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Residential Traffic Exposure and Childhood Leukemia:

A Systematic Review and Meta-analysis

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Abstract

Context—Exposure to elevated concentrations of traffic-related air pollutants in the near-road environment is associated with numerous adverse human health effects, including childhood cancer, which has been increasing since 1975. Results of individual epidemiologic studies have been inconsistent. Therefore, a meta-analysis was performed to examine the association between residential traffic exposure and childhood cancer.

Evidence acquisition—Studies published between January 1980 and July 2011 were retrieved from a systematic search of 18 bibliographic databases. Nine studies meeting the inclusion criteria were identified. Weighted summary ORs were calculated using a random effects model for outcomes with four or more studies. Subgroup and sensitivity analyses were performed.

Evidence synthesis—Childhood leukemia was positively associated (summary OR=1.53, 95% CI=1.12, 2.10) with residential traffic exposure among seven studies using a postnatal exposure window (e.g., childhood period or diagnosis address) and there was no association (summary OR=0.92, 95% CI=0.78, 1.09) among four studies using a prenatal exposure window (e.g., pregnancy period or birth address). There were too few studies to analyze other childhood cancer outcomes.

Conclusions—Current evidence suggests that childhood leukemia is associated with residential traffic exposure during the postnatal period, but not during the prenatal period. Additional well-designed epidemiologic studies that use complete residential history to estimate traffic exposure, examine leukemia subtypes, and control for potential confounding factors are needed to confirm these findings. As many people reside near busy roads, especially in urban areas, precautionary public health messages and interventions designed to reduce population exposure to traffic might be warranted.

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Introduction

In recent years, public health concern has grown regarding population exposure to traffic-related air pollutants and adverse human health effects. Numerous studies have documented that concentrations of traffic-related air pollutants are highest in the near-road environment.[1–4] In North America, an estimated 30%–45% of people in large urban areas live near major roads,[5] suggesting increased exposure to traffic-related air pollution and risk of adverse health outcomes.

Epidemiologic studies of health effects associated with residential traffic exposure have used varied exposure assessment methods. One approach uses monitored or modeled concentrations of specific traffic-related air pollutants to investigate the potential causal agent(s) associated with health outcomes.[6] Exposure assessments based on monitoring data do not reflect local variation in pollutant concentrations and are limited to areas with air pollution monitors.[7] Assessments based on modeling can capture local variations but are computationally complex, requiring detailed data that might not be readily available.[7] A common alternative approach uses direct measures of traffic, commonly referred to as "traffic proximity measures," which incorporate both distance to roads and indicators of traffic density (e.g., distance to a major road and traffic density within a buffer). Traffic proximity measures capture the overall mixture of tailpipe emissions; fugitive emissions from brake, tire, and roadway wear; and other factors, including noise. A large, growing body of scientific research has shown an association between residential traffic proximity measures and adverse health outcomes, including asthma, respiratory symptoms, and lung function[8–12]; cardiovascular disease[13–15]; adverse reproductive outcomes[16,17]; and premature mortality.[18–20] Studies of traffic exposure and childhood cancer have provided inconclusive results.[5]

The incidence of childhood cancer in the U.S. has been increasing since 1975.[21] The most common form of childhood cancer is leukemia, which represents approximately one third of all cancers among children aged 0–14 years.[22] By subtype, acute lymphoblastic leukemia (ALL) accounts for 79% of childhood leukemia cases, followed by acute myeloblastic leukemia (AML) and other rarer types.[22] Although ALL can occur throughout one's life span, the median age of diagnosis is 14 years with peak incidence occurring between age 2 and 14 years.[23,24]

The etiologic mechanism is unknown for approximately 90% of childhood leukemia cases.[25] Much of this uncertainty results from potential multifactorial etiologies and complex gene–environment interactions.[26] Established risk factors for childhood leukemia include age, gender, race/ethnicity, prenatal exposure to x-rays, exposure to therapeutic radiation and chemotherapeutic agents, and specific genetic syndromes.[23,26] Other potential risk factors include exposure to benzene and poly-aromatic hydrocarbons (PAHs), which are components of traffic emissions.[26–28] The role of SES as a risk factor for childhood leukemia is controversial, and some investigators recommend that SES be examined as a potential confounder in future epidemiologic studies.[26]

Meta-analyses of observational studies can summarize existing evidence and inform future epidemiologic and mechanistic research by exploring the potential reasons for heterogeneity among the included studies.[29] This systematic review and meta-analysis is part of a larger effort by the CDC to synthesize the growing body of evidence on the association between residential traffic exposure and numerous health outcomes, without any prior judgment of the specific pollutants or related factors. This specific study examines the association between residential traffic exposure and childhood cancer.

Findings and Recommendations from Other Reviews

No meta-analysis has been published to date of studies assessing the association between residential traffic exposure and childhood cancer. In 2010, the Health Effects Institute (HEI) issued a Special Report that summarized and synthesized information on the health effects of traffic-related air pollution.[5] On the basis of a review of five childhood cancer studies, the HEI report concluded that the evidence was “inadequate and insufficient” to make inferences for causality between exposure to traffic pollution and any childhood cancer, including childhood leukemia.[5]

Methods

Literature Search

A comprehensive literature search was performed to identify studies examining the association between residential traffic exposure and any health outcome, including childhood cancer. Electronic searches were conducted in 18 bibliographic databases: MEDLINE+, Embase, PsycINFO, Cochrane, Eric, Sociological Abstracts, Social Services Abstracts, Health and Safety Sciences Abstracts, CINAHL, EconLit, Web of Science, Transportation Research Information Services (TRIS), Global Health, Science Direct, LILACS, Enviroline, Dissertation Abstracts, and Pollution Abstracts. A search strategy was created for use in MEDLINE+ and was adapted to fit the other databases. It included MeSH terms and key words representing three constructs that were combined using the “AND” operator as follows: 1) “health” (which included general terms such as disease, illness, and mortality, in addition to outcome-specific terms such as cancer, neoplasm, and leukemia), 2) “vehicle emissions” (which included terms for pollution, emissions, and exhaust combined with terms for traffic, vehicles, and roads), and 3) “exposure” (e.g., proximity, distance, density, and intensity). The electronic search was limited to English-language articles published and indexed from January 1980 through July 2011.

Inclusion Criteria

This systematic review included peer-reviewed journal articles, abstracts, scientific reports, and dissertations. For inclusion in the overall review, studies had to (1) be an original study; (2) use an individual-level analytic design with a control group (i.e., cross-sectional, case-control, or cohort design); (3) use a traffic exposure measure based on the distance to roads and traffic density (i.e., not measured or modeled concentrations of specific traffic-related pollutants); (4) assess traffic exposure at the residential address (i.e., not the postal code or census tract level); (5) provide or be able to compute an effect size that estimates the association between residential traffic exposure and a health outcome (e.g., OR, relative risk

[RR], standardized incidence ratio [SIR]); and (6) be conducted in a "high-income economy" country, as designated by the World Bank.[30] This specific review is limited to studies of childhood cancer.

Study Selection and Data Extraction

All citations were independently screened for inclusion by two coders in three sequential steps: title, abstract, and full text. For each included citation, data extraction was performed independently by two coders, who were blinded to journal and authors' names and affiliations, using a standard form that included information on: study design, health outcome assessment, traffic exposure assessment, participant characteristics, statistical analysis, and effect estimates and 95% CIs. This information was entered into a Microsoft Access database and discrepancies were resolved by the two coders.

Study quality was assessed using a subset of the extracted information. A study quality scale was developed using elements of existing scales[31–33] and methodological factors specific to this review (e.g., type of observational study design, quality of traffic exposure assessment, and quality of health outcome assessment). The scale included 17 items with a maximum possible score of 40. Studies were categorized as either high or low quality for subgroup analyses.

From each study, one effect estimate per health outcome was selected based on the following independent considerations: it (1) represented the longest exposure window (e.g., childhood period preferred over pregnancy period or birth address); (2) best characterized traffic exposure (e.g., multiple road metric preferred over single road metric); (3) compared the highest to the lowest exposure category; (4) addressed confounding by sociodemographic and behavioral factors (e.g., adjusted OR preferred over crude OR); and (5) was not adjusted for measured or modeled concentrations of traffic-related air pollutants (i.e., to avoid possible over adjustment).

Statistical Analysis

A meta-analysis was conducted for childhood cancer outcomes with four or more independent effect estimates. All but one of the included studies quantified the association between traffic exposure and childhood cancer using ORs. Weighted summary ORs and 95% CIs were calculated using a random-effects model to provide an overall estimate of the strength of the association between residential traffic exposure and each childhood cancer outcome. The random-effects model was chosen a priori, as exposure metrics, populations, and contexts were expected to vary substantially between studies. The analysis plan included sensitivity and subgroup analyses and assessment of heterogeneity and publication bias. All statistical analyses were conducted using Comprehensive Meta-Analysis (version 2.2.055).[34] The software will not calculate the SE if the 95% CIs are not symmetric on a log scale, which can occur as a result of rounding. In these situations, the single confidence limit (upper or lower) that conservatively resulted in a larger estimated SE was selected.

Sensitivity Analyses

A one-study-removed sensitivity analysis was conducted to determine whether any individual study overly influenced the summary OR.[35] Sensitivity analyses were conducted to assess the effect of potential outliers and inclusion of other effect estimates on the findings.

Heterogeneity

Heterogeneity was assessed using the Q test[36] and I^2 statistic.[37] The I^2 value, which can range from 0% to 100%, reflects the proportion of variability in the summary estimate that can be attributed to between-study heterogeneity; values of 25%, 50%, and 75% were considered low, moderate, and high, respectively.[38]

Subgroup Analyses

To examine the role of potential effect modifiers and explore heterogeneity sources, subgroup analyses were conducted on variables with a minimum of two studies per subgroup. Subgroup weighted summary ORs were calculated using a random-effects model with a pooled estimate of tau-squared. A Q-test based on ANOVA was used to compare summary effects between subgroups. I^2 was calculated for each subgroup. The following study characteristics were considered for subgroup analyses: study location, study time period, age of the study population, source of controls, type of exposure metric, timing of exposure assessment, cancer type, control for SES, and study quality. A study was considered to control for SES if the results were adjusted for income, occupation, or education level of either parent or the household, or if the authors reported that adjustment for these factors had little effect on their findings.

Publication Bias

Publication bias was evaluated by visually inspecting a funnel plot[39] and conducting the Begg and Mazumdar rank correlation test,[40] Egger's test of the intercept,[41] and Orwin's fail-safe N analysis.[42] For the Orwin's fail-safe N analysis, the trivial OR was set at 1.10 and the mean OR for the missing studies was assumed to be null or 1.00.

Results

Evidence Synthesis

The literature search yielded more than 17,500 citations that were screened for inclusion. Eleven citations that met the inclusion criteria had childhood cancer as an outcome.[43–53] After the studies were extracted and unblinded, two of the citations were found to have examined the same, or a subset of the same, study population as another included study. In the case of Reynolds et al. 2001[48] and 2004,[49] the later citation was retained because it reported on the full study population; the earlier citation reported on a pilot study among a population subset. In the case of Savitz et al.[50] and Pearson et al.,[46] the latter citation conducted an independent reanalysis of the Savitz et al. study population using a slightly different exposure metric. Savitz et al. was retained because it reported a smaller, more

conservative effect estimate and provided additional study details that resulted in a higher quality score.

Among the nine unique childhood cancer studies, eight case-control studies reported ORs and one population-based study reported SIRs as the effect measure. The population-based study by Visser et al.[52] calculated SIRs for all cancer sites, all hematologic malignancies, and ALL among children. All eight case-control studies examined childhood leukemia (i.e., leukemia, acute leukemia, or ALL) and three of eight studies examined other childhood cancer outcomes (i.e., all cancer sites, lymphomas, central nervous system tumors, brain tumors, and soft tissue tumors) (Table 1). A meta-analysis of the eight childhood leukemia case-control studies was conducted; inclusion of the population-based study was examined in the sensitivity analysis. There was an insufficient number of studies (<four) to conduct meta-analyses for the other childhood cancer outcomes.

Descriptive Results

The characteristics of the eight case-control childhood leukemia studies are summarized in Table 1. Seven studies used population-based controls and Steffen et al.[51] used hospital-based controls. Four studies were conducted in the U.S.[45,49,50,53] and four were conducted in Europe.[43,44,47,51] The study time frame (i.e., year of diagnosis) ranged from 1968 to 2004. Six studies included children aged 0–14 years at diagnosis; Langholz et al.[45] included children aged 0–10 years and Reynolds et al.[49] included children aged 0–4 years.

A variety of traffic exposure measures were used across the eight studies; however, each study used only one traffic exposure measure that met our inclusion criteria. Three studies[45,49,53] used “multiple road measures” (e.g., cumulative traffic density within a 500-ft radius or distance-weighted traffic density within a 1500-ft buffer) and five studies[43,44,47,50,51] used “single road” measures (e.g., distance to the nearest major road or traffic density on the street of residence), of which Steffen et al.[51] was based on self-reports. In addition, the studies assessed traffic exposure at various time points and periods, representing different exposure windows. Five of the studies assessed exposure using a single residential location such as address at the time of birth,[49] at the time of diagnosis, [43,44,50] and of the longest duration between birth and diagnosis.[45] Von Behren et al.[53] presented results for three exposure windows: birth address, diagnosis address, and time-weighted lifetime average (i.e., childhood period). Rasschou-Nielsen et al.[47] and Steffen et al.[51] each examined two period-based exposure windows, the pregnancy and childhood periods. All eight studies addressed potential confounding by known individual risk factors of age and gender, either through matching or statistical adjustment. Three studies addressed potential confounding by SES through statistical adjustment for income, occupation, or education.[43,50,53] Savitz et al.[50] presented crude ORs and reported qualitatively that adjustment for a number of covariates, including gender, age, and father’s education level, had little effect on their findings.

Meta-analysis Results

The results of the initial meta-analysis of eight case-control studies indicated a positive association between childhood leukemia and residential traffic exposure (OR=1.39, 95%

CI=1.03, 1.88) with a moderate to high degree of heterogeneity (Q=16.42, df=7, p=0.02, I^2=57.4%). Examination of potential sources of heterogeneity determined that a meaningful difference in the effect estimate existed by exposure window. Thus, separate meta-analyses were conducted for two exposure windows. The exposure windows were categorized as "prenatal" (i.e., pregnancy period or birth address) and "postnatal" (i.e., childhood period, diagnosis address, or address of longest duration). The three studies that analyzed more than one exposure window within the same study population were included in both meta-analyses.

Postnatal exposure window—The weighted summary OR was 1.53 (95% CI=1.12, 2.10) for the seven studies that used a postnatal exposure window to assess residential traffic exposure. Figure 1 shows a forest plot of the OR and 95% CI from each study and the weighted summary OR and 95% CI. In four instances in which rounding by the study authors resulted in an asymmetric 95% CI, the lower[43,45] or upper[47,51] CI that conservatively resulted in a larger estimated SE was selected. There was a low-to-moderate degree of heterogeneity in the effect estimates across the seven studies (Q=9.64, df=6, p=0.14, I^2=37.8%).

In the subgroup analyses, no statistically significant differences were observed in the subgroup summary ORs by study location, study time period, type of exposure metric, cancer type, control for SES, or quality score (Table 2). For each variable, the within-subgroup heterogeneity was moderate (I^2=42%–62%) for the subgroup that contained Savitz et al.[50] and low (I^2=0%–15%) for the other subgroup. Too few studies per subgroup existed to conduct subgroup analyses by other study characteristics (e.g., age of study population or source of controls).

In the one-study-removed sensitivity analysis, the weighted summary OR remained statistically significant in all instances, ranging from 1.33 (95% CI=1.05, 1.69) when Savitz et al.[50] was removed to 1.71 (95% CI=1.20, 2.42) when Steffen et al.[51] was removed. In addition, removal of Savitz et al. eliminated all evidence of heterogeneity among the remaining six studies (I^2 decreased from 37.8% to 0%), suggesting that this study's large effect estimate (OR=4.7) could be an outlier. Thus, further sensitivity analyses with this study were conducted. Using a smaller, more conservative OR from Savitz et al. (i.e., OR=2.7 for exposure to ≥5000 vehicles per day vs <500 vehicles per day) slightly reduced the summary OR from 1.53 to 1.48 (95% CI=1.13, 1.92) and decreased heterogeneity among the seven studies (I^2=20.8%). These sensitivity analyses suggest that no single study was overly influential in determining the weighted summary OR.

The impact of including the population-based study by Visser et al.[52] (SIR=2.5, 95% CI=0.8, 5.9) in the meta-analysis was assessed by entering the SIR in the software as an OR (i.e., SE was estimated on a log scale). The random effects weighted summary OR increased slightly from 1.53 to 1.57 (95% CI=1.17, 2.12) with the inclusion of Visser et al.

Visual inspection of the funnel plot revealed some evidence of publication bias. The Begg and Mazumdar rank correlation test (one-tailed p=0.02) and Egger's test of the intercept (one-tailed p<0.01) were both statistically significant, indicating the presence of publication

bias. However, the Orwin's fail-safe N calculation determined that 19 missing studies reporting a null effect (OR=1.0) would be needed to reduce the fixed-effects summary OR from 1.41 to 1.10.

Prenatal exposure window—The weighted summary OR was 0.92 (95% CI=0.78, 1.09) for the four studies that used a prenatal exposure window.[47,49,51,53] There was no evidence of heterogeneity (Q=0.96, df=3, p=0.81, I^2=0.0%) or publication bias. No statistically significant differences were observed in the subgroup analysis for any of the study characteristics examined (data not shown).

Discussion

This systematic review and meta-analysis examined the current body of evidence on residential exposure to traffic and childhood leukemia and found that the association is dependent on the time period used to estimate traffic exposure. According to seven published studies, there is a positive and significant association between childhood leukemia and high residential traffic exposure during the postnatal period. No association was found among the four studies that assessed traffic exposure during the prenatal period. Although a statistical test was not conducted to compare the summary ORs because of the dependency on effect estimates, the non-overlapping 95% CIs indicate that the summary ORs differ between the prenatal and postnatal exposure windows. This finding is supported by the three studies that analyzed more than one exposure window within the same population. Specifically, these three studies reported a smaller effect estimate when birth or pregnancy address was used compared to their postnatal exposure effect estimate. In two instances, the prenatal exposure OR was <1.0 and the postnatal exposure OR was >1.0.[47,51] These findings confirm the importance of assessing exposure timing in childhood cancer studies[26,54,55] and suggest that the critical exposure window for childhood leukemia associated with proximity to traffic might occur after birth.

The finding that residential exposure to traffic is associated with childhood leukemia is supported by a number of recent studies. Traffic emissions represent a primary source of known carcinogens, including benzene.[56] Recent mechanistic studies suggest that benzene exposures can initiate both ALL and AML.[57] Previous studies have reported an association between childhood leukemia and modeled ambient concentrations of benzene near the place of residence.[58–60] Two of these studies also examined the association between leukemia subtypes and benzene exposure and found stronger associations for AML than for ALL.[59,60] Additionally, Vinceti et al. reported independent but weaker associations between childhood cancer and exposure to traffic-related particulate matter with a diameter ≤10 μm (PM_{10}).[59]

The findings of this meta-analysis reflect the current literature, and the interpretation of results should take into consideration the methodological limitations of the included studies. First, inconsistent traffic exposure measures were used across individual studies. Accordingly, residential traffic exposure was examined by comparing "high" versus "low" traffic exposure, which prohibited conclusions about a specific distance or traffic density associated with an increased odds of childhood leukemia.

Second, residential mobility could result in exposure misclassification, particularly when estimating exposure using a single point-in-time birth or diagnosis address. Studies have shown a high degree of mobility among U.S. children with leukemia, with 50%–66% having different birth and diagnosis addresses.[47,49,55] Two of eight included studies conducted a subgroup analysis by residential mobility, and both reported stronger associations between traffic exposure and childhood leukemia among children with a stable residential history.[43,50]

Third, all but two of the original studies, and consequently this meta-analysis, aggregated childhood leukemia subtypes as a single outcome. Von Behren et al.[53] included only cases of ALL in their analysis and did not make comparisons with non-ALL subtypes. Amigou et al.[43] is the only included study that stratified their results by leukemia subtype, and they reported no difference in the magnitude of association between ALL and non-ALL subtypes. Use of an aggregate outcome measure could bias the results toward the null if traffic exposure affects leukemia subtypes differentially.[59,60] Thus, the results from this meta-analysis represent the average association across all types of leukemia.

Fourth, the assessment of potential confounders, such as SES and exposure to electromagnetic fields, varied across the individual studies. In the U.S., individuals with a lower SES have greater exposure to traffic than those with a higher SES;[61–63] however, this association might not hold in European cities.[52] The literature is inconsistent regarding the association between SES and childhood leukemia, with results varying by study location and time period, study design, and type of SES measure used.[64–66] Three of the included studies adjusted for SES in multivariate analyses, but only Savitz et al. commented on whether adjustment attenuated the association.[43,50,53] Additionally, previously conducted meta-analyses and pooled analyses have found an association between electromagnetic fields and childhood leukemia.[67] Only one included study assessed the impact of controlling for electromagnetic fields and reported slightly reduced ORs between traffic exposure and childhood leukemia.[45]

This meta-analysis was limited by the small number of included studies, which prohibited extensive exploration of potentially important sources of heterogeneity. Subgroup analyses could not be conducted for all variables of interest, and the small sample size limited the power to detect statistically significant differences between subgroups.

This study has several strengths. To our knowledge, it is the first systematic review and meta-analysis to examine traffic exposure and childhood leukemia by exposure window. A comprehensive search strategy minimized the likelihood that relevant studies were missed. Rigorous coding and data abstraction procedures ensured accurate data collection. The results were robust to a number of sensitivity analyses.

Conclusions

Nationwide, more than 10% of the U.S. population resides near major roads,[68] and in large urban areas the estimate can be as high as 30%–45%.[5]

The finding that residential exposure to traffic after birth is associated with increased risk of childhood leukemia can inform pre-cautionary health messages targeted to the general public and professionals responsible for community design. Simple information on the distance to roads or amount of traffic on nearby roads can be used when making personal residential location choices. Urban planners and transportation engineers can use the results of this review to inform future land-use planning and transportation systems. For example, residential exposure to traffic could be reduced by minimizing the development of high-density residential buildings near busy roads. However, public health and planning professionals involved in the design of communities will need to balance the potentially competing public health goals of promoting physical activity, preventing injuries, and reducing traffic exposure.

Given the findings of this review and the biological plausibility of an association between childhood leukemia and traffic-related air pollutants, further research is warranted. Specifically, well-designed epidemiologic studies of residential traffic exposure that estimate traffic exposure using complete residential history, assess associations by leukemia subtypes, and examine known and suspected confounding factors are needed to verify these findings. In addition, further examination of the association between residential traffic exposure and other health outcomes is needed to help guide public health interventions and strategies to reduce population exposure to traffic-related air pollution.

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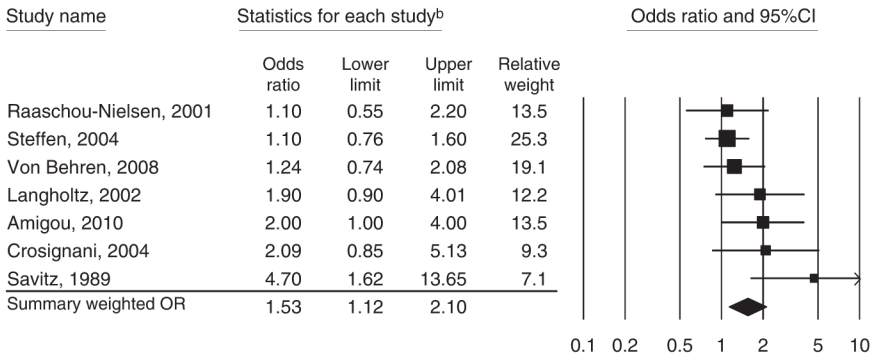

Figure 1.

Forest plot of case-control studies examining the association between residential traffic exposure assessed during the postnatal period[a] and childhood leukemia, and the random effects weighted summary OR and 95% CI

Note: The weighted summary OR is derived from the random effects model. For each study, the center of the box denotes the OR, the horizontal line denotes the 95% CI, and the size of the box is proportional to the study's weight in the calculation of the overall effect. The weighted summary OR is denoted by the center of the diamond and the 95% CI is denoted by the points of the diamond.

[a]Includes studies that assessed residential traffic exposure throughout the childhood period, at the time of diagnosis, or at the address of longest duration between birth and diagnosis

[b]Because of asymmetric 95% CIs due to rounding, either the lower (Amigou and Langholtz) or upper (Raaschou-Nielsen and Steffen) confidence limit was selected to calculate the SE and the opposite confidence limit Thus, the 95% CI values shown for these four studies are not identical to those of the published results.

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Table 1

Characteristics of included case-control studies examining the association between residential traffic exposure and childhood leukemia

Reference	Study location and time frame	Cancer types	Number of leukemia cases/ controls	Age of subjects (years)	Exposure measure type	Exposure window	Traffic exposure categories (high vs low)	Covariates addressed in analysis[a]
Amigou et al., 2011[41]	France; 2003–2004	Acute leukemia (ALL and ANLL subtypes)	763/1681	0–14	Single road (proximity to major road)	Diagnosis address	<500 m from both Class 1 and Class 2 roads vs >500 m from any Class 1, 2, or 3 roads[b]	Age, gender, SES[c]
Crosignani et al., 2004[42]	Italy; 1978–1997	Leukemia	120/480	0–14	Single road (proximity to major road)	Diagnosis address	<20 m to road with >10,000 vpd vs >150 m to road with <10,000 vpd	Age, gender
Langholz et al., 2002[43]	U.S. (Los Angeles County, California); 1978–1984	Leukemia	212/202	0–10	Multiple road (DWTD within 1500-ft radius)	Residence of longest duration	Approximately ≥28,000 vpd vs <2,000 vpd	Age, gender
Raaschou-Nielsen et al., 2001[45]	Denmark; 1968–1991	Leukemia; CNS; lymphoma; 3 types combined	986/1972	0–14	Single road (traffic density on street of residence)	Pregnancy period; childhood period[d]	≥10,000 vpd vs <500 vpd	Age, gender, calendar time
Reynolds et al., 2004[47]	U.S. (California); 1988–1997	All cancer sites; leukemia; CNS	1728/3456	0–4	Multiple road (traffic density within 500-ft radius)	Birth address	≥236,000 VMT/mi^2 vs 0 VMT/mi^2 (no major road within 500 ft)	Age, gender, race
Savitz et al., 1989[48]	U.S. (Denver Colorado); 1976–1983	All caner sites; leukemia; lymphoma; brain; soft tissue; other	98/262	0–14	Single road (traffic density on street of residence)	Diagnosis address	≥10,000 vpd vs <500 vpd	Age, gender, year of diagnosis, residence type, birth location, maternal age, maternal smoking, paternal education, per capita income[e]
Steffen et al., 2004[49]	France; 1995–1999	Acute leukemia	280/285	0–14	Single road (self-report proximity to major road)	Pregnancy period; childhood period[f]	<50 m from heavy traffic road vs not	Age, gender, ethnicity, center
Von Behren et al., 2008[51]	U.S. (Northern California); 1995– 2002	ALL	310/396	0–14	Multiple road (traffic density within 500-ft radius)	Birth address; diagnosis address; childhood period	≥91,462 VMT/mi^2 vs 0 VMT/mi^2 (no major road within 500 ft)	Age, gender, race, ethnicity, income

[a] Potential confounding by covariates can be addressed in the analysis through matching and appropriate use of conditional logistic regression, adjustment in a multivariate model, or indication by authors that adjustment for these factors had little effect on their findings

[b] Class 1, high-speed freeways and bypasses; Class 2, main roads connecting Class 1 roads; Class 3, secondary roads

[c] SES measured by the highest (maternal or paternal) professional/occupational category of parents at the time of the interview

[d] Childhood period includes addresses from birth through 12 months before diagnosis

[e] Savitz et al. presented the unadjusted OR and reported qualitatively that adjustment for age, gender, year of diagnosis, birth location, paternal education, and per capita income had little to no effect on the OR. Simultaneous adjustment for residence type, mother's age, mother's smoking, and wire configuration code at diagnosis slightly reduced the OR, but adjusted findings were only presented for the dichotomous exposure variable

[f] Study participants were asked about exposure to heavy traffic roads in the vicinity (<50 m) of the children's homes. It is not clear how the data were aggregated to represent the pregnancy and childhood periods

ALL, acute lymphoblastic leukemia; ANLL, acute non-lymphoblastic leukemia; CNS, central nervous system; DWTD, distance-weighted traffic density; VMT, vehicle miles traveled; vpd, vehicles per day.

Table 2

Weighted summary ORs for case-control studies examining the association between postnatal rehidential traffic exposure and childhood leukemia, stratified by study characteristics

Variable	Subgroup (no. of studies)	Subgroup summary OR[a] (95% CI)	*p*-value[b]	I^2 value (%)[c]
Study location	U.S. (3)	1.84 (1.08, 3.13)	0.42	60.1
	Europe (4)	1.39 (0.91, 2.13)		15.3
Study time period	Pre-1995 (4)	1.89 (1.18, 3.02)	0.24	42.0
	1995 or later (3)	1.31 (0.89, 1.93)		9.7
Type of exposure metric	Multiple road (2)	1.48 (0.79, 2.78)	0.81	0.0
	Single road (5)	1.62 (1.06, 2.48)		54.5
Cancer type[d]	Leukemia (4)	1.83 (1.22, 2.75)	0.59	42.0
	Acute leukemia (2)	1.26 (0.91, 1.75)		54.8
Control for SES	Yes (3)	1.87 (1.12, 3.11)	0.35	61.1
	No (4)	1.36 (0.90, 2.07)		1.0
Quality score[e]	≥Median score (4)	1.84 (1.22, 2.78)	0.18	42.2
	<Median score (3)	1.23 (0.81, 1.88)		0.0

[a] Subgroup summary OR is derived from a random effects model using pooled estimates of tau-squared

[b] *p*-value from Q-test based on ANOVA. $p<0.05$ indicates that the summary effect OR is statistically different between subgroups

[c] Subgroup I^2 values show the proportion of variability in the subgroup summary estimate that can be attributed to between-study heterogeneity. Subgroups with moderate I^2 values (40%–62%) include the Savitz et al. study[48]

[d] Leukemia outcomes were defined as "leukemia," "acute leukemia," or "acute lymphoblastic leukemia (ALL)." Results from the one study that examined ALL (von Behren et al.[51]) are not included in this subgroup analysis

[e] Quality score: range=23–35, median=30