, year of birth, maternal cigarette smoking during pregnancy, census tract median family income, census tract proportion of population who are visibly minority, and census tract proportion of the adult female population 25–64 y of age who completed postsecondary education
Magnani et al. 2016	Italy	1998–2001	All leukemias (ALL+ANLL)	648 (565+80/968	0–10	Traffic density using main roads' length	Traffic density using main roads' length within area of 500 m in four categories as cut point (0, 10th, 50th, 90th percentiles) to four different types of residence	Residence at birth Residence of longest duration Residence for at least 50% of life Residence considered the highest exposed	Italian Association of Pediatric Hematology and Oncology Registry	Community selection with face-to-face not-blinded interview. Response rates for case/controls of 91.7% and 70.8%	Sex, age, and region	Sex, age, region, parental education, and parental smoking
Pearson et al. 2000	Colorado	1978–1983	All leukemias	97/259	0–14	Traffic density in vehicles per day estimated in highest vs. lowest category; two different models	Traffic density within 750-ft distance-weighted traffic density using six categories: <500, 500–4,999, 5,000–9,999 10,000–14,999, 15,000–19,999, ≥20,000	Residence at diagnosis	Colorado Central Cancer Registry	Community selection by not-blinded telephone interviews with random digit dialing method	Sex, age, and telephone exchange area	None
	Denmark	1968–1991	All leukemias	986/5,506	0–14							

Table 1. (*Continued.*)

Reference	Region	Study period	Type of cancer	Cases/controls	Age (y)	Exposure assessment	Methods	Type of residence	Case selection	Control selection	Matching variables	Adjustment factors
Raaschou-Nielsen et al. 2001	Denmark	1968–1991	ALL + AML			Traffic density as vehicles per day, and pollutant (benzene and NO_2) exposure during childhood and pregnancy	Traffic density estimated in vehicles/day using four categories: <500, 500 – <5,000, 5,000 – <10,000, ≥10,000 in both childhood and pregnancy. Pollutant exposure using a modified version of the Operational Street Pollution Model and 50th, 90th, and 99th percentiles as cutoff points (data in 1,000 ppb-days) resulted in four categories for benzene (<3.8, 3.8 – <10.4, 10.4 – <27.0, ≥27.0 during childhood, <0.5, 0.5 – <1.3, 1.3 – <3.5, ≥3.5 during pregnancy) and for NO_2 (<11.5, 11.5 – <29.4, 29.4 – <57.8, ≥57.8 during childhood, <3.8, 3.8 – <10.4, 10.4 – <27.0, ≥27.0 during pregnancy)	Residence at diagnosis	Danish Cancer Registry	Danish Central Population Registry	Sex, age, and calendar time	Urban development, geographic region, type of residence, electromagnetic fields, mother's age, and birth order
Raaschou-Nielsen et al. 2018				727 + 125/5,428	0–14	Benzene exposure during childhood and pregnancy	Pollution Model and 50th and 90th percentiles as cutoff points resulted in three categories for benzene during childhood (<3.9, 3.9 – ≤10.9, >10.9×1,000 ppb-days or <1.7, 1.7 – ≤3.7, >3.7 ppb) and pregnancy (<0.5, 0.5 – ≤1.3, >1.3×1,000 ppb-days or <1.8, 1.8 – ≤4.6, >4.6 ppb)	Residence at diagnosis	Danish Cancer Registry	Danish Central Population Registry	Sex, age, and calendar time	Degree of urbanization, geographic region, type of residence, electromagnetic fields, mother's age, and birth order
Reynolds et al. 2001	California	1988–1994	All leukemias	90/349	0–5	Traffic density using average number of cars per day (ADT)	ADT of road segments within a 550-ft radius from home address and divided into three categories: no ADT (reference), <75th and ≥75th percentiles	Residence at birth	California Cancer Registry	Community selection from birth certificates	Sex and birth year	Sex, birth year, ethnicity, and median child family income
Reynolds et al. 2004	California	1988–1997	All leukemias (and ALL)	1,728 (1,407)/3,456	0–4	Traffic density and road density	Traffic density using combination of road length and vehicle	Residence at birth	California Cancer Registry	Community selection from birth certificates	Sex and birth year	Sex, birth year, and ethnicity

Table 1. (Continued.)

Reference	Region	Study period	Type of cancer	Cases/controls	Age (y)	Exposure assessment	Methods	Type of residence	Case selection	Control selection	Matching variables	Adjustment factors
							traffic counts. Road density: summary of total road length (in miles per square mile) within 500-ft radius. For both, 25th, 50th, 75th, and 90th percentiles were used as cut points					
Savitz and Feingold 1989	Colorado	1976–1983	All leukemias (and ALL)	98 (79)/262	0–14 (0–4, 5–14)	Traffic density in vehicles per day estimated in four different models	Traffic density at the address of residence using street maps of Denver Standard Metropolitan Statistical Area: vehicles/day divided into two or three categories: <500 vs. ≥500 or <500, 500–4,999, ≥5,000, or <500, 500–9,999, ≥10,000 or <500 vs. ≥10,000	Residence at diagnosis	Colorado Central Cancer Registry	Community recruitment by random digit dial, data collection via telephone interview. Overall response rate of 75%	Sex, age, and telephone exchange area	Sex, age, year of diagnosis, type of residence, location at birth, mother's age, father's education, and per capita income and wire configuration code at diagnosis
Spycher et al. 2015	Switzerland	1990–2008	All leukemias (and ALL)	532 (416)/2,096,402 (total cohort)	0–15 (0–4)	Distance from heavy traffic roads	Distance to the nearest highway (<100, 100 – <250, 250 – <500, ≥500 m)	Residence at diagnosis	Swiss Childhood Cancer Registry	Swiss resident population <16 y of age at the national censuses of 1990 and 2000	Not applicable	Sex, birth year, urbanization, socioeconomic position, educational level of household head, number of persons per room, nationality, background ionizing radiation (terrestrial gamma and cosmic rays), distance to the nearest power line, and strength of electromagnetic fields from broadcast transmitters
Steffen et al. 2004	France	1995–1999	All leukemias (ALL + ANLL)	280 (240 + 49)/285	0–14	Traffic density using main roads' density	Traffic density using presence of heavy traffic roads within 50 m from residence (all roads types, secondary road or main street, primary road and motorway or similar road)	Residence at diagnosis	Hospitals of Nancy, Lille, Lyon, and Paris	Hospital recruitment with face-to-face interviews to assess exposure	Sex, age, ethnic origin, and hospital	Sex, age, ethnic origin, and hospital
Symanski et al. 2016	Texas	1995–2011	ALL	1,248/12,172	0–4	Benzene, 1,3-butadiene and POM exposure	Air pollutants (benzene, 1,3-butadiene, and POM) exposure levels based	Residence at birth	Texas Cancer Registry	Community controls from Texas Department of State Health	Birth year and month	Birth year and month, air pollutants (benzene, 1,3-butadiene, POM),

Table 1. (*Continued.*)

Reference	Region	Study period	Type of cancer	Cases/controls	Age (y)	Exposure assessment	Methods	Type of residence	Case selection	Control selection	Matching variables	Adjustment factors
							on 1996, 1999, 2002, and 2005 NATA models			Services vital statistics birth records		census tract, maternal age, infant birth weight, sex, and maternal race/ethnicity
Tamayo-Uria et al. 2018	Spain	1996–2011	All leukemias (ALL + AML)	1,061 (846 + 174)/6,447	0–14	Traffic density using annual average daily traffic and distance to busy roads	Traffic density using Navteq software function to characterize road classes, their proximity and traffic density within multiple buffers (50, 100, 200, and 500 m) from the residence	Residence at diagnosis for cases, at birth for controls	Spanish Registry of Childhood Tumours (RETI-SEHOP)	Community controls from Birth Registry of the Spanish Statistical Office	Sex, birth year, and, autonomous region of residence	Sex, birth year, autonomous region of residence, socioeconomic status, industrial pollution, and crop exposure
Vinceti et al. 2012	Italy	1998–2009	All leukemias (ALL + AML)	83 (64 + 19)/332	0–14 (0–5, 5–14)	Benzene and PM$_{10}$ exposure	Average and maximum hourly levels of benzene and PM$_{10}$ estimated through the CALINE dispersion model and divided into quartiles: cut points for average benzene (<0.10, 0.10 – <0.25, 0.25 – <0.50, ≥0.50 μg/m^3)	Residence at diagnosis	Italian Association of Pediatric Hematology and Oncology Registry	Community selection from Local Health Units of Modena and Reggio Emilia	Sex, birth year, and province of residence	Benzene and PM$_{10}$ average and maximum hourly levels
Visser et al. 2004	Netherlands	1989–1997	ALL	5/total population	0–14	Traffic density as residence along busiest main roads	Traffic density measured as residence along main roads with traffic identity score ≥10,000. Traffic density score was calculated using daily traffic intensity, counting cars for 1 and truck for 10	Residence at 1998 or date of death	Amsterdam Cancer Registry	Amsterdam resident population	Not applicable	5-y-of-age group and sex-specific standardized incidence rate
Von Behren et al. 2008	California	1995–2002	ALL	310/396	0–15	Traffic density in total vehicle miles traveled per square mile	Traffic density in total vehicle miles traveled per square mile within 500-ft radius using 0th, 50th, and 75th percentiles as cut points (no roads, 1–38,499, 38,500–91,461, ≥91,462)	Residence at birth, at diagnosis and the average lifetime	Hospitals participating in Northern California Childhood Leukemia Study	Community selection from birth certificates. Participation rates for cases/controls of 86% and 84%.	Sex, age, Hispanic ethnicity, and mother's race	Sex, age, Hispanic ethnicity, mother's race, and household income category
Weng et al. 2008	Taiwan	1995–2005	All leukemias	308/308	0–14	NO$_2$ levels from 66 air monitoring stations	NO$_2$ levels divided into three categories: <20.90, 20.99–25.34, 26.33–44.85 ppb	Place of usual residence indicated in death certificate	Death certificates using ICD codes	Death certificates	Sex, birth year, and death year	Socioeconomic status

Figure 2 legend shading: light gray ░ = Pollutant assessment; dark gray ▒ = Dose-response pollutant assessment not included in the dose-response meta-analysis; black █ = Dose-response pollutant assessment included in the dose-response meta-analysis.

Reference	Traffic count	Road density	Distance	Composite index	Benzene	1,3-butadiene	NO₂	PM₁₀	PM₂.₅	Residence at birth/pregnancy	Residence at diagnosis	Asia	Europe	North America	Age < 6 years	Age ≥ 6 years	Age < & ≥ 6 years	Population-based (involuntary)	Population-based (voluntary)	Hospital-based
Abdul Rahman 2008			█								░	░					░			░
Amigou 2011	▒	▒		░			▒				░		░				░		░	
Badaloni 2013	▒	█			█			▒	▒		░		░				░		░	
Crosignani 2004			█		█						░		░					░		
Feychting 1998							█				░		░				░	░		
Ghosh 2013											░			░	░			░		
Harrison 1999			█								░		░				░			░
Heck 2013				░						░				░	░			░		
Heck 2014					█	▒	█				░			░	░			░		
Houot 2015	█	█			█		█				░		░		░	░	░	░		
Janitz 2016		░					█				░			░	░			░		
Janitz 2017					█						░			░	░			░		
Langholz 2002	█	░									░			░			░		░	
Lavigne 2017				░						░			░		░			░	░	
Magnani 2016		█									░		░				░	░	░	
Pearson 2000	█										░			░			░	░		
Raaschou-Nielsen 2001	█	░			▒		░				░		░				░	░		
Raaschou-Nielsen 2018					█						░		░				░	░		
Reynolds 2001	░										░			░	░			░		
Reynolds 2004	█	█									░			░	░			░		
Savitz 1989	▒	░									░			░			░		░	
Spycher 2015			█								░		░				░	░		
Steffen 2004				░							░		░				░		░	
Symanski 2016				░	░	░					░			░			░	░		
Tamayo-Uria 2018				░							░		░		░			░		
Vinceti 2012				░	█			▒			░		░				░	░		
Visser 2004				░							D		░		░			░		
Von Behren 2008				░							░			░			░	░	░	
Weng 2008							█				D	░					░	░		

Legend:

░ Pollutant assessment

▒ Dose-response pollutant assessment not included in the dose-response meta-analysis

█ Dose-response pollutant assessment included in the dose-response meta-analysis

Figure 2. Characteristics of included studies according to traffic pollution assessment, and other characteristics. Composite index, combination of various measures of traffic density; D, residential address retrieved from death certificate; distance, distance between the residence and a major road; NO₂, nitrogen dioxide; PM, particulate matter; road density, sum of the length of roads within a defined area around the residence; traffic count, estimated number of vehicles per day in the roads within a defined distance from the residence. For population-based studies, we indicated whether exposure assessment depended upon acceptance to participate in the study (voluntary) or it was based solely on residential address, without contacting the participants (involuntary).

death certificate. Some studies used residential address during pregnancy or at birth; only two studies evaluated exposures both at and after birth (Figure 2).

Table 1 provides details of characteristics of each eligible study, including confounding factors they considered. All but two studies accounted for sex and age, generally as matching

variables, and all but four included a measure of socioeconomic status in the regression model. The databases with extracted data used for both highest versus lowest (see Excel Table S1) and dose–response meta-analysis (see Excel Table S2) are included and described in the Supplemental Excel File.

Highest versus Lowest Meta-Analysis

Tables 2 and 3 present the summary RR and 95% CIs comparing the highest with lowest exposure categories for each exposure assessment method and the corresponding forest plots are shown in Figures S1–S15. As shown in Table 2, the summary RR comparing the highest to lowest exposure categories from studies using traffic density to assess air pollution exposure and leukemia risk was slightly elevated, being RR = 1.09 (95% CI: 1.00, 1.20). Of the eight studies that investigated benzene exposure, two involved the same population. For the remaining seven, the summary RR = 1.27 (95% CI: 1.03, 1.56). Of the eligible studies assessing NO_2 exposure, two were updated versions of previous reports. The eight independent studies of NO_2 exposure yielded a summary RR = 1.04 (95% CI: 0.90, 1.19). We observed a moderate association for PM_{10} and childhood leukemia [two studies, summary RR = 1.20 (95% CI: 0.70, 2.04)], but the association was much weaker for $PM_{2.5}$ [three studies, summary RR = 1.05 (95% CI: 0.94, 1.16)]. 1,3-butadiene was associated with increased disease risk, based on two studies [summary RR = 1.45 (95% CI: 1.08, 1.95)] (Table 3).

In analyses stratified by disease subtype (Tables 2 and 3; see also Figures S1–S6), RR estimates were found to differ markedly only for benzene exposure, for which the summary RR became 1.09 (95% CI: 0.88, 1.36) for ALL, based on seven studies, and 1.84 (95% CI: 1.31, 2.59) for AML, based on five studies. No such change in RR according to leukemia subtype was found for traffic indicators, for NO_2 or for PM. 1,3-Butadiene exposure was associated with a higher RR for AML compared with ALL, but the summary estimates were statistically unstable, being based on two studies only. For the aforementioned pollutants, RRs according to disease subtype were roughly the same after restricting the analysis to children <6 y of age, with the exception of the summary RRs associated with benzene exposure, showing a larger difference between AML and ALL in this younger subgroup (Tables 2 and 3; see also Figures S7–S11). Data for older children, however, were based on one study only, and the RR was imprecise (Tables 2 and 3; see also Figures S12–S15). In general, for other air pollution exposure metrics, results were somewhat stronger among younger children, but there were few studies with data on children ≥6 y of age, and the latter results were statistically unstable.

In analyses stratified by study region, the North American studies showed a summary RR = 1.02 (95% CI: 0.89, 1.16) and 1.21 (95% CI: 1.04, 1.41) for traffic density and benzene exposure, respectively (Tables 2 and 3; see also Figures S1–S6). For European studies, the corresponding estimates were higher, that is, RR = 1.25 (95% CI: 1.05, 1.49) for traffic indicators and 1.36

Table 2. Summary risk ratios (RRs) of childhood leukemia in the highest exposure category versus the lowest one for traffic density, benzene, and nitrogen dioxide (NO_2) exposure, for all studies and stratified by age at diagnosis, leukemia subtype, exposure timing, and region.

Indicator	All children					Preschool children (<6 y of age)					Children ≥6 y of age				
	n	RR	95% CI	I^2 (%)	τ^2	n	RR	95% CI	I^2 (%)	τ^2	n	RR	95% CI	I^2 (%)	τ^2
Traffic density															
All leukemia	16	1.09	1.00, 1.20	56.2	0.012	7	1.00	0.93, 1.09	67.0	0.006	3	1.05	0.96, 1.15	10.0	0.002
Subtype															
ALL	9	1.05	0.96, 1.16	34.7	0.005	3	1.02	0.99, 1.05	0.0	0.000	1	1.00	0.92, 1.09	—	0.000
AML	5	1.09	0.86, 1.38	70.0	0.034	2	1.03	0.77, 1.38	87.7	0.039	1	1.25	1.02, 1.53	—	0.000
Exposure timing															
At birth	5	0.98	0.90, 1.06	30.9	0.003	4	0.95	0.85, 1.05	52.4	0.006	1	1.15	0.78, 1.70	—	0.000
At diagnosis	14	1.32	1.12, 1.55	50.7	0.033	3	1.27	0.95, 1.71	81.0	0.049	2	1.05	0.94, 1.17	24.6	0.004
Region															
Asia	1	1.27	0.51, 3.17	—	0.000	—					—				
Europe	9	1.25	1.05, 1.49	50.4	0.026	3	1.05	0.87, 1.25	63.8	0.017	1	1.05	0.95, 1.17	—	0.000
North America	6	1.02	0.89, 1.16	65.4	0.014	4	0.98	0.84, 1.15	74.9	0.017	2	1.09	0.72, 1.64	17.4	0.032
Benzene															
All leukemia	7	1.27	1.03, 1.56	52.4	0.043	4	1.39	1.03, 1.87	27.9	0.035	2	1.08	0.64, 1.82	0.0	0.000
Subtype															
ALL	7	1.09	0.88, 1.36	51.8	0.034	3	1.19	1.00, 1.40	0.0	0.000	1	0.69	0.27, 1.78	—	0.000
AML	5	1.84	1.31, 2.59	0.0	0.000	2	3.21	1.39, 7.42	0.0	0.000	1	0.43	0.04, 4.79	—	0.000
Exposure timing															
At birth	3	1.21	1.04, 1.41	0.0	0.000	3	1.22	1.03, 1.43	0.0	0.000	1	1.14	0.63, 2.08	—	0.000
At diagnosis	4	1.36	0.92, 2.00	65.2	0.125	1	3.30	1.03, 10.59	—	0.000	1	0.90	0.31, 2.60	—	0.000
Region															
Asia	—					—					—				
Europe	4	1.36	0.92, 2.00	65.2	0.125	1	3.30	1.03, 10.59	—	0.000	1	0.90	0.31, 2.60	—	0.000
North America	3	1.21	1.04, 1.41	0.0	0.000	3	1.22	1.03, 1.43	0.0	0.000	1	1.14	0.63, 2.08	—	0.000
NO_2															
All leukemia	8	1.04	0.90, 1.19	55.5	0.023	4	1.03	0.90, 1.18	14.9	0.004	1	0.89	0.42, 1.89	—	0.000
Subtype															
ALL	4	1.02	0.89, 1.18	55.6	0.011	2	1.10	0.92, 1.32	46.2	0.008	—				
AML	4	0.97	0.79, 1.19	0.0	0.000	2	0.86	0.60, 1.23	0.0	0.000	—				
Exposure timing															
At birth	4	1.07	0.96, 1.19	0.0	0.000	4	1.03	0.90, 1.18	14.9	0.004	1	0.89	0.42, 1.89	—	0.000
At diagnosis	4	1.17	0.82, 1.67	74.9	0.093	—					—				
Region															
Asia	1	2.29	1.44, 3.64	—	0.000	—					—				
Europe	4	0.91	0.82, 1.00	0.0	0.000	1	0.79	0.52, 1.20	—	0.000	—				
North America	3	1.06	0.95, 1.18	0.0	0.000	3	1.06	0.94, 1.19	1.7	0.000	1	0.89	0.42, 1.89	—	0.000

Note: —, data not available; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CI, confidence interval; I^2, I-squared statistic; RR, risk ratio; τ^2, tau-squared statistic.

(95% CI: 0.92, 2.00) for benzene exposure. When exposure timing in relation to leukemia occurrence was taken into account, studies assessing exposure on the basis of either child's residence at diagnosis or the longest place of residence yielded a higher summary RR for traffic density of 1.32 (95% CI: 1.12, 1.55) and for benzene 1.36 (95% CI: 0.92, 2.00). When exposure assessment was based on maternal residence at birth or during pregnancy, the RR = 0.98 (95% CI: 0.90, 1.06) for traffic indicators and 1.21 (95% CI: 1.04, 1.41) for benzene.

Dose–Response Meta-Analysis

In the dose–response meta-analysis, five studies (Abdul Rahman et al. 2008; Harrison et al. 1999; Houot et al. 2015; Janitz et al. 2016; Langholz et al. 2002) had no value assigned to open-ended categories at the end of the exposure scale. For these we entered a value 20% higher or lower than the closest cut points. In the analysis of traffic density indicators, the restricted cubic spline analysis (Figure 3) showed little association between leukemia RR and the number of vehicles per day (Langholz et al. 2002; Pearson et al. 2000; Raaschou-Nielsen et al. 2001; Reynolds et al. 2004) in the street closest to the child's residence, except at the highest exposure levels where a small and statistically imprecise excess risk emerged (Figure 3A). Three studies used a similar measure of road density around the child's residence (Houot et al. 2015; Magnani et al. 2016; Reynolds et al. 2004), yielding results comparable with those obtained for the vehicles per day metric (Figure 3B). Distance from a major nearby road (Abdul Rahman et al. 2008; Badaloni et al. 2013; Crosignani et al. 2004; Harrison et al. 1999; Houot et al. 2015; Spycher et al. 2015) showed little association

with RR until 150 m from the road's edge, below which an indication of a higher RR emerged and increased steeply with decreasing distance (Figure 3C). For benzene (Crosignani et al. 2004; Heck et al. 2014; Houot et al. 2015; Janitz et al. 2017; Raaschou-Nielsen et al. 2018; Vinceti et al. 2012), there was an approximately linear increase in estimated risk starting from the lowest levels of benzene exposure (1–15 µg/m³), as shown in Figure 4. After stratifying by leukemia subtype, we found a considerably stronger association between benzene exposure and risk of AML (Heck et al. 2014; Houot et al. 2015; Janitz et al. 2017; Raaschou-Nielsen et al. 2018; Vinceti et al. 2012) than we found for ALL (Crosignani et al. 2004; Heck et al. 2014; Houot et al. 2015; Janitz et al. 2017; Raaschou-Nielsen et al. 2018; Vinceti et al. 2012). Concerning NO₂ (Badaloni et al. 2013; Feychting et al. 1998; Heck et al. 2014; Houot et al. 2015; Janitz et al. 2016; Weng et al. 2008), the dose–response meta-analysis showed some evidence of an excess risk starting from 40 µg/m³ to the maximum amount investigated, 60 µg/m³, although the increase was statistically unstable (Figure 5). Subgroup analysis according to disease type showed that this excess risk at the higher exposure levels was limited to ALL (Figure 5). The dose–response analysis could not be carried out for 1,3-butadiene or for PM, due to the limited number of studies reporting the information needed for such an analysis.

Sensitivity Analyses and Publication Bias

We repeated all analyses after systematically excluding each study in turn from the meta-analysis (see Table S4–S5 and Figures S16–S18). None of these analyses appreciably changed the various summary estimates. Use of alternative estimates for

Table 3. Summary risk ratios (RRs) for association of childhood leukemia with particulate matter ($PM_{2.5}/PM_{10}$) and 1,3-butadiene comparing the highest versus the lowest exposure categories for all studies and stratified by age at diagnosis, leukemia subtype, exposure timing, and region.

Indicator	All children					Preschool children (<6 y of age)					Children ≥6 y of age				
	n	RR	95% CI	I^2 (%)	τ^2	n	RR	95% CI	I^2 (%)	τ^2	n	RR	95% CI	I^2 (%)	τ^2
$PM_{2.5}$															
All leukemia	3	1.05	0.94, 1.16	0.0	0.000	3	1.04	0.94, 1.16	0.0	0.000	—				
Subtype															
ALL	2	1.11	0.95, 1.31	0.0	0.000	2	1.11	0.95, 1.31	0.0	0.000	—				
AML	2	1.00	0.87, 1.13	0.0	0.000	2	1.00	0.87, 1.13	0.0	0.000	—				
Exposure timing															
At birth	3	1.05	0.94, 1.16	0.0	0.000	3	1.04	0.94, 1.16	0.0	0.000	—				
At diagnosis	—					—					—				
Region															
Europe	1	1.00	0.72, 1.39	—	0.000	1	0.94	0.62, 1.43	—	0.000	—				
North America	2	1.05	0.94, 1.17	0.0	0.000	2	1.05	0.94, 1.17	0.0	0.000	—				
PM_{10}															
All leukemia	2	1.20	0.70, 2.04	43.5	0.075	2	1.09	0.66, 1.80	12.3	0.028	1	1.50	0.48, 4.70	—	0.000
Subtype															
ALL	1	1.45	0.73, 2.87	—	0.000	1	1.50	0.52, 4.33	—	0.000	1	1.39	0.54, 3.57	—	0.000
AML	1	1.30	0.41, 4.14	—	0.000	1	1.21	0.18, 8.16	—	0.000	1	1.18	0.25, 5.56	—	0.000
Exposure timing															
At birth	1	1.00	0.70, 1.42	—	0.000	1	0.97	0.62, 1.51	—	0.000	—				
At diagnosis	1	1.80	0.82, 3.97	—	0.000	1	1.90	0.60, 6.01	—	0.000	1	1.50	0.48, 4.70	—	0.000
Region															
Europe	2	1.20	0.70, 2.04	43.5	0.075	2	1.09	0.66, 1.80	12.3	0.028	1	1.50	0.48, 4.70	—	0.000
North America	—					—					—				
1,3—Butadiene															
All leukemia	2	1.45	1.08, 1.95	28.0	0.025	2	1.45	1.08, 1.95	28.0	0.025	—				
Subtype															
ALL	2	1.31	1.11, 1.54	0.0	0.000	2	1.31	1.11, 1.54	0.0	0.000	—				
AML	1	2.35	1.02, 5.40	—	0.000	1	2.35	1.02, 5.40	—	0.000	—				
Exposure timing															
At birth	2	1.45	1.08, 1.95	28.0	0.025	2	1.45	1.08, 1.95	28.0	0.025					
At diagnosis	—					—									
Region															
Europe	—					—					—				
North America	2	1.45	1.08, 1.95	28.0	0.025	2	1.45	1.08, 1.95	28.0	0.025	—				

Note: —, data not available; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CI, confidence interval; I^2, I-squared statistic; RR, risk ratio; τ^2, tau-squared statistic.
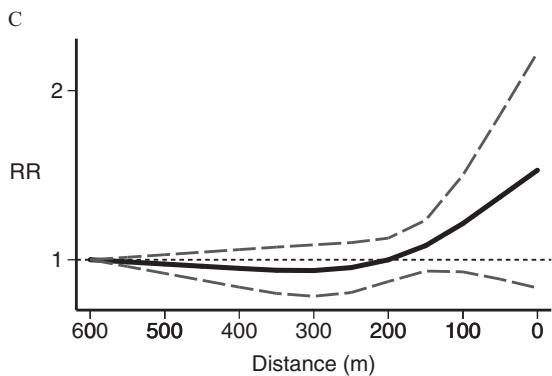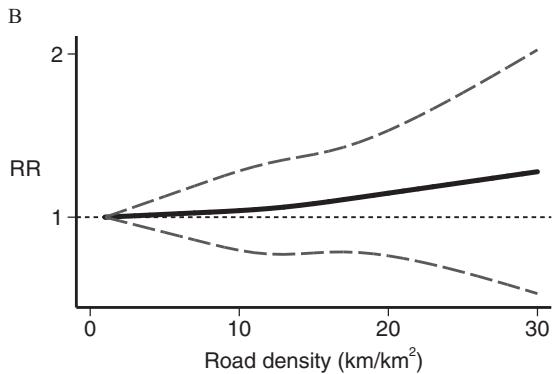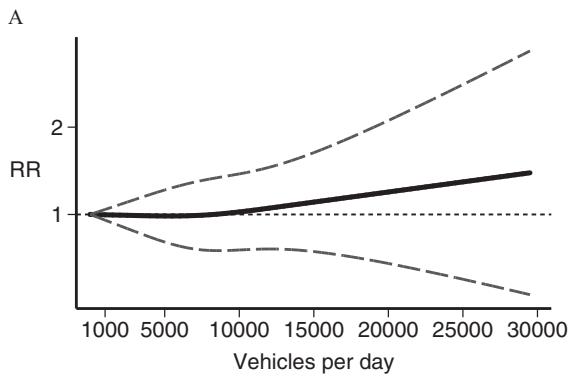
Figure 3. Dose–response meta-analysis of childhood leukemia risk from traffic indicators using (A) vehicles per day count (Langholz et al. 2002; Pearson et al. 2000; Raaschou-Nielsen et al. 2001, Reynolds et al. 2004), (B) road density in km/km^2 (Houot et al. 2015; Magnani et al. 2016; Reynolds et al. 2004), and (C) residential distance from a major road in meters (Abdul Rahman et al. 2008; Badaloni et al. 2013; Crosignani et al. 2004; Harrison et al. 1999; Houot et al. 2015; Spycher et al. 2015). Spline curve (black solid line) with 95% confidence limits (gray dashed lines). RR, risk ratio.

the highest and lowest exposure categories with unknown mean/median values, that is, entering a $\pm 15\%$ value instead of $\pm 20\%$ with relation to the closest (lower and upper) available boundary, also had little effect on the results (see Figures S19–S21). Funnel plots based on the different exposure assessment methods showed a slightly asymmetric distribution, especially for traffic and benzene, and therefore we could not entirely rule out the occurrence of publication bias (Figure S22). Finally, we report study-specific dose–response trends in addition to the overall dose–response meta-analyses in Figures S23–S25.

Discussion

The reviewed literature of epidemiologic studies and the combined dose–response meta-analysis appear to support a relation
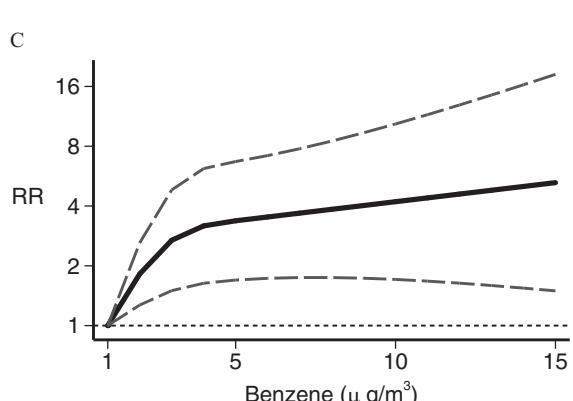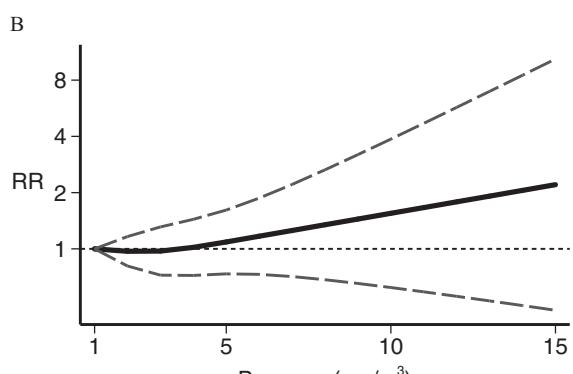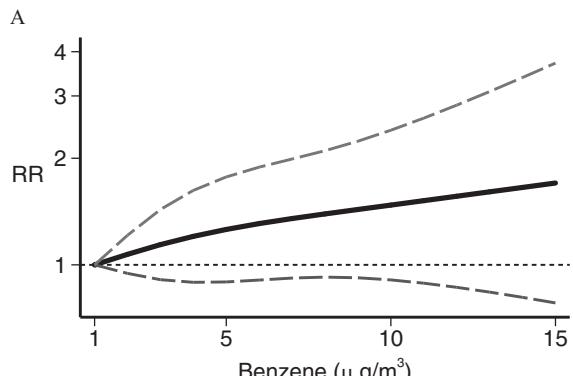
Figure 4. Dose–response meta-analysis of childhood leukemia risk from benzene exposure for (A) all leukemias (Crosignani et al. 2004; Heck et al. 2014; Houot et al. 2015; Janitz et al. 2017; Raaschou-Nielsen et al. 2018; Vinceti et al. 2012), (B) acute lymphoblastic leukemia only (Crosignani et al. 2004; Heck et al. 2014; Houot et al. 2015; Janitz et al. 2017; Raaschou-Nielsen et al. 2018; Vinceti et al. 2012), and (C) acute myeloid leukemia only (Heck et al. 2014; Houot et al. 2015; Janitz et al. 2017; Raaschou-Nielsen et al. 2018; Vinceti et al. 2012). Spline curve (black solid line) with 95% confidence limits (gray dashed lines). RR, risk ratio.

of air pollution, and particularly benzene emissions from motorized traffic, with the risk of childhood leukemia (Table 2 and Figure 4); the strongest associations were found with AML and there was little evidence of any threshold of exposure. For exposure to NO$_2$, little evidence for an association was found except at the highest levels of exposure (Table 3 and Figure 5). Based on a limited number of studies, there was some association with 1,3-butadiene (Table 3) and a weak association with PM$_{10}$ (Table 3), although the dose–response curve could not be assessed for these contaminants.

Air pollution has not been unanimously considered to be associated with childhood leukemia (Sun et al. 2014) due to some inconsistencies across epidemiologic studies (Schüz and Erdmann
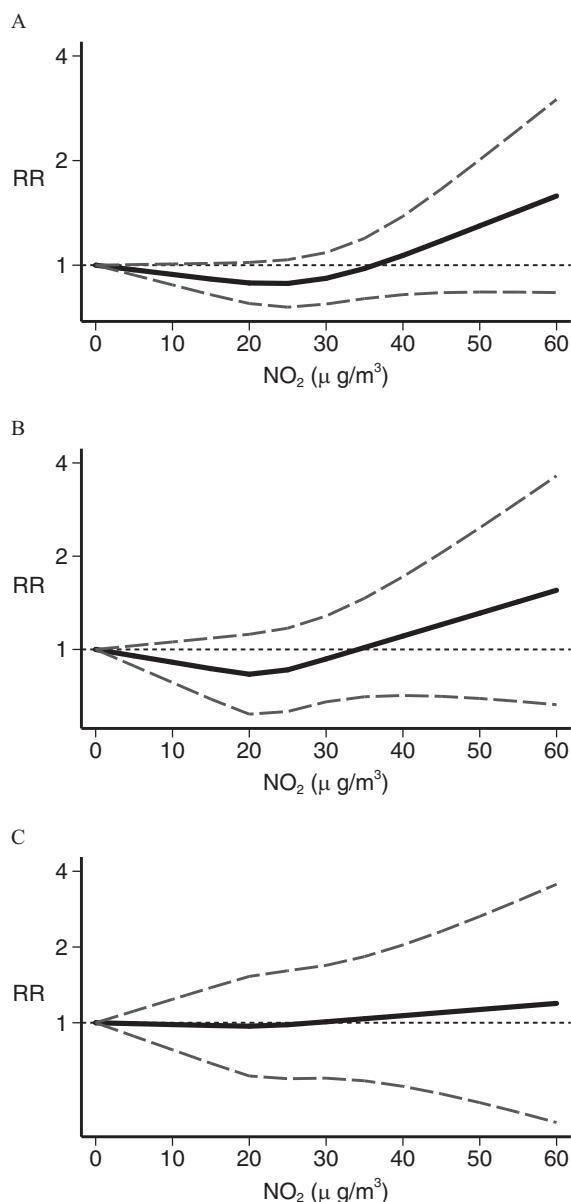
Figure 5. Dose–response meta-analysis of childhood leukemia risk from NO$_2$ exposure for (A) all leukemias (Badaloni et al. 2013; Feychting et al. 1998; Heck et al. 2014; Houot et al. 2015; Janitz et al. 2016; Weng et al. 2008), (B) acute lymphoblastic leukemia only (Heck et al. 2014; Houot et al. 2015; Janitz et al. 2016), and (C) acute myeloid leukemia only (Heck et al. 2014; Houot et al. 2015; Janitz et al. 2016). Spline curve (black solid line) with 95% confidence limits (gray dashed lines). RR, risk ratio.

2016), although most of the recent reviews tend to support such a relation (Boothe et al. 2014; Carlos-Wallace et al. 2016; Filippini et al. 2015; IARC 2016, 2018; Spycher et al. 2017; Steinmaus and Smith 2017). In some instances, the reevaluation of previous databases by conducting stratified analyses for leukemia subtypes has identified associations between benzene exposure from motorized traffic and disease risk, particularly AML, that had previously gone undetected (Raaschou-Nielsen et al. 2001, 2018). In the present review, we took advantage of the availability of nine recently published studies, a reanalysis of a former study (Heck et al. 2014), and a new method for dose–response spline regression analysis (Crippa et al. 2018a) to assess for the first time, to the best of our knowledge, the shape of the relation of exposure to benzene, NO$_2$, and traffic density with childhood leukemia risk. We also attempted to identify

thresholds of exposure, timing of exposure, and the roles of some potential effect modifiers.

A role of outdoor air pollution in childhood leukemia etiology is supported by several laboratory studies, which have provided biological plausibility for this association (Andreoli et al. 2012; Arayasiri et al. 2010; Bollati et al. 2007; Buthbumrung et al. 2008; Carlos-Wallace et al. 2016; D'Andrea and Reddy 2018; Elliott et al. 2017; Jiang et al. 2016; Loomis et al. 2013; McKenzie et al. 2017; Suk et al. 2016; Vattanasit et al. 2014). A review published by the IARC in 2016 defined air pollution as carcinogenic due to its ability to induce lung cancer in humans. This review reported evidence from animal and mechanistic studies supporting the carcinogenicity of air pollution for lung cancer and identified the several inorganic and organic components of air pollution classified as established, probable, or possible carcinogens (IARC 2016). However, with reference to the above evidence, it should be noted that many of the laboratory studies were carried out using mixtures, precluding identification of the specific pollutants responsible for the increased risk. Evidence from animal carcinogenicity data and mechanistic data has also recently been made available, specifically for benzene (IARC 2018), showing the capacity of this compound to generate reactive electrophilic metabolites, induce oxidative stress, and DNA damage as well as immunotoxic and hematotoxic effects.

Although exposure to benzene, an established leukemogen in adults for the acute myeloid form (IARC 2018), was associated with disease risk in our analysis, exposure assessed through traffic indicators such as road density or distance showed limited association with childhood leukemia (Figure 3). This discrepancy may indicate that traffic-related metrics are less sensitive as a measure of outdoor air pollutants than modeled levels of carcinogenic pollutants such as benzene and 1,3-butadiene, as has been reported elsewhere (Wu et al. 2011). This would explain the smaller estimates of effect seen when using surrogate measures of exposure (Table 2). The higher risk observed for families living within 150 m of a major road is of considerable interest, however, because it suggests a distance potentially usable by policymakers considering placement of schools or other facilities for children. This 150-m corridor is characterized by high levels of carcinogenic air pollutants, including heavy metals and benzene, with a sudden drop in their concentration outside that range (Karner et al. 2010).

A few of the studies we reviewed have suggested that other air pollutants, such as 1,3-butadiene and selenium (Heck et al. 2014; Knox 2006; Symanski et al. 2016; Vinceti et al. 2012), may be associated with childhood leukemia risk. However, few studies have controlled for other pollutants simultaneously (Heck et al. 2014; Symanski et al. 2016). Therefore, we acknowledge that an etiologic relation between air pollution and childhood leukemia risk, which is supported by our findings and appears to be mainly attributable to benzene, might be at least partly due to other pollutants in outdoor air that covary with benzene emissions (Ghosh et al. 2012; Heck et al. 2014; Vinceti et al. 2012; Wilhelm et al. 2011), acting either alone or as mixtures. In the two published studies on 1,3-butadiene, correlations with benzene were high (Heck et al. 2014; Symanski et al. 2016). Exposure assessment methods based on denser air pollution monitoring networks or more sophisticated air pollution models may be better able to differentiate between the effects of benzene and 1,3-butadiene and, more generally, to tease apart the influence of each toxic agent.

Our meta-analysis suggested a differential effect of traffic-related benzene exposure according to the clinical subtype of leukemia, that is, a much higher risk associated with AML compared with ALL (Table 2 and Figure 3). Conversely, little evidence of such a differential relation with disease type emerged when assessing exposure through traffic indicators and PM levels. For

NO$_2$, a pollutant so far not recognized as a carcinogen, the association appeared to be limited to ALL and to the highest exposure levels only (Table 3 and Figure 5).

We observed higher RRs associated with benzene exposure in the postnatal period compared with the perinatal window of exposure (Table 2). We found higher estimates for benzene exposure in younger (<6 y of age) compared with older children, although for the latter, little data were available. There was also an indication of an interaction between exposure window and age given that the excess disease risk associated with benzene exposure at diagnosis compared with exposure at birth was limited to the youngest children, although based on only one study. A previous meta-analysis investigating the association between traffic exposure and childhood leukemia risk found similar results, that is, a higher summary RR for exposure at diagnosis than for exposure at birth or gestation; effect–measure modification by age was not investigated in that study (Carlos-Wallace et al. 2016).

We also detected slightly stronger RRs for benzene exposure in Europe compared with North America (Table 2). This difference might result from misclassification of exposure stemming from greater residential mobility in North America (Lupo et al. 2010; Tee Lewis et al. 2019; Urayama et al. 2009) or by the larger influence of postnatal exposure assessment in European studies. We also note that there is a much larger percentage of diesel cars in Europe than in North America (Neumaier 2014), possibly reflecting differences in pollutant exposure characterizing the two regions. Another potential source of discrepancy might be the use in some of the U.S. studies of methods based on a "nearest-neighbor" exposure assessment that has been carried out at the census tracts level or using a limited number of air monitors (Heck et al. 2014; Symanski et al. 2016). These methods likely yield a lower spatial resolution compared with person-level exposure data based on air pollution dispersion modeling at the residential address, thus adding to exposure misclassification and likely diluting the RRs.

Some degree of unmeasured confounding may have occurred in the studies, due to sources of outdoor air pollution such as oil and gas development (Elliott et al. 2017; McKenzie et al. 2017) and industrial sources (García-Pérez et al. 2015; Park et al. 2017), indoor air pollution from heating sources and dust (Whitehead et al. 2011, 2015), passive smoking (Metayer et al. 2016b; Pyatt and Hays 2010), magnetic field exposure (Amoon et al. 2018), and socioeconomic factors (Kehm et al. 2018b). However, most of these factors are unlikely to play a major role in disease etiology, and some studies we included in the meta-analysis, particularly the most recent ones, took into account several potential confounding factors, yielding results in line with the overall meta-analysis (Table 1 shows the confounding factors considered in each study). In addition, we systematically used the most adjusted RRs to carry out our meta-analysis. The occurrence of selection bias could also be ruled out particularly for the most recent studies, including all those assessing benzene exposure in relation to disease risk given that they were population-based and not dependent on voluntary participation.

In conclusion, in this systematic review and dose–response meta-analysis, we found that traffic-related air pollution, particularly exposure to benzene, was associated with excess risk of childhood leukemia. No apparent minimal threshold of exposure emerged for benzene, whereas analyses for traffic density and NO$_2$ gave evidence of such a threshold. Disease subtype, windows of exposure and child's age appeared to modify these associations.

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