2019 Childhood Leukemia International Consortium (CLIC) and CLIC+ Scientific Annual Meeting
November 18-20, 2019 – Lyon

Does outdoor air pollution cause childhood leukemia? A systematic review and dose-response meta-analysis

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Background

A causal link between outdoor air pollution from motorized traffic and childhood leukemia has been proposed, but some older studies suffer from methodological drawbacks and no analyses have examined the dose-response relation. In this review, we investigated the extent to which outdoor air pollution, especially as resulting from traffic-related contaminants, affects the risk of childhood leukemia.

Methods

We performed online database search up to October 10, 2019 to retrieve eligible observational studies. We carried out a meta-analysis, whenever possible with a one-stage dose-response approach using a restricted cubic spline regression model, our intent being to investigate the extent to which traffic-related air pollution affects the risk of childhood leukemia.

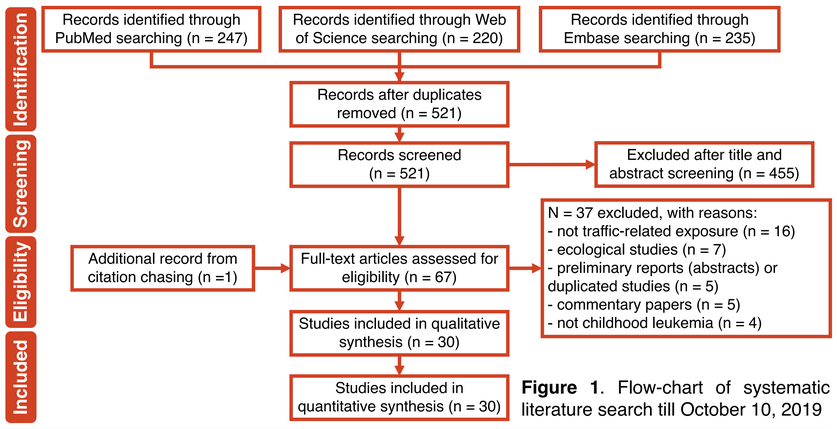

Figure 1. Flow-chart of systematic literature search till October 10, 2019

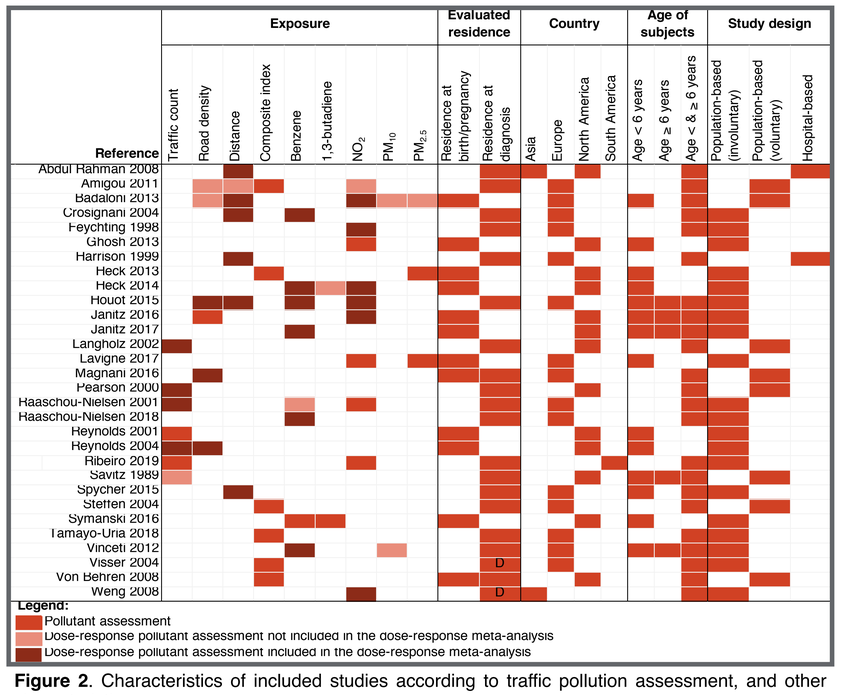

Figure 2. Characteristics of included studies according to traffic pollution assessment, and other characteristics.

Results

We found 30 studies eligible to be included in our review (**Figure 1**). Exposure assessment either to motorized traffic and related contaminants was based on various traffic-related metrics (number of vehicles in the closest roads, road density, and distance from major roads), or on measured or modeled levels of air contaminants such as benzene, nitrogen dioxide, 1,3-butadiene, and particulate matter (**Figure 2**). Summary risk ratios of childhood leukemia in the highest exposure category versus the lowest one for traffic density, benzene and nitrogen dioxide exposure are shown in **Table 1**. In the dose-response analysis, we found an indication of increased but imprecise association between disease risk and traffic indicators, measured as number of vehicles in the closest roads, road density, and distance from major roads near the child's residence, only at the highest levels of exposure (**Figure 3**). Similarly, exposure to nitrogen dioxide showed little association with leukemia risk except at the highest levels (**Figure 4**). Conversely, we found that benzene exposure was positively and approximately linearly associated with risk of childhood leukemia, particularly for acute myeloid leukemia, among children under 6 years of age, and when exposure assessment at the time of diagnosis was used (**Figure 5**).

	All children				Pre-school children (<6 years)				Children ≥ 6 years			
Indicator	n	RR	95% CI	I^2	n	RR	95% CI	I^2	n	RR	95% CI	I^2
Traffic density												
All leukemia	17	1.11	(1.02, 1.21)	57.4	7	1.00	(0.93, 1.09)	67.0	3	1.05	(0.96, 1.15)	10.0
Subtype												
ALL	9	1.05	(0.96, 1.16)	34.7	3	1.02	(0.99, 1.05)	0.0	1	1.00	(0.92, 1.09)	-
AML	6	1.13	(0.97, 1.32)	66.2	2	1.03	(0.77, 1.38)	87.7	1	1.25	(1.02, 1.53)	-
Exposure timing												
At birth	5	0.98	(0.90, 1.06)	30.9	4	0.95	(0.85, 1.05)	52.4	1	1.15	(0.78, 1.70)	-
At diagnosis	15	1.26	(1.11, 1.42)	45.9	3	1.27	(0.95, 1.71)	81.0	2	1.05	(0.94, 1.17)	24.6
Region												
Asia	1	1.27	(0.51, 3.17)	-	-				-			
Europe	9	1.25	(1.05, 1.49)	50.4	3	1.05	(0.87, 1.25)	63.8	1	1.05	(0.95, 1.17)	-
North America	6	1.02	(0.89, 1.16)	65.4	4	0.98	(0.84, 1.15)	74.9	2	1.09	(0.72, 1.64)	17.4
South America	1	1.21	(1.07, 1.37)	-	-				-			
Benzene												
All leukemia	7	1.27	(1.03, 1.56)	52.4	4	1.39	(1.03, 1.87)	27.9	2	1.08	(0.64, 1.82)	0.0
Subtype												
ALL	7	1.09	(0.88, 1.36)	51.8	3	1.19	(1.00, 1.40)	0.0	1	0.69	(0.27, 1.78)	-
AML	5	1.84	(1.31, 2.59)	0.0	2	3.21	(1.39, 7.42)	0.0	1	0.43	(0.04, 4.79)	-
Exposure timing												
At birth	3	1.21	(1.04, 1.41)	0.0	3	1.22	(1.03, 1.43)	0.0	1	1.14	(0.63, 2.08)	-
At diagnosis	4	1.36	(0.92, 2.00)	65.2	1	3.30	(1.03, 10.59)	-	1	0.90	(0.31, 2.60)	-
Region												
Europe	4	1.36	(0.92, 2.00)	65.2	1	3.30	(1.03, 10.59)	-	1	0.90	(0.31, 2.60)	-
North America	3	1.21	(1.04, 1.41)	0.0	3	1.22	(1.03, 1.43)	0.0	1	1.14	(0.63, 2.08)	-
NO_2												
All leukemia	9	1.09	(0.96, 1.24)	61.8	4	1.03	(0.90, 1.18)	14.9	1	0.89	(0.42, 1.89)	-
Subtype												
ALL	4	1.02	(0.89, 1.18)	55.6	2	1.10	(0.92, 1.32)	46.2	-			
AML	5	1.12	(0.93, 1.34)	35.8	2	0.86	(0.60, 1.23)	0.0	-			
Exposure timing												
At birth	4	1.07	(0.96, 1.19)	0.0	4	1.03	(0.90, 1.18)	14.9	1	0.89	(0.42, 1.89)	-
At diagnosis	5	1.22	(0.95, 1.56)	76.9	-				-			
Region												
Asia	1	2.29	(1.44, 3.64)	-	-				-			
Europe	4	0.91	(0.82, 1.00)	0.0	1	0.79	(0.52, 1.20)	-	-			
North America	3	1.06	(0.95, 1.18)	0.0	3	1.06	(0.94, 1.19)	1.7	1	0.89	(0.42, 1.89)	-
South America	1	1.21	(1.07, 1.37)	-	-				-			

Table 1. Summary risk ratios (RR) of childhood leukemia in the highest exposure category versus the lowest one for traffic density, benzene and nitrogen dioxide (NO_2) exposure.

Dose-response meta-analysis. Legend: Spline curve (red solid line) with 95% confidence limits (gray dashed lines). RR, risk ratio.

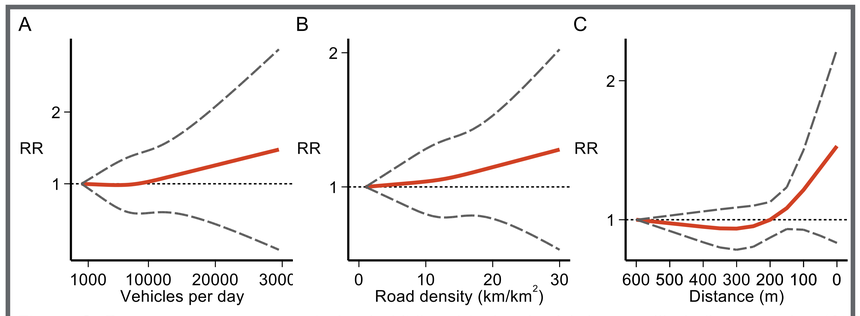

Figure 3. Dose-response meta-analysis of childhood leukemia risk from traffic indicators using (A) vehicles per day count, (B) road density in km/km2, and (C) residential distance from a major road in meters.

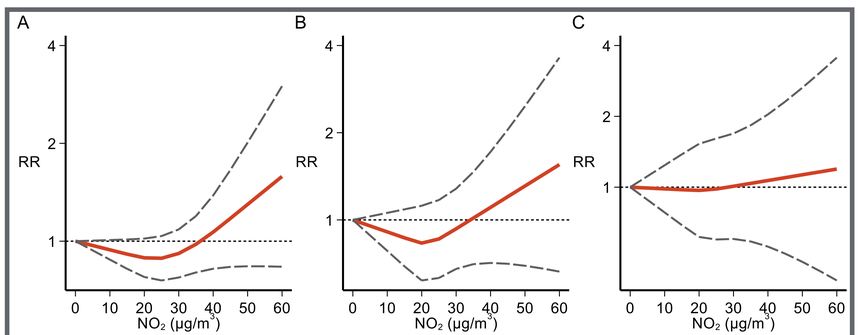

Figure 4. Dose-response meta-analysis of childhood leukemia risk from NO_2 exposure for all leukemias (A), acute lymphoblastic leukemia only (B), and acute myeloid leukemia only (C).

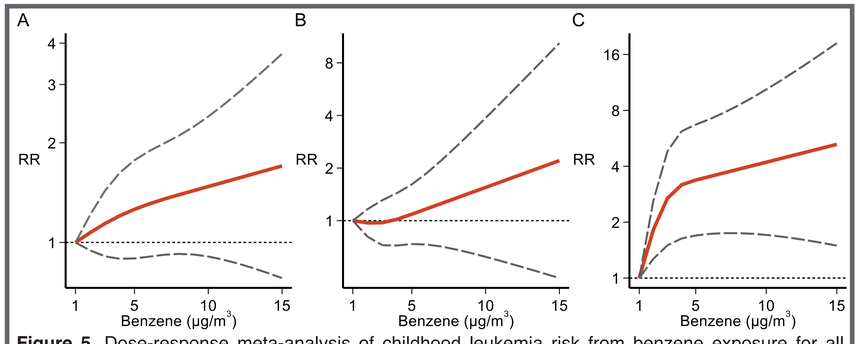

Figure 5. Dose-response meta-analysis of childhood leukemia risk from benzene exposure for all leukemias (A), acute lymphoblastic leukemia only (B), and acute myeloid leukemia only (C).

Conclusions

Overall, 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, especially the myeloid subtype and in the youngest children. No apparent minimal threshold of exposure emerged for benzene, while analyses for traffic density and NO2 gave evidence of such a threshold.

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