

RESEARCH ARTICLE

No Association between Traffic Density and Risk of Childhood Leukemia: a Meta-analysis

Xiao-Xi Sun¹, Shan-Shan Zhang², Xiao-Ling Ma^{1*}

Abstract

Background: While many studies have concluded that local traffic density is positively associated with childhood leukemia, the results are inconsistent. We therefore performed a meta-analysis to assess the relationship between traffic density and the risk of childhood leukemia. **Methods:** A systematic literature review was carried out using PubMed, EMBASE, and the Cochrane Library from January 1979 to December 2013. We selected and assessed journal articles evaluating the relationship between local traffic density and the risk of leukemia in children. The analysis was carried out using STATA version 12.0. **Results:** A total of 11 articles, including 12 estimates of effect, were included in our meta-analysis. The summary effect size from the random-effects model, expressed as an odds ratio, was 1.03 (95% CI: 0.98-1.09, $p=0.002$). No significant association between traffic density and the risk of childhood leukemia was found. Similar conclusions were found on subgroup analysis. **Conclusions:** The results of our meta-analysis suggested no association between traffic density and the risk of childhood leukemia. This implies that living in close proximity to roads with heavy traffic may not increase the risk of childhood leukemia. However, further high-quality prospective trials are needed to support these results.

Keywords: Traffic density - childhood leukemia - meta-analysis

Asian Pac J Cancer Prev, 15 (13), 5229-5232

Introduction

Although leukemia is the most common cancer in children its causes are still largely unknown (Belson et al., 2007). However, a number of studies have identified lots of potential risk factors (Rajabli et al., 2013; Zheng et al., 2013; Kumar et al., 2014). Benzene exposure has previously been identified as one such factor that can increase the risk of adult leukemia. In particular, emissions from road traffic, which are a source of environmental exposure to aromatic compounds, including low doses of benzene, have been studied as a causative agent for leukemia (Smith et al., 1998; Duarte-Davidson et al., 2001).

There was a hypothesis that living close to heavy-traffic roads may increase the risk of childhood leukemia (Amigou et al., 2011). The association between heavily traveled roads and childhood leukemia risk was first reported in an early case-control study of electromagnetic fields (Wertheimer et al., 1979). Although a number of studies have used traffic density as a proxy indicator of exposure for evaluating the effects of traffic-related pollution, their results have been inconsistent. We therefore conducted a meta-analysis to better characterize the association between local traffic density and the risk of childhood leukemia.

Materials and Methods

Literature search

Two independent authors identified relevant studies published between January 1979 and December 2013 using Pubmed, EMBASE and the Cochrane Library. The following search terms were used: (i) traffic, roads; (ii) leukemia, cancer, tumor; (iii) case-control studies.

Study selection

Studies were considered eligible for inclusion in our analysis if they met the following criteria: (1) case-control study design; (2) original study; (3) provided information that could be used to evaluate the relationship between traffic density and leukemia and generate an odds ratio (OR) or relative risk (RR) estimate; (4) research subjects were children (aged \leq 15); (5) published in English (6) provided a clear definition of traffic density. Search results that were abstracts or reviews, or which used duplicate data, were excluded from our analysis.

Data extraction

Two authors independently ascertained the characteristics of each study, including: first author's surname, country or origin, year of publication, number of cases and participants (or controls), type of leukemia

¹Department of Laboratory Medicine, Anhui Provincial Hospital, Anhui Medical University, Hefei, ²School of medicine, Shandong University, Ji'nan, China *For correspondence: xiaolingma@126.com

studied, duration of study period, ages of subjects and definition of traffic density.

Assessment of study quality

Assessment of the quality of those studies included in our analysis was based on Newcastle-Ottawa Scale (NOS); a standardized tool for comparing the quality of case-control and cohort studies (Wells et al., 2011). A star system of the NOS (range from 0 to 9 stars) has been developed for the evaluation.

Statistical analysis

Fixed-effects models were used to pool risk estimates for those studies that reported separate results for ranks rather than a combined estimate (Xu et al., 2012; Chen et al., 2013). Adjusted ORs were extracted from each study to estimate a summary OR with 95% CIs. Heterogeneity was evaluated using the Cochran Q and I² statistic (Higgins et al., 2002). Our results were considered to have been affected by heterogeneity if $p < 0.05$ or $I^2 > 50\%$. In this case, a random-effects model was used to calculate our pooled estimates; otherwise a fixed-effects model was used. Further subgroup analysis was carried out if significant heterogeneity was identified. Additionally, a sensitivity analysis was conducted by excluding each study in turn to evaluate the influence of each individual study on our pooled estimate. The potential for publication bias was assessed using Begg's test, Egger's test and a funnel plot. All analyses were performed using STATA version 12.0.

Results

Literature search

Figure 1 shows a flow diagram of the study selection process. Of a total of 432 records extracted from Pubmed, EMBASE and the Cochrane Library database, 403 were excluded after screening their titles and abstracts. After undertaking a full-text review of the remaining 19 articles, a further eight were excluded from our analysis. Of these eight studies, three could not provide sufficient data to estimate an association between traffic density and the risk of leukemia (Harrison et al., 1999; Visser et al., 2004; Knox et al., 2006), two used duplicate data (London et al., 1991; Pearson et al., 2000), two did not provide a clear definition of traffic density (Steffen et al., 2004; Badaloni et al., 2013) and one did not use data from children

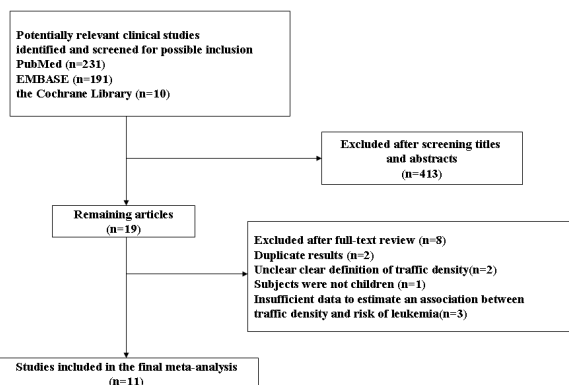


Figure 1. Flowchart Showing the Process for Study Selection

(Nordlinder et al., 1997). Our final meta-analysis included 11 studies with a total of 12 estimates of effect (Savitz et al., 1989; Raaschou-Nielsen et al., 2001; Reynolds et al., 2001; 2002; 2004 ; Langholz et al., 2002; Crosignani et al., 2004; Von Behren et al., 2008; Bräuner et al., 2010; Amigou et al., 2011; Heck et al., 2013).

Study characteristics

Table 1 shows the characteristics of the 11 studies selected for inclusion in our analysis. These studies were published between 1989 and 2013, with study periods ranging from 2 to 27 years. Seven studies were conducted in the USA, two in Denmark, one in Italy and one in France. Six of these studies defined traffic density as the number of vehicles per day, three as vehicle miles traveled per square mile, one as cumulative lengths of class 1 and 2 roads within 500m of subjects' place of residence and one as the number of vehicles per day multiplied by the total kilometers of roads per square kilometer. Of all the studies included, three received a NOS star rating score of 8, while three had a score of 7, four a score of 6, and only one a score of 5.

Meta-analysis

Our results showed a moderate degree of heterogeneity across the 11 sample estimates ($I^2=63.3\%$, $p=0.002$), confirming that a random-effects model was appropriate for calculating the summary odds ratio. Figure 2 shows the results of our pooled analysis (OR=1.03, 95% CI: 0.98-1.09, $p=0.002$), which found no statistically significant association between traffic density and the risk of childhood leukemia.

Table 2 shows the results of our subgroup analysis. The pooled OR from the seven studies conducted in the USA was 1.02 (95% CI: 0.99-1.05, $p=0.071$). At the same time, the result for the four studies that were not conducted in the USA was similar, with a pooled OR of 1.22 (95% CI: 0.98-1.53, $p=0.001$). When we evaluated the effect of traffic density with respect to the length of the study period, the pooled OR from the six studies undertaken over a period of less than ten years was 1.06 (95% CI: 1.00-1.13, $p=0.162$) while the pooled OR for the five studies with a duration of more than ten years was

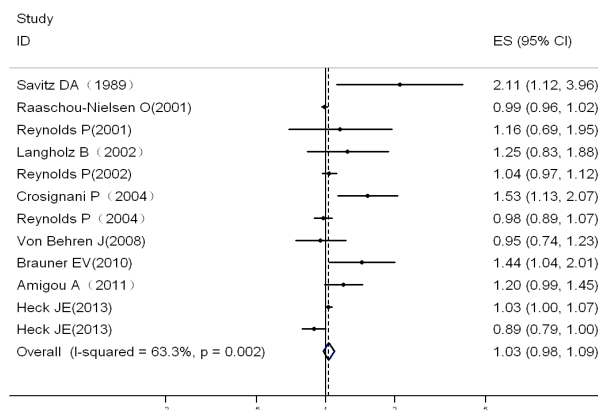


Figure 2. Forest Plot Showing the Overall Association between Traffic Density and the Risk of Leukemia. Summary odds ratios were calculated using a random effects model for all studies. The odds ratios (with 95% CIs) are given for each study, along with the final combined results

Table 1. Characteristics of Studies Included in the Meta-analysis

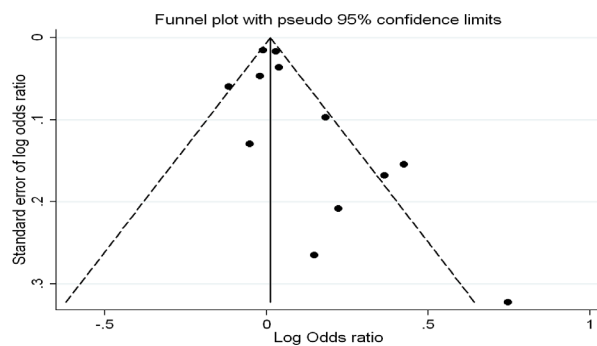
| References | Country | Study period (years) | Age | Case/Control | Leukemia type | Definition of traffic density | NOS Score |
|---------------------------|---------|----------------------|-----|-----------------|---------------|--|-----------|
| Savitz DA (1989) | USA | 1976-1983(8) | <14 | 98/262 | Unknow | vehicles per day | 6 |
| Raaschou-Nielsen O (2001) | Denmark | 1968-1991(24) | <15 | 986/1972 | ALL/ANLL | vehicles per day | 8 |
| Reynolds P (2001) | USA | 1988-1994(7) | <5 | 90/349 | Unknow | vehicles per day | 7 |
| Langholz B (2002) | USA | 1978-1984(7) | <10 | 212/202 | Unknow | vehicles per day | 6 |
| Reynolds P (2002) | USA | 1988-1994(7) | <15 | 2443/population | ALL/ANLL | vehicle miles traveled per square mile | 5 |
| Crosignani P (2004) | Italy | 1978-1997(20) | <14 | 120/480 | Unknow | vehicles per day | 7 |
| Reynolds P (2004) | USA | 1988-1997(10) | <5 | 1728/8730 | Unknow | vehicle miles traveled per square mile | 8 |
| Von Behren J (2008) | USA | 1995-2002(8) | <15 | 310/396 | ALL | vehicle miles traveled per square mile | 8 |
| Bräuner EV (2010) | Denmark | 1968-1994(27) | <15 | 985/1969 | ALL/ANLL | vehicles per day | 6 |
| Amigou A (2011) | French | 2003-2004(2) | <15 | 763/1681 | ALL/ANLL | cumulative lengths of class 1 and 2 roads within 500 m of the residence* | 7 |
| Heck JE (2013) | USA | 1998-2007(10) | <6 | 1467/77892 | ALL/AML | vehicle number per day*meter/meter ² | 6 |

*Class 1 roads consisted of high-speed free-ways and bypasses, class 2 roads mean main roads connecting class 1 roads

Table 2. Associations between Traffic Density and Risk of Leukemia: Subgroup Analysis

| Subgroup | No. of studies | OR (95% CI) | p value for Q-test | I ² Statistic |
|-------------------------------|----------------|-----------------|--------------------|--------------------------|
| Country | | | | |
| USA | 7 | 1.02(0.99-1.05) | 0.071 | 46.30% |
| Other countries ^a | 4 | 1.22(0.98-1.53) | 0.001 | 81.50% |
| Duration of study | | | | |
| <10 years | 6 | 1.06(1.00-1.13) | 0.162 | 36.70% |
| ≥10 years | 5 | 1.01(0.95-1.07) | 0.002 | 74.10% |
| NOS score | | | | |
| ≤6 | 5 | 1.04(0.95-1.15) | 0.008 | 68.20% |
| ≥7 | 6 | 1.05(0.96-1.15) | 0.033 | 58.80% |
| Definition of traffic density | | | | |
| Vehicles per day | 6 | 1.31(1.02-1.67) | 0.002 | 74.40% |
| Other definition ^b | 5 | 1.02(0.99-1.05) | 0.089 | 47.60% |

^aIncludes studies from Denmark, Italy and France; ^bThese definitions include vehicle miles traveled per square mile, cumulative lengths of class 1 and 2 roads within a 500m radius of subjects' place of residence and daily number of vehicles number per day*meter per square meter

**Figure 3. Funnel Plot to Detect Publication Bias**

1.01 (95% CI: 0.95-1.07, $p=0.002$). When we separately evaluated those studies with a NOS star rating score of more than 7, the pooled OR was 1.05 (95% CI: 0.96-1.15, $p=0.033$) while the five studies with a score of less than 6 stars gave an OR of 1.04 (95% CI: 0.95-1.15, $p=0.008$). Finally, the six studies in which traffic density was defined as the number of vehicles per day gave a pooled OR of 1.31 (95% CI: 1.02-1.67, $p=0.002$) while the result for the five remaining studies in which traffic density was not defined as the number of vehicles per day was 1.02 (95% CI: 0.99-1.05, $p=0.089$).

Sensitivity analysis and tests for publication bias

We conducted a sensitivity analysis by excluding each individual study in turn to determine whether this altered our final results. There was little change in our

effect estimates, suggesting that our results were robust. Further analysis using Begg's test ($p=0.15$) and Egger's test ($p=0.068$) suggested that publication bias was unlikely to have affected our final results. Finally, the funnel plot was found to be symmetrical (Figure 3).

Discussion

To our knowledge, this is the first meta-analysis to test the association between local traffic density and childhood leukemia. Our results did not demonstrate a significant increase in the risk of childhood leukemia for those subjects living near roads with heavy traffic. The pooled estimate was robust through sensitivity analyses and had no observed publication bias.

Leukemia as the most common childhood cancer occurs when the genetic and environmental factors interact in a multistage sequence. (Kumar et al., 2014). Several studies (Weng et al., 2008a; 2008b; Vinceti et al., 2012) have reported that traffic-related air pollution may increase the risk of childhood leukemia due to benzene and nitrogen dioxide emissions. While our meta-analysis gave a pooled OR of 1.03 (95% CI: 0.98-1.09, $p=0.002$), the lower and upper 95% CI values were 0.98 to 1.09 respectively, suggesting that the association between traffic density and risk of leukemia was of borderline statistical significance. Similar results were also observed in our subgroup analysis. Overall, our findings indicated that we cannot entirely rule out any association between traffic density and risk of childhood leukemia. Further prospective studies are therefore needed improve these estimates of effect.

The present study had some limitations, however. First, all the studies included used a case-control design, which may have introduced recall and selection bias. Additionally, a number of confounding factors were inherent in the primary studies, such as living conditions, parents' level of education and lifestyle factors, could have influenced our results, although all the studies included in our analysis provided adjusted risk estimates. Second, we found evidence that our summary odd ratios and the results of our subgroup analyses may have been influenced by heterogeneity. This was unsurprising, however, because of the variation in methods of assessment of traffic density, type of leukemia studied, characteristics of the study population, study duration and adjustment for potential

confounders across the different studies. As with previous meta-analyses in which unexplained heterogeneity had been identified, we accounted for this by using random-effects models in which the effects underlying the results of different studies are assumed to be drawn from a normal distribution (Higgins et al., 2009). Third, the definitions of traffic density varied across the studies included in our analysis. We therefore assessed the effect of traffic density regardless of the definition used. Finally, the possibility of publication bias should be considered because of the fact that all articles included in our analysis were written in English and that our search criteria excluded unpublished studies although no publication bias was observed in the present study.

In conclusion, the results of our meta-analysis suggest that living in proximity to roads with heavy traffic may not be associated with increased risk of childhood leukemia. Additional high-quality studies with a prospective design and adjustment for potential confounding factors are needed to improve estimates of effect and to strengthen the evidence for any possible association between exposure to traffic pollution and risk of leukemia among children.

Acknowledgements

The work supported by Anhui Provincial Natural Science Foundation (Grant no. 1408085MH188). Our thanks would be given to Jilong Shen for his expert technical assistance.

References

- Amigou A, Sermage-Faure C, Orsi L, et al (2011). Road traffic and childhood leukemia: the ESCALE study (SFCE). *Environ Health Perspect*, **119**, 566.
- Badaloni C, Ranucci A, Cesaroni G, et al (2013). Air pollution and childhood leukaemia: a nationwide case-control study in Italy. *Occup Environ Med*, **70**, 876-83.
- Belson M, Kingsley B, Holmes A (2007). Risk factors for acute leukemia in children: a review. *Environ Health Perspect*, **115**, 138.
- Bräuner EV, Andersen CE, Andersen HP, et al (2010). Is there any interaction between domestic radon exposure and air pollution from traffic in relation to childhood leukemia risk? *Cancer Causes Control*, **21**, 1961-4.
- Chen GC, Lv DB, Pang Z, et al (2013). Fruits and vegetables consumption and risk of non-Hodgkin's lymphoma: a meta-analysis of observational studies. *Int J Cancer*, **133**, 190-200.
- Crosignani P, Tittarelli A, Borgini A, et al (2004). Childhood leukemia and road traffic: a population-based case-control study. *Int J Cancer*, **108**, 596-9.
- Duarte-Davidson R, Courage C, Rushton L, et al (2001). Benzene in the environment: an assessment of the potential risks to the health of the population. *Occup Environ Med*, **58**, 2-13.
- Harrison RM, Leung P-L, Somervaille L, et al (1999). Gilman E. Analysis of incidence of childhood cancer in the West Midlands of the United Kingdom in relation to proximity to main roads and petrol stations. *Occup Environ Med*, **56**, 774-80.
- Heck JE, Wu J, Lombardi C, et al (2013). Childhood cancer and traffic-related air pollution exposure in pregnancy and early life. *Environ Health Perspect*, **121**, 1385.
- Higgins J, Thompson SG (2002). Quantifying heterogeneity in a meta-analysis. *Stat Med*, **21**, 1539-58.
- Higgins J, Thompson SG, Spiegelhalter DJ (2009). A re-evaluation of random-effects meta-analysis. *J R Stat Soc Ser A Stat Soc*, **172**, 137-59.
- Knox E (2006). Roads, railways, and childhood cancers. *J Epidemiol Community Health*, **60**, 136-41.
- Kumar A, Vashist M, Rathee R (2014). Maternal factors and risk of childhood leukemia. *Asian Pac J Cancer Prev*, **15**, 781-4.
- Langholz B, Ebi KL, Thomas DC, et al (2002). Traffic density and the risk of childhood leukemia in a Los Angeles case-control study. *Ann Epidemiol*, **12**, 482-7.
- London SJ, Thomas DC, Bowman JD, et al (1991). Exposure to residential electric and magnetic fields and risk of childhood leukemia. *Am J Epidemiol*, **134**, 923-37.
- Nordlinder R, Järholm B (1997). Environmental exposure to gasoline and leukemia in children and young adults-an ecology study. *Int Arch Occup Environ Health*, **70**, 57-60.
- Pearson RL, Wachtel H, Ebi KL (2000). Distance-weighted traffic density in proximity to a home is a risk factor for leukemia and other childhood cancers. *J Air Waste Manag Assoc*, **50**, 175-80.
- Raaschou-Nielsen O, Hertel O, Thomsen BL, et al (2001). Air pollution from traffic at the residence of children with cancer. *Am J Epidemiol*, **153**, 433-43.
- Rajabli N, Naeimi-Tabeie M, Jahangirrad A, et al (2013). Epidemiology of leukemia and multiple myeloma in Golestan, Iran. *Asian Pac J Cancer Prev*, **14**, 2333-6.
- Reynolds P, Elkin E, Scalf R, et al (2001). A case-control pilot study of traffic exposures and early childhood leukemia using a geographic information system. *Bioelectromagnetics*, **22**, S58-S68.
- Reynolds P, Von Behren J, Gunier RB, et al (2002). Traffic patterns and childhood cancer incidence rates in California, United States. *Cancer Causes Control*, **13**, 665-73.
- Reynolds P, Von Behren J, Gunier RB, et al (2004). Residential exposure to traffic in California and childhood cancer. *Epidemiology*, **15**, 6-12.
- Savitz DA, Feingold L (1989). Association of childhood cancer with residential traffic density. *Scand J Work Environ Health*, **15**, 360-3.
- Smith MT, Zhang L (1998). Biomarkers of leukemia risk: benzene as a model. *Environ Health Perspect*, **106**, 937.
- Steffen C, Auclerc M, Auvrignon A, et al (2004). Acute childhood leukaemia and environmental exposure to potential sources of benzene and other hydrocarbons; a case-control study. *Occup Environ Med*, **61**, 773-8.
- Vinceti M, Rothman KJ, Crespi CM, et al (2012). Leukemia risk in children exposed to benzene and PM10 from vehicular traffic: a case-control study in an Italian population. *Eur J Epidemiol*, **27**, 781-90.
- Visser O, van Wijnen JH, van Leeuwen FE (2004). Residential traffic density and cancer incidence in Amsterdam, 1989-1997. *Cancer Causes Control*, **15**, 331-9.
- Von Behren J, Reynolds P, Gunier RB, et al (2008). Residential traffic density and childhood leukemia risk. *Cancer Epidemiol Biomarkers Prev*, **17**, 2298-301.
- Wells G, Shea B, O'Connell D, et al (2011). The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. URL: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
- Weng H-H, Tsai S-S, Chen C-C, et al (2008). Childhood leukemia development and correlation with traffic air pollution in Taiwan using nitrogen dioxide as an air pollutant marker. *J Toxicol Environ Health A*, **71**, 434-8.
- Weng H-H, Tsai S-S, Chiu H-F, et al (2008). Childhood leukemia and traffic air pollution in Taiwan: petrol station density as an indicator. *J Toxicol Environ Health A*, **72**, 83-7.
- Wertheimer N, Leeper E (1979). Electrical wiring configurations and childhood cancer. *Am J Epidemiol*, **109**, 273-84.
- Xu T, Zhang YH (2012). Association of psoriasis with stroke and myocardial infarction: meta-analysis of cohort studies. *Br J Dermatol*, **167**, 1345-50.
- Zheng R-Z, Zhang Q-H, He Y-X, et al (2013). Historical long-term exposure to pentachlorophenol causing risk of cancer-a community study. *Asian Pac J Cancer Prev*, **14**, 811-6.