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Supplemental Material

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

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Table of Contents

Table S1. Detailed PECOS statement used for identification of search strategies implemented on online databases.

Table S2. Newcastle - Ottawa quality assessment scale for included studies: details used for study score assignment. High quality choices are identified with a 'star' (i.e. asterisk). A maximum of one 'star' for each item within the 'Selection' and 'Exposure/Outcome' categories; maximum of two 'stars' for 'Comparability' can be identified.

Table S3. Newcastle - Ottawa quality assessment scale (NOS) for included studies: details of score assignment for each included study, divided according to case-control and cohort study design. S-1 through S-4 correspond to the 'Selection' questions, C-1 and C-2 correspond to the 'Comparability' questions, E-1 through E-3 correspond to the 'Exposure' questions, and O-1 through O-3 correspond to the 'Outcome' questions reported in Table S2. Letters stand for answers to each question reported in Table S2, and number in parenthesis indicate if the given answer identified a high (1) or low (0) quality rank. 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.

Table S4. 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, for all studies and stratified by age at diagnosis, leukemia subtype, exposure timing, and region. Results of leave-one-out sensitivity analysis of range of summary RR ('min RR' and 'max RR') investigating the influence of each individual study on the overall meta-analysis summary estimates.

Table S5. Summary risk ratios (RR) 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. Results of leave-one-out sensitivity analysis of range of summary RR ('min RR' and 'max RR') investigating the influence of each individual study on the overall meta-analysis summary estimates.

Figure S1. Risk ratio (RR) of childhood leukemia from indicators of traffic exposure for all children: all studies (A); by leukemia subtype (B); by exposure window, i.e. residence at birth vs. at diagnosis (C); by region/continent (D). The area of each gray square is proportional to the inverse of the variance of the estimated log RR. Black diamonds represent point estimates of RR and horizontal lines represent their 95% confidence intervals (CIs). The open diamonds represent the combined RR for each subgroup and the overall RR for all studies. The solid line represents RR=1. The dash line represents the point estimate of overall RR for all studies.

Figure S2. Risk ratio (RR) of childhood leukemia and leukemia subtype from benzene exposure for all children: all studies (A); by leukemia subtype (B); by exposure window, i.e. residence at birth vs. at diagnosis (C); by region/continent (D). The area of each gray square is proportional to the inverse of the variance of the estimated log RR. Black diamonds represent point estimates of RR and horizontal lines represent their 95% confidence intervals (CIs). The open diamonds represent the combined RR for each subgroup and the overall RR for all studies. The solid line represents RR=1. The dash line represents the point estimate of overall RR for all studies.

Figure S3. Risk ratio (RR) of childhood leukemia and leukemia subtype from air NO_2 exposure for all children: all studies (A); by leukemia subtype (B); by exposure window, i.e. residence at birth vs. at diagnosis (C); by region/continent (D). The area of each gray square is proportional to the inverse of the variance of the estimated log RR. Black diamonds represent point estimates of RR and horizontal lines represent their 95% confidence intervals (CIs). The open diamonds represent the combined RR for each subgroup and the overall RR for all studies. The solid line represents RR=1. The dash line represents the point estimate of overall RR for all studies.

Figure S4. Risk ratio (RR) with 95% confidence interval (CI) of childhood leukemia from particulate matter ($PM_{2.5}$) for all children: all studies (A); by leukemia subtype (B); by exposure window, i.e. residence at birth vs. at diagnosis (C); by region/continent (D). The area of each gray square is proportional to the inverse of the variance of the estimated log RR. Black diamonds represent point estimates of RR and horizontal lines represent their 95% confidence intervals (CIs). The open diamonds represent the combined RR for each subgroup and the overall RR for all studies. The solid line represents RR=1. The dash line represents the point estimate of overall RR for all studies.

Figure S5. Risk ratio (RR) with 95% confidence interval (CI) of childhood leukemia from particulate matter (PM_{10}) for all children: all studies (A); by leukemia subtype (B); by exposure window, i.e. residence at birth vs. at diagnosis (C); by region/continent (D). The area of each gray square is proportional to the inverse of the variance of the estimated log RR. Black diamonds represent point estimates of RR and horizontal lines represent their 95% confidence intervals (CIs). The open diamonds represent the combined RR for each subgroup and the overall RR for all studies. The solid line represents RR=1. The dash line represents the point estimate of overall RR for all studies.

Figure S6. Risk ratio (RR) of childhood leukemia and leukemia subtype from 1,3-butadiene exposure for all children (all pre-school, i.e. <6 years): all studies (A); by leukemia subtype (B); by exposure window, i.e. residence at birth vs. at diagnosis (C); by region/continent (D). The area of each gray square is proportional to the inverse of the variance of the estimated log RR. Black diamonds represent point estimates of RR and horizontal lines represent their 95% confidence intervals (CIs). The open diamonds represent the combined RR for each subgroup and the overall RR for all studies. The solid line represents RR=1. The dash line represents the point estimate of overall RR for all studies.

Figure S7. Risk ratio (RR) of childhood leukemia from indicators of traffic exposure restricted to pre-school children: all studies (A); by leukemia subtype (B); by exposure window, i.e. residence at birth vs. at diagnosis (C); by region/continent (D). The area of each gray square is proportional to the inverse of the variance of the estimated log RR. Black diamonds represent point estimates of RR and horizontal lines represent their 95% confidence intervals (CIs). The open diamonds represent the combined RR for each subgroup and the overall RR for all studies. The solid line represents RR=1. The dash line represents the point estimate of overall RR for all studies.

Figure S8. Risk ratio (RR) of childhood leukemia and leukemia subtype from benzene exposure restricted to pre-school children: all studies (A); by leukemia subtype (B); by exposure window, i.e. residence at birth vs. at diagnosis (C); by region/continent (D). The area of each gray square is proportional to the inverse of the variance of the estimated log RR. Black diamonds represent point estimates of RR and horizontal lines represent their 95% confidence intervals (CIs). The open diamonds represent the combined RR for each subgroup and the overall RR for all studies. The solid line represents RR=1. The dash line represents the point estimate of overall RR for all studies.

Figure S9. Risk ratio (RR) of childhood leukemia and leukemia subtype from air NO_2 exposure restricted to pre-school children: all studies (A); by leukemia subtype (B); by exposure window, i.e. residence at birth vs. at diagnosis (C); by region/continent (D). The area of each gray square is proportional to the inverse of the variance of the estimated log RR. Black diamonds represent point estimates of RR and horizontal lines represent their 95% confidence intervals (CIs). The open diamonds represent the combined RR for each subgroup and the overall RR for all studies. The solid line represents RR=1. The dash line represents the point estimate of overall RR for all studies.

Figure S10. Risk ratio (RR) with 95% confidence interval (CI) of childhood leukemia from particulate matter (PM$_{2.5}$) restricted to pre-school children: all studies (A); by leukemia subtype (B); by exposure window, i.e. residence at birth vs. at diagnosis (C); by region/continent (D). The area of each gray square is proportional to the inverse of the variance of the estimated log RR. Black diamonds represent point estimates of RR and horizontal lines represent their 95% confidence intervals (CIs). The open diamonds represent the combined RR for each subgroup and the overall RR for all studies. The solid line represents RR=1. The dash line represents the point estimate of overall RR for all studies.

Figure S11. Risk ratio (RR) with 95% confidence interval (CI) of childhood leukemia from particulate matter (PM$_{10}$) restricted to pre-school children: all studies (A); by leukemia subtype (B); by exposure window, i.e. residence at birth vs. at diagnosis (C); by region/continent (D). The area of each gray square is proportional to the inverse of the variance of the estimated log RR. Black diamonds represent point estimates of RR and horizontal lines represent their 95% confidence intervals (CIs). The open diamonds represent the combined RR for each subgroup and the overall RR for all studies. The solid line represents RR=1. The dash line represents the point estimate of overall RR for all studies.

Figure S12. Risk ratio (RR) of childhood leukemia from indicators of traffic exposure restricted to older (>6 years) children: all studies (A); by leukemia subtype (B); by exposure window, i.e. residence at birth vs. at diagnosis (C); by region/continent (D). The area of each gray square is proportional to the inverse of the variance of the estimated log RR. Black diamonds represent point estimates of RR and horizontal lines represent their 95% confidence intervals (CIs). The open diamonds represent the combined RR for each subgroup and the overall RR for all studies. The solid line represents RR=1. The dash line represents the point estimate of overall RR for all studies.

Figure S13. Risk ratio (RR) of childhood leukemia and leukemia subtype from benzene exposure restricted to older (>6 years) children: all studies (A); by leukemia subtype (B); by exposure window, i.e. residence at birth vs. at diagnosis (C); by region/continent (D). The area of each gray square is proportional to the inverse of the variance of the estimated log RR. Black diamonds represent point estimates of RR and horizontal lines represent their 95% confidence intervals (CIs). The open diamonds represent the combined RR for each subgroup and the overall RR for all studies. The solid line represents RR=1. The dash line represents the point estimate of overall RR for all studies.

Figure S14. Risk ratio (RR) of childhood leukemia from NO$_2$ exposure restricted to older (>6 years) children: all studies (A); by exposure window, i.e. residence at birth vs. at diagnosis (C); by region/continent (C). The area of each gray square is proportional to the inverse of the variance of the estimated log RR. Black diamonds represent point estimates of RR and horizontal lines represent their 95% confidence intervals (CIs). The open diamonds represent the combined RR for each subgroup and the overall RR for all studies. The solid line represents RR=1. The dash line represents the point estimate of overall RR for all studies.

Figure S15. Risk ratio (RR) with 95% confidence interval (CI) of childhood leukemia from particulate matter (PM_{10}) restricted to pre-school children: all studies (A); by leukemia subtype (B); by exposure window, i.e. residence at birth vs. at diagnosis (C); by region/continent (D). The area of each gray square is proportional to the inverse of the variance of the estimated log RR. Black diamonds represent point estimates of RR and horizontal lines represent their 95% confidence intervals (CIs). The open diamonds represent the combined RR for each subgroup and the overall RR for all studies. The solid line represents RR=1. The dash line represents the point estimate of overall RR for all studies.

Figure S16. Sensitivity analysis with summary estimate with 95% confidence interval (CI) of childhood leukemia from indicators of traffic exposure for all children after removal of single study result (leave-one-out analysis): all studies (A); by leukemia subtype (B); by exposure window, i.e. residence at birth vs. at diagnosis (C); by region/continent (D). Each given named study is omitted when computing the overall meta-analysis summary estimate. Hollow circles represent point estimates of RR and horizontal dotted lines represent their 95% confidence intervals (CIs). The solid lines represent the point estimate of overall RR for all studies with its 95% CI.

Figure S17. Sensitivity analysis with summary estimate with 95% confidence interval (CI) of childhood leukemia from benzene exposure for all children after removal of single study result (leave-one-out analysis): all studies (A); by leukemia subtype (B); by exposure window, i.e. residence at birth vs. at diagnosis (C); by region/continent (D). Each given named study is omitted when computing the overall meta-analysis summary estimate. Hollow circles represent point estimates of RR and horizontal dotted lines represent their 95% confidence intervals (CIs). The solid lines represent the point estimate of overall RR for all studies with its 95% CI.

Figure S18. Sensitivity analysis with summary estimate with 95% confidence interval (CI) of childhood leukemia from nitrogen dioxide exposure for all children after removal of single study result (leave-one-out analysis): all studies (A); by leukemia subtype (B); by exposure window, i.e. residence at birth vs. at diagnosis (C); by region/continent (D). Each given named study is omitted when computing the overall meta-analysis summary estimate. Hollow circles represent point estimates of RR and horizontal dotted lines represent their 95% confidence intervals (CIs). The solid lines represent the point estimate of overall RR for all studies with its 95% CI.

Figure S19. Sensitivity analysis entering a ±15% value instead of ±20 in the dose-response meta-analysis of childhood leukemia risk from traffic indicators using vehicles per day count (A), road density in km/km^2 (B), and distance from a major road in meters (C). Overall spline curve (black solid line) with 95% confidence limits (black dashed lines). RR: risk ratio.

Figure S20. Sensitivity analysis entering a ±15% value instead of ±20 in the dose-response meta-analysis of childhood leukemia risk from benzene exposure of all leukemia (A), acute lymphoblastic leukemia only (B), and acute myeloid leukemia only (C). Overall spline curve (black solid line) with 95% confidence limits (black dashed lines). RR: risk ratio.

Figure S21. Sensitivity analysis entering a ±15% value instead of ±20 in the dose-response meta-analysis of childhood leukemia risk from nitrogen dioxide exposure of all leukemia (A), acute lymphoblastic leukemia only (B), and acute myeloid leukemia only (C). Overall spline curve (black solid line) with 95% confidence limits (black dashed lines). RR: risk ratio.

Figure S22. Funnel plots for publication bias for traffic density, benzene, nitrogen dioxide (NO_2), particulate matter ($PM_{2.5}/PM_{10}$), and 1,3-butadiene indicators. Black diamonds represent studies included in each analysis, the x-axis indicates the study effect/results through its risk ratio (RR), and the y-axis indicates study precision through its standard error. The outer dashed lines indicate the triangular region within which 95% of studies are expected to lie in the absence of both biases and heterogeneity. The solid vertical line corresponds to overall summary RR from meta-analysis of included studies.

Figure S23. Dose-response meta-analysis of childhood leukemia risk from traffic indicators using vehicles per day count (A), road density in km/km^2 (B), and distance from a major road in meters (C). Overall spline curve (black solid line) with 95% confidence limits (black dashed lines) and the study-specific trends showing the influence of variation across studies (gray solid lines). RR: risk ratio.

Figure S24. Dose-response meta-analysis of childhood leukemia risk from benzene exposure of all leukemia (A), acute lymphoblastic leukemia only (B), and acute myeloid leukemia only (C). Overall spline curve (black solid line) with 95% confidence limits (black dashed lines) and the study-specific trends showing the influence of variation across studies (gray solid lines). RR: risk ratio.

Figure S25. Dose-response meta-analysis of childhood leukemia risk from NO_2 exposure of all leukemia (A), acute lymphoblastic leukemia only (B), and acute myeloid leukemia only (C). Overall spline curve (black solid line) with 95% confidence limits (black dashed lines) and the study-specific trends showing the influence of variation across studies (gray solid lines). RR: risk ratio.

Additional File- Excel Document

References

Table S1. Detailed PECOS statement used for identification of search strategies implemented on online databases.

(A) PECOS statement:	• Population: non-adult population aged less than 18 years, including infant, child and adolescent population. • Exposure: exposure to any type of traffic-related outdoor air pollutants emitted from motorized vehicles, including benzene and derivatives, particulate matter, nitrogen oxides. Any type of traffic exposure assessment was considered, including exposure through air monitoring data, dispersion models based on motorized traffic, major roads near the place of residence (assessed either using the distance of main/major roads from subjects' residence, or the density of major roads around subjects' residence), or number of cars or trucks on nearby roads (e.g. vehicle traffic count). • Comparator: non-exposed or lower exposure subjects were considered the baseline comparator for the highest versus lowest analysis. For the dose-response analysis, continuous non-linear exposure from null exposure to highest reported exposure was tested. • Outcome: any type of acute childhood leukemia, overall leukemias and the main subtypes, acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML). • Study design: both case-control and cohort epidemiological studies were considered eligible for the review.
	PECOS research question: Among children, i.e. subjects aged less than 18 years (population) exposed to traffic-related air pollution, what is the effect of high exposure to outdoor pollutants (exposure) compared to the non-exposed or lower exposed subjects (comparator) in the same population on risk of childhood leukemia (outcome) evaluated in case-control and cohort epidemiological investigations (study design)?

(B) Database	Search strategy
PubMed	((air pollution[MH] NOT air pollution, indoor[MH]) OR traffic-related pollution[MH] OR particulate matter[MH] OR particulate matter[TIAB] OR particulate matter[OT] OR benzene[MH] OR (benzene derivatives[MH] AND air pollut*) OR benzene[TIAB] OR benzene[OT] OR nitrogen oxides[MH] OR nitrogen oxides[TIAB] OR nitrogen oxides[OT] OR motor vehicle[MH] OR vehicle emission[MH] OR motor vehicle[TIAB] OR vehicle emission[TIAB] OR motor vehicle[OT] OR vehicle emission[OT]) AND ((leukemia[MH] OR leukaemia[TIAB] OR leukemia[TIAB] OR childhood leukemia[TIAB]) AND (child[MH] OR infant[MH] OR adolescent[MH] OR child[TIAB] OR infant[TIAB] OR adolescent[TIAB] OR childhood[TIAB] OR children[TIAB])) NOT ((animals [MH] OR plants [MH]) NOT humans [MH]) NOT review[PT]
Web of Science	((((TS=(air pollution) OR TI=(air pollution)) OR (TS=(traffic) OR TI=(traffic)) OR (TS=(benzene) OR TI=(benzene)) OR (TS=(nitrogen oxides) OR TI=(nitrogen oxides)) OR (TS=(particulate matter) OR TI=(particulate matter)) OR (TS=(vehicle emission) OR TI=(vehicle emission))) AND ((TS=(leukemia) OR TI=(leukemia) OR TS=(leukaemia) OR TI=(leukaemia)) OR TI=(childhood leukemia)) AND (TS=(child OR infant OR adolescent) OR TI=(child OR infant OR adolescent))))
Embase	('air pollution'/exp OR 'traffic'/exp OR 'benzene'/exp OR 'nitrogen oxides'/exp OR 'particulate matter'/exp OR 'vehicle emission'/exp) AND 'leukemia'/exp AND ('child'/exp OR 'infant'/exp OR 'adolescent'/exp) AND 'human'/exp

Table S2. Newcastle - Ottawa quality assessment scale for included studies: details used for study score assignment. High quality choices are identified with a 'star' (i.e. asterisk). A maximum of one 'star' for each item within the 'Selection' and 'Exposure/Outcome' categories; maximum of two 'stars' for 'Comparability' can be identified.

(A) Newcastle - Ottawa quality assessment scale	
Selection (for case-control studies)	**Comparability (both case-control and cohort studies)**

1) Is the case definition adequate?
    a) yes, with independent validation*
    b) yes, e.g., record linkage or based on self-report
    c) no description
 2) Representativeness of the cases
    a) consecutive or obviously representative series of cases*
    b) potential for selection biases or not stated
 3) Selection of Controls
    a) community controls*
    b) hospital controls
    c) no description or not representative of the population
 4) Definition of Controls
    a) no history of disease (endpoint)*
    b) no description of source
	1) Comparability of cases and controls/cohorts on the basis of the design or analysis: (yes/no answer)
	   - study controls for age (y*/n)
	   - study controls for socio-economic status (y*/n)

Selection (for cohort studies)	**Exposure (for case-control studies)**
	 1) Ascertainment of exposure
	    a) secure record (e.g. surgical records)*
	    b) structured interview where blind to case/control status*
	    c) interview not blinded to case/control status
	    d) written self-report or medical record only
	    e) no description

1) Representativeness of the exposed cohort
    a) truly representative of the average children population in the community*
    b) somewhat representative of the average children population in the community
    c) selected group of users, e.g. volunteers
    d) no description of the derivation of the cohort
 2) Selection of the non-exposed cohort
    a) drawn from the same community as the exposed cohort*
    b) drawn from a different source
    c) no description of the derivation of the not exposed cohort
 3) Ascertainment of exposure
    a) secure record (e.g. surgical records)*
    b) structured interview*
    c) written self-report
    d) no description
 4) Demonstration that outcome of interest was not present at start of study
    a) yes*
    b) no
	2) Same method of ascertainment for cases and controls
	    a) yes*
	    b) no
	 3) Non-response rate
	    a) same rate for both groups*
	    b) non-respondents described
	    c) rate different and no designation
	 Outcome (for cohort studies)
	 1) Assessment of outcome
	    a) independent blind assessment*
	    b) record linkage*
	    c) self-report
	    d) no description
	 2) Was follow-up long enough for outcomes to occur
	    a) yes (5 years of follow up period was considered adequate for children diagnosed before 5, and 10 years if diagnosed before 15)*
	    b) no
	 3) Adequacy of follow up of cohorts
	    a) complete follow up accounted for **100% of subjects***
	    b) subjects lost to follow up unlikely to introduce bias – **lost at follow-up ≤5%***
	    c) follow up rate **<95%** and no description of those lost
	    d) no statement

Table S3. Newcastle - Ottawa quality assessment scale (NOS) for included studies: details of score assignment for each included study, divided according to case-control and cohort study design. S-1 through S-4 correspond to the 'Selection' questions, C-1 and C-2 correspond to the 'Comparability' questions, E-1 through E-3 correspond to the 'Exposure' questions, and O-1 through O-3 correspond to the 'Outcome' questions reported in Table S2. Letters stand for answers to each question reported in Table S2, and number in parenthesis indicate if the given answer identified a high (1) or low (0) quality rank. 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.

Reference	Selection				Comparability		Exposure/Outcome			Total Score
Case-control studies	*S-1*	*S-2*	*S-3*	*S-4*	*C-1*	*C-2*	*E-1*	*E-2*	*E-3*	
(Abdul Rahman et al. 2008)	a (1)	b (0)	b (0)	a (1)	n (0)	y (1)	c (0)	a (1)	a (1)	5
(Amigou et al. 2011)	a (1)	b (0)	c (0)	a (1)	y (1)	y (1)	a (1)	a (1)	a (1)	7
(Badaloni et al. 2013)	a (1)	b (0)	c (0)	a (1)	y (1)	y (1)	c (0)	a (1)	a (1)	6
(Crosignani et al. 2004)	a (1)	a (1)	a (1)	a (1)	y (1)	y (1)	a (1)	a (1)	a (1)	9
(Feychting et al. 1998)	a (1)	a (1)	a (1)	a (1)	y (1)	y (1)	a (1)	a (1)	a (1)	9
(Ghosh et al. 2013)	a (1)	a (1)	a (1)	a (1)	y (1)	y (1)	a (1)	a (1)	a (1)	9
(Harrison et al. 1999)	a (1)	a (1)	b (0)	a (1)	n (0)	n (0)	a (1)	a (1)	a (1)	6
(Heck et al. 2013)	a (1)	a (1)	a (1)	a (1)	y (1)	y (1)	a (1)	a (1)	a (1)	9
(Heck et al. 2014)	a (1)	a (1)	a (1)	a (1)	y (1)	y (1)	a (1)	a (1)	a (1)	9
(Houot et al. 2015)	a (1)	a (1)	a (1)	a (1)	y (1)	y (1)	a (1)	a (1)	a (1)	9
(Janitz et al. 2016)	a (1)	a (1)	a (1)	a (1)	y (1)	y (1)	a (1)	a (1)	a (1)	9
(Janitz et al. 2017)	a (1)	a (1)	a (1)	a (1)	y (1)	y (1)	a (1)	a (1)	a (1)	9
(Langholz et al. 2002)	a (1)	a (1)	c (0)	a (1)	y (1)	n (0)	a (1)	a (1)	a (1)	7
(Magnani et al. 2016)	a (1)	b (0)	c (0)	a (1)	y (1)	y (1)	c (0)	a (1)	a (1)	6
(Pearson et al. 2000)	a (1)	b (0)	a (1)	a (1)	y (1)	y (1)	a (1)	a (1)	c (0)	7
(Raaschou-Nielsen et al. 2001)	a (1)	a (1)	a (1)	a (1)	y (1)	y (1)	a (1)	a (1)	a (1)	9
(Raaschou-Nielsen et al. 2018)	a (1)	a (1)	a (1)	a (1)	y (1)	y (1)	a (1)	a (1)	a (1)	9
(Reynolds et al. 2001)	a (1)	a (1)	a (1)	a (1)	y (1)	y (1)	a (1)	a (1)	a (1)	9
(Reynolds et al. 2004)	a (1)	a (1)	a (1)	a (1)	y (1)	y (1)	a (1)	a (1)	a (1)	9
(Savitz and Feingold 1989)	a (1)	b (0)	a (1)	a (1)	y (1)	y (1)	a (1)	a (1)	c (0)	7
(Steffen et al. 2004)	a (1)	a (1)	b (0)	a (1)	y (1)	y (1)	b (0)	a (1)	a (1)	7
(Symanski et al. 2016)	a (1)	a (1)	a (1)	a (1)	y (1)	y (1)	a (1)	a (1)	a (1)	9
(Tamayo-Uria et al. 2018)	a (1)	a (1)	a (1)	a (1)	y (1)	y (1)	a (1)	b (0)	a (1)	8
(Vinceti et al. 2012)	a (1)	a (1)	a (1)	a (1)	y (1)	y (1)	a (1)	a (1)	a (1)	9
(Von Behren et al. 2008)	a (1)	b (0)	a (1)	a (1)	y (1)	y (1)	a (1)	a (1)	a (1)	8
(Weng et al. 2008)	a (1)	b (0)	a (1)	a (1)	y (1)	n (0)	a (1)	a (1)	a (1)	7
Cohort studies	*S-1*	*S-2*	*S-3*	*S-4*	*C-1*	*C-2*	*O-1*	*O-2*	*O-3*	
(Lavigne et al. 2017)	a (1)	a (1)	a (1)	a (1)	y (1)	y (1)	b (1)	a (1)	a (1)	9
(Spycher et al. 2015)	a (1)	a (1)	a (1)	a (1)	y (1)	y (1)	b (1)	b (1)	a (1)	9
(Visser et al. 2004)	a (1)	a (1)	a (1)	a (1)	y (1)	n (0)	b (1)	a (1)	a (1)	8

Table S4. 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, for all studies and stratified by age at diagnosis, leukemia subtype, exposure timing, and region. Results of leave-one-out sensitivity analysis of range of summary RR ('min RR' and 'max RR') investigating the influence of each individual study on the overall meta-analysis summary estimates.

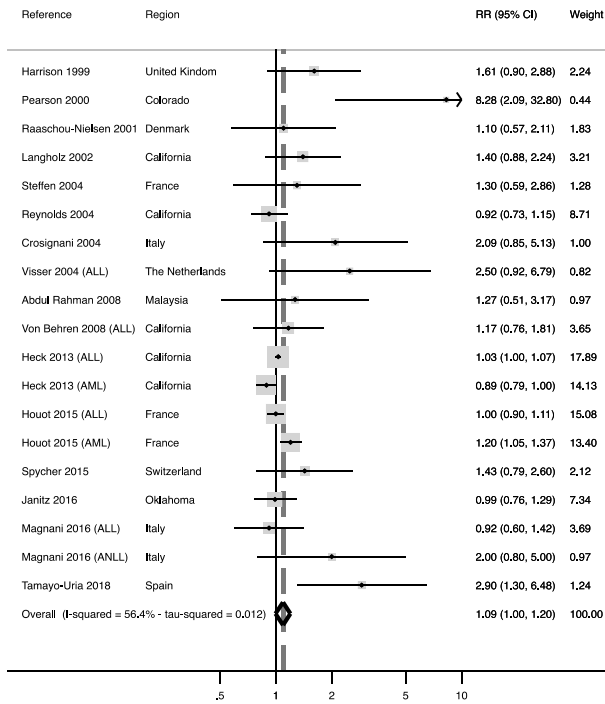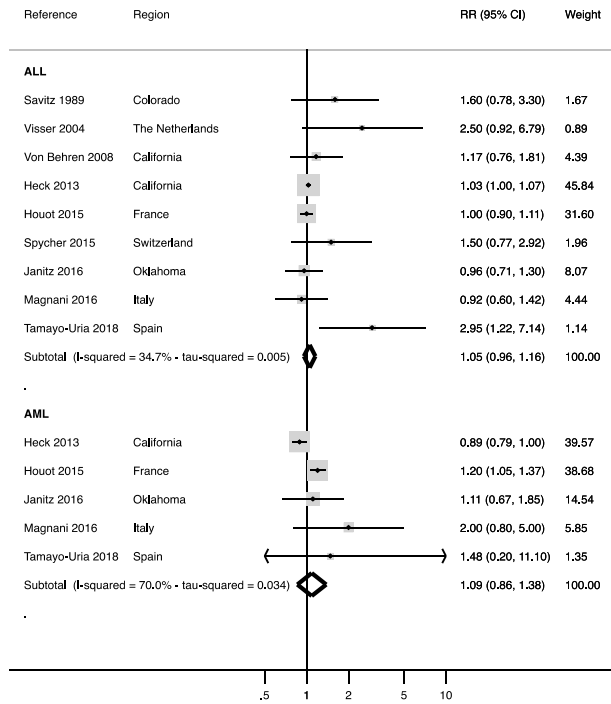| Indicator	n	RR	95% CI	min RR	max RR	n	RR	95% CI	min RR	max RR	n	RR	95% CI	min RR	max RR
	All children					Pre-school children (<6 years)					Children ≥ 6 years				
Traffic density															
All leukemia	16	1.09	(1.00, 1.20)	1.07	1.15	7	1.00	(0.93, 1.09)	0.98	1.03	3	1.05	(0.96, 1.15)	1.02	1.10
Subtype															
ALL	9	1.05	(0.96, 1.16)	1.03	1.15	3	1.02	(0.99, 1.05)	1.01	1.02	1	1.00	(0.92, 1.09)	-	-
AML	5	1.09	(0.86, 1.38)	0.99	1.21	2	1.03	(0.77, 1.38)	0.89	1.20	1	1.25	(1.02, 1.53)	-	-
Exposure timing															
At birth	5	0.98	(0.90, 1.06)	0.92	1.03	4	0.95	(0.85, 1.05)	0.89	1.00	1	1.15	(0.78, 1.70)	-	-
At diagnosis	14	1.32	(1.12, 1.55)	1.25	1.41	3	1.27	(0.95, 1.71)	1.11	2.17	2	1.05	(0.94, 1.17)	1.01	1.11
Region															
Asia	1	1.27	(0.51, 3.17)	-	-	-					-				
Europe	9	1.25	(1.05, 1.49)	1.18	1.36	3	1.05	(0.87, 1.25)	0.98	1.11	1	1.05	(0.95, 1.17)	-	-
North America	6	1.02	(0.89, 1.16)	0.99	1.07	4	0.98	(0.84, 1.15)	0.96	1.05	2	1.09	(0.72, 1.64)	0.92	1.16
Benzene															
All leukemia	7	1.27	(1.03, 1.56)	1.22	1.36	4	1.39	(1.03, 1.87)	1.22	1.66	2	1.08	(0.64, 1.82)	0.93	1.16
Subtype															
ALL	7	1.09	(0.88, 1.36)	1.03	1.18	3	1.19	(1.00, 1.40)	1.17	1.38	1	0.69	(0.27, 1.78)	-	-
AML	5	1.84	(1.31, 2.59)	1.76	1.56	2	3.21	(1.39, 7.42)	2.61	5.46	1	0.43	(0.04, 4.79)	-	-
Exposure timing															
At birth	3	1.21	(1.04, 1.41)	1.19	1.38	3	1.22	(1.03, 1.43)	1.19	1.52	1	1.14	(0.63, 2.08)	-	-
At diagnosis	4	1.36	(0.92, 2.00)	1.17	1.56	1	3.30	(1.03, 10.59)	-	-	1	0.90	(0.31, 2.60)	-	-
Region															
Asia	-					-					-				
Europe	4	1.36	(0.92, 2.00)	1.17	1.56	1	3.30	(1.03, 10.59)	-	-	1	0.90	(0.31, 2.60)	-	-
North America	3	1.21	(1.04, 1.41)	1.19	1.38	3	1.22	(1.03, 1.43)	1.19	1.52	1	1.14	(0.63, 2.08)	-	-
NO₂															
All leukemia	8	1.04	(0.90, 1.19)	0.98	1.07	4	1.03	(0.90, 1.18)	0.98	1.06	1	0.89	(0.42, 1.89)	-	-
Subtype															
ALL	4	1.02	(0.89, 1.18)	0.95	1.08	2	1.10	(0.92, 1.32)	1.02	1.23	-				
AML	4	0.97	(0.79, 1.19)	0.92	1.01	2	0.86	(0.60, 1.23)	0.71	0.95	-				
Exposure timing															
At birth	4	1.07	(0.96, 1.19)	1.02	1.12	4	1.03	(0.90, 1.18)	0.98	1.06	1	0.89	(0.42, 1.89)	-	-
At diagnosis	4	1.17	(0.82, 1.67)	0.92	1.36	-					-				
Region															
Asia	1	2.29	(1.44, 3.64)	-	-	-					-				
Europe	4	0.91	(0.82, 1.00)	090	0.94	1	0.79	(0.52, 1.20)	-	-	-				
North America	3	1.06	(0.95, 1.18)	1.00	1.09	3	1.06	(0.94, 1.19)	1.01	1.10	1	0.89	(0.42, 1.89)	-	-

Note: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CI, confidence interval; n, number of studies; RR, risk ratio.

Table S5. Summary risk ratios (RR) 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. Results of leave-one-out sensitivity analysis of range of summary RR ('min RR' and 'max RR') investigating the influence of each individual study on the overall meta-analysis summary estimates.

Indicator		All children					Pre-school children (<6 years)					Children ≥ 6 years			
	n	RR	95% CI	min RR	max RR	n	RR	95% CI	min RR	max RR	n	RR	95% CI	min RR	max RR
PM$_{2.5}$															
All leukemia	3	1.05	(0.94, 1.16)	1.02	1.06	3	1.04	(0.94, 1.16)	1.01	1.06	-				
Subtype															
ALL	2	1.11	(0.95, 1.31)	1.10	1.20	2	1.11	(0.95, 1.31)	1.10	1.20	-				
AML	2	1.00	(0.87, 1.13)	0.85	1.03	2	1.00	(0.87, 1.13)	0.85	1.03	-				
Exposure timing															
At birth	3	1.05	(0.94, 1.16)	1.02	1.06	3	1.04	(0.94, 1.16)	1.01	1.06	-				
At diagnosis	-					-					-				
Region															
Europe	1	1.00	(0.72, 1.39)	-	-	1	0.94	(0.62, 1.43)	-	-	-				
North America	2	1.05	(0.94, 1.17)	1.02	1.07	2	1.05	(0.94, 1.17)	1.02	1.07	-				
PM$_{10}$															
All leukemia	2	1.20	(0.70, 2.04)	1.00	1.80	2	1.09	(0.66, 1.80)	0.97	1.90	1	1.50	(0.48, 4.70)	-	-
Subtype															
ALL	1	1.45	(0.73, 2.87)	-	-	1	1.50	(0.52, 4.33)	-	-	1	1.39	(0.54, 3.57)	-	-
AML	1	1.30	(0.41, 4.14)	-	-	1	1.21	(0.18, 8.16)	-	-	1	1.18	(0.25, 5.56)	-	-
Exposure timing															
At birth	1	1.00	(0.70, 1.42)	-	-	1	0.97	(0.62, 1.51)	-	-	-				
At diagnosis	1	1.80	(0.82, 3.97)	-	-	1	1.90	(0.60, 6.01)	-	-	1	1.50	(0.48, 4.70)	-	-
Region															
Europe	2	1.20	(0.70, 2.04)	1.00	1.80	2	1.09	(0.66, 1.80)	0.97	1.90	1	1.50	(0.48, 4.70)	-	-
North America	-					-					-				
1,3-butadiene															
All leukemia	2	1.45	(1.08, 1.95)	1.31	1.91	2	1.45	(1.08, 1.95)	1.31	1.91	-				
Subtype															
ALL	2	1.31	(1.11, 1.54)	1.28	1.73	2	1.31	(1.11, 1.54)	1.28	1.73	-				
AML	1	2.35	(1.02, 5.40)	-	-	1	2.35	(1.02, 5.40)	-	-	-				
Exposure timing															
At birth	2	1.45	(1.08, 1.95)	1.31	1.91	2	1.45	(1.08, 1.95)	1.31	1.91					
At diagnosis	-					-									
Region															
Europe	-					-					-				
North America	2	1.45	(1.08, 1.95)	1.31	1.91	2	1.45	(1.08, 1.95)	1.31	1.91	-				

Note: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CI, confidence interval; n, number of studies; RR, risk ratio.
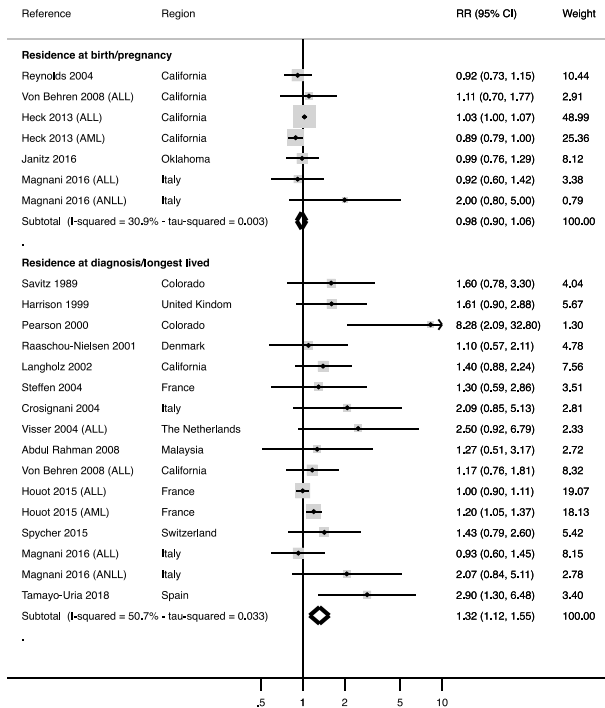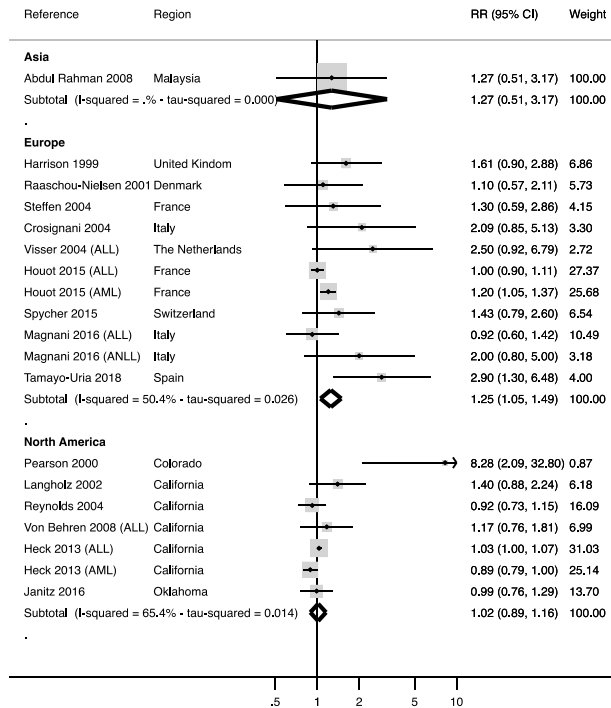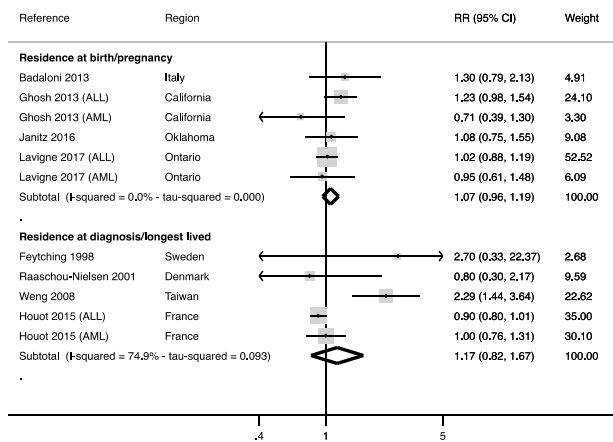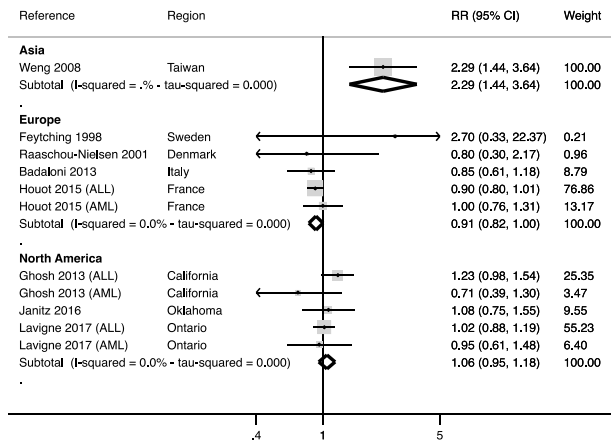
Figure S1. Risk ratio (RR) of childhood leukemia from indicators of traffic exposure for all children: all studies (A); by leukemia subtype (B); by exposure window, i.e. residence at birth vs. at diagnosis (C); by region/continent (D). The area of each gray square is proportional to the inverse of the variance of the estimated log RR. Black diamonds represent point estimates of RR and horizontal lines represent their 95% confidence intervals (CIs). The open diamonds represent the combined RR for each subgroup and the overall RR for all studies. The solid line represents RR=1. The dash line represents the point estimate of overall RR for all studies.
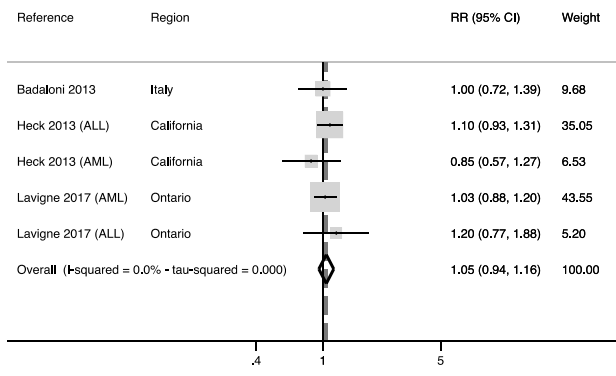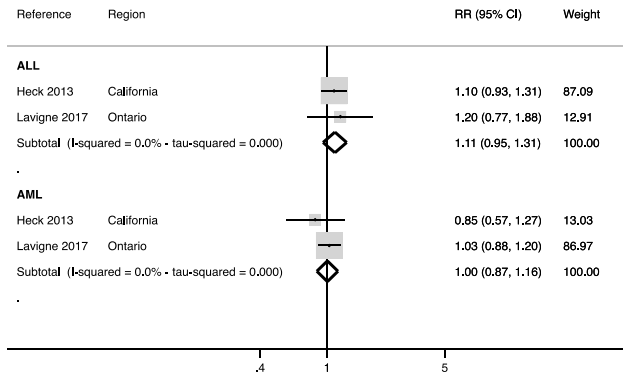
Figure S2. Risk ratio (RR) of childhood leukemia and leukemia subtype from benzene exposure for all children: all studies (A); by leukemia subtype (B); by exposure window, i.e. residence at birth vs. at diagnosis (C); by region/continent (D). The area of each gray square is proportional to the inverse of the variance of the estimated log RR. Black diamonds represent point estimates of RR and horizontal lines represent their 95% confidence intervals (CIs). The open diamonds represent the combined RR for each subgroup and the overall RR for all studies. The solid line represents RR=1. The dash line represents the point estimate of overall RR for all studies.
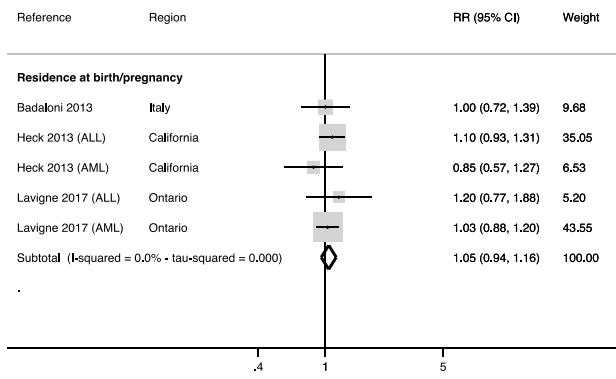
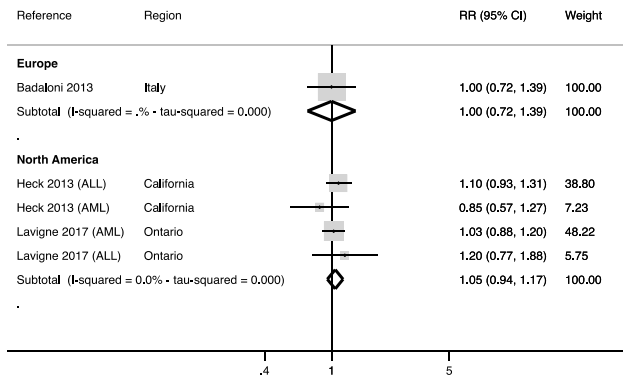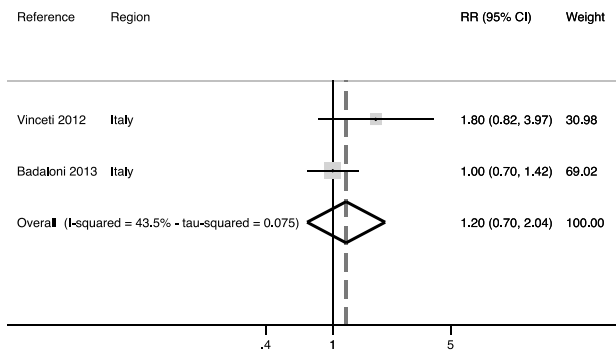**Figure S3.** Risk ratio (RR) of childhood leukemia and leukemia subtype from air NO$_2$ exposure for all children: all studies (A); by leukemia subtype (B); by exposure window, i.e. residence at birth vs. at diagnosis (C); by region/continent (D). The area of each gray square is proportional to the inverse of the variance of the estimated log RR. Black diamonds represent point estimates of RR and horizontal lines represent their 95% confidence intervals (CIs). The open diamonds represent the combined RR for each subgroup and the overall RR for all studies. The solid line represents RR=1. The dash line represents the point estimate of overall RR for all studies.

A

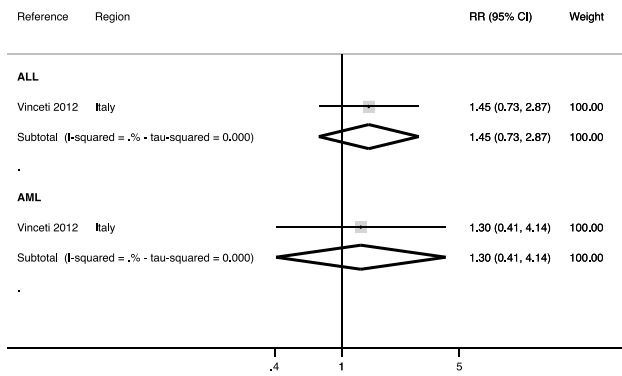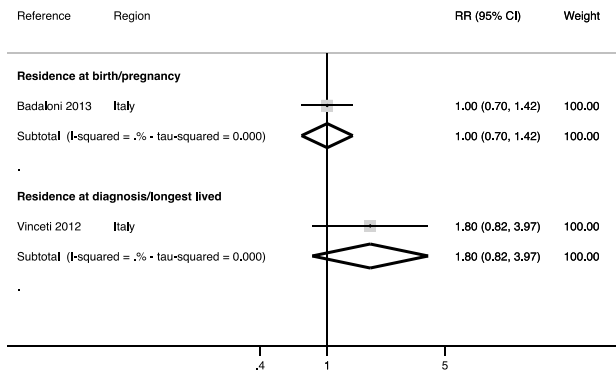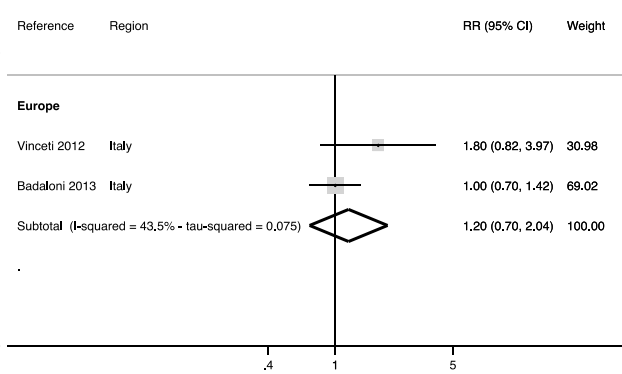| Reference	Region		RR (95% CI)	Weight
Badaloni 2013	Italy		1.00 (0.72, 1.39)	9.68
Heck 2013 (ALL)	California		1.10 (0.93, 1.31)	35.05
Heck 2013 (AML)	California		0.85 (0.57, 1.27)	6.53
Lavigne 2017 (AML)	Ontario		1.03 (0.88, 1.20)	43.55
Lavigne 2017 (ALL)	Ontario		1.20 (0.77, 1.88)	5.20
Overall (I-squared = 0.0% - tau-squared = 0.000)			1.05 (0.94, 1.16)	100.00

.4 1 5

B

Reference	Region		RR (95% CI)	Weight
ALL				
Heck 2013	California		1.10 (0.93, 1.31)	87.09
Lavigne 2017	Ontario		1.20 (0.77, 1.88)	12.91
Subtotal (I-squared = 0.0% - tau-squared = 0.000)			1.11 (0.95, 1.31)	100.00
.				
AML				
Heck 2013	California		0.85 (0.57, 1.27)	13.03
Lavigne 2017	Ontario		1.03 (0.88, 1.20)	86.97
Subtotal (I-squared = 0.0% - tau-squared = 0.000)			1.00 (0.87, 1.16)	100.00
.				

.4 1 5

C

Reference	Region		RR (95% CI)	Weight
Residence at birth/pregnancy				
Badaloni 2013	Italy		1.00 (0.72, 1.39)	9.68
Heck 2013 (ALL)	California		1.10 (0.93, 1.31)	35.05
Heck 2013 (AML)	California		0.85 (0.57, 1.27)	6.53
Lavigne 2017 (ALL)	Ontario		1.20 (0.77, 1.88)	5.20
Lavigne 2017 (AML)	Ontario		1.03 (0.88, 1.20)	43.55
Subtotal (I-squared = 0.0% - tau-squared = 0.000)			1.05 (0.94, 1.16)	100.00
.				

.4 1 5

D

Reference	Region		RR (95% CI)	Weight
Europe				
Badaloni 2013	Italy		1.00 (0.72, 1.39)	100.00
Subtotal (I-squared = .% - tau-squared = 0.000)			1.00 (0.72, 1.39)	100.00
.				
North America				
Heck 2013 (ALL)	California		1.10 (0.93, 1.31)	38.80
Heck 2013 (AML)	California		0.85 (0.57, 1.27)	7.23
Lavigne 2017 (AML)	Ontario		1.03 (0.88, 1.20)	48.22
Lavigne 2017 (ALL)	Ontario		1.20 (0.77, 1.88)	5.75
Subtotal (I-squared = 0.0% - tau-squared = 0.000)			1.05 (0.94, 1.17)	100.00
.				

.4 1 5

Figure S4. Risk ratio (RR) with 95% confidence interval (CI) of childhood leukemia from particulate matter ($PM_{2.5}$) for all children: all studies (A); by leukemia subtype (B); by exposure window, i.e. residence at birth vs. at diagnosis (C); by region/continent (D). The area of each gray square is proportional to the inverse of the variance of the estimated log RR. Black diamonds represent point estimates of RR and horizontal lines represent their 95% confidence intervals (CIs). The open diamonds represent the combined RR for each subgroup and the overall RR for all studies. The solid line represents RR=1. The dash line represents the point estimate of overall RR for all studies.
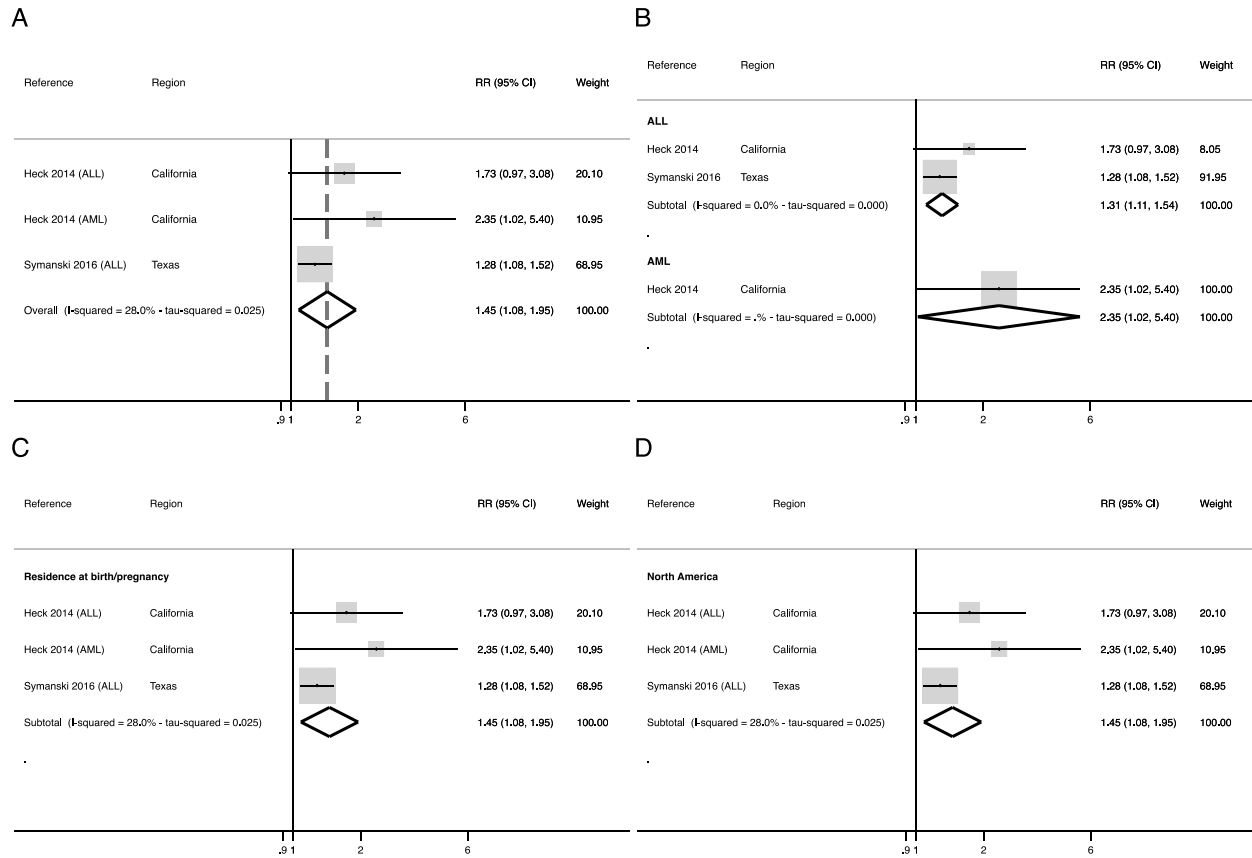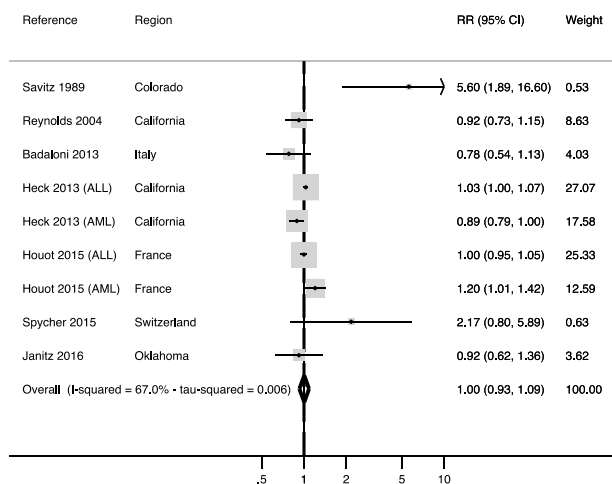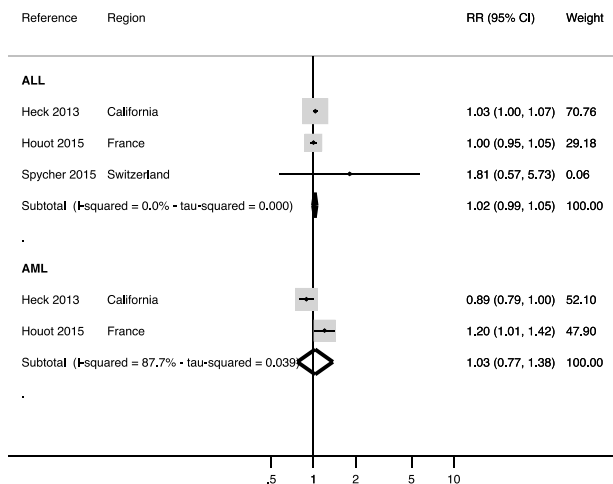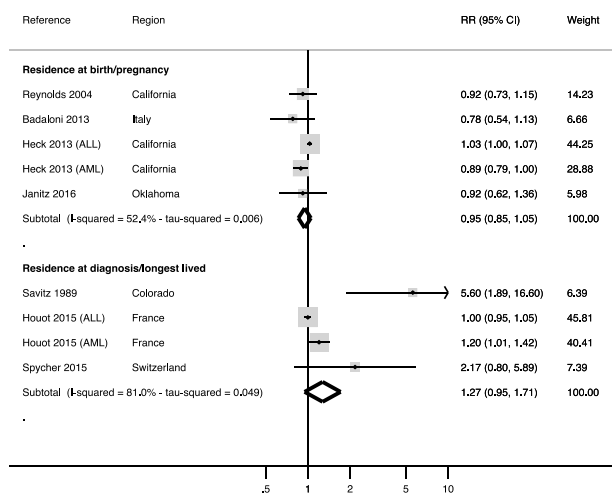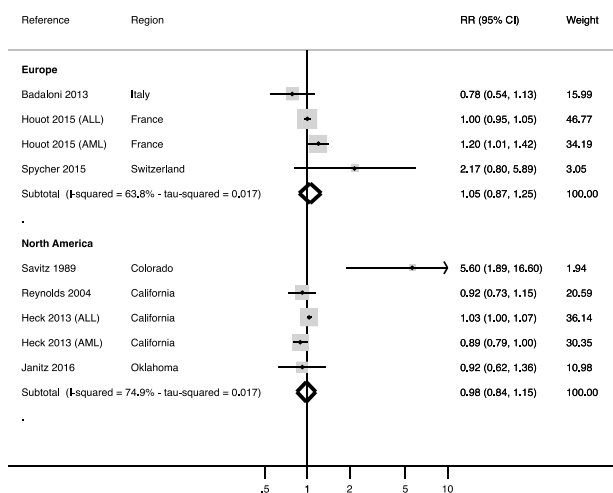
Figure S5. Risk ratio (RR) with 95% confidence interval (CI) of childhood leukemia from particulate matter (PM$_{10}$) for all children: all studies (A); by leukemia subtype (B); by exposure window, i.e. residence at birth vs. at diagnosis (C); by region/continent (D). The area of each gray square is proportional to the inverse of the variance of the estimated log RR. Black diamonds represent point estimates of RR and horizontal lines represent their 95% confidence intervals (CIs). The open diamonds represent the combined RR for each subgroup and the overall RR for all studies. The solid line represents RR=1. The dash line represents the point estimate of overall RR for all studies.
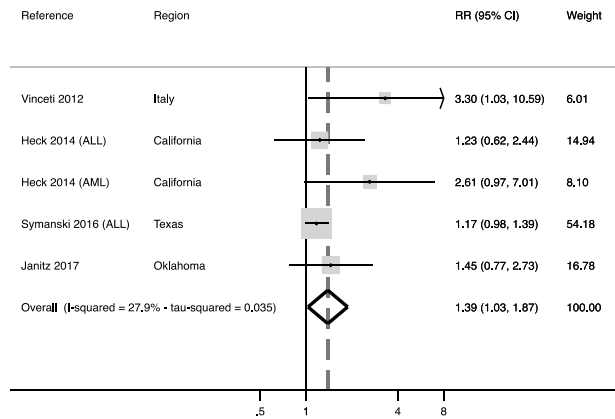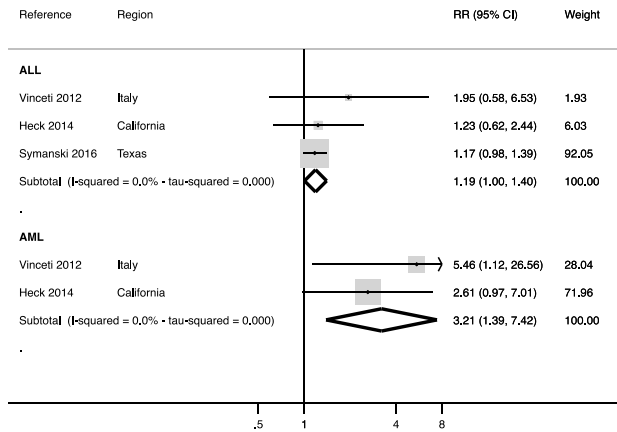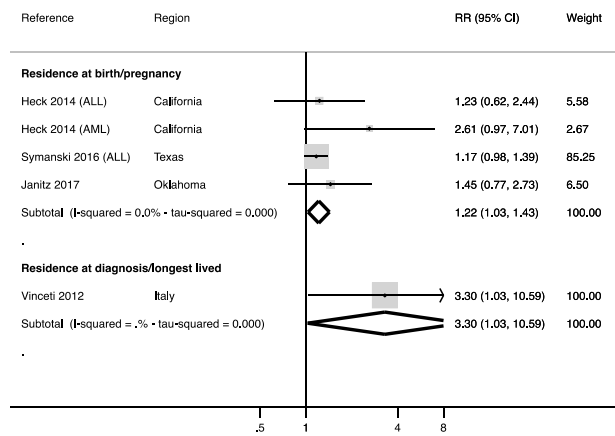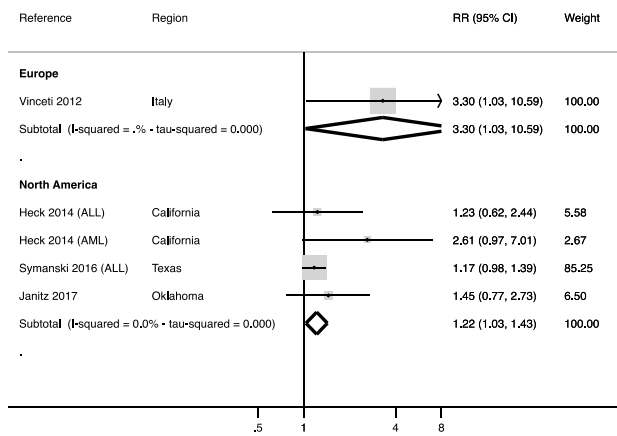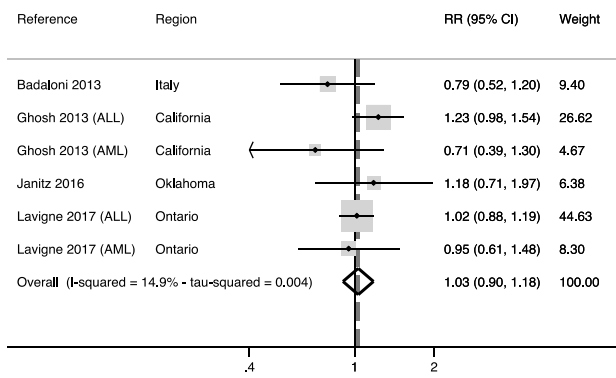
A

Reference	Region		RR (95% CI)	Weight
Heck 2014 (ALL)	California		1.73 (0.97, 3.08)	20.10
Heck 2014 (AML)	California		2.35 (1.02, 5.40)	10.95
Symanski 2016 (ALL)	Texas		1.28 (1.08, 1.52)	68.95
Overall (I-squared = 28.0% - tau-squared = 0.025)			1.45 (1.08, 1.95)	100.00

.9 1   2   6

B

Reference	Region		RR (95% CI)	Weight
ALL				
Heck 2014	California		1.73 (0.97, 3.08)	8.05
Symanski 2016	Texas		1.28 (1.08, 1.52)	91.95
Subtotal (I-squared = 0.0% - tau-squared = 0.000)			1.31 (1.11, 1.54)	100.00
.				
AML				
Heck 2014	California		2.35 (1.02, 5.40)	100.00
Subtotal (I-squared = .% - tau-squared = 0.000)			2.35 (1.02, 5.40)	100.00
.				

.9 1   2   6

C

Reference	Region		RR (95% CI)	Weight
Residence at birth/pregnancy				
Heck 2014 (ALL)	California		1.73 (0.97, 3.08)	20.10
Heck 2014 (AML)	California		2.35 (1.02, 5.40)	10.95
Symanski 2016 (ALL)	Texas		1.28 (1.08, 1.52)	68.95
Subtotal (I-squared = 28.0% - tau-squared = 0.025)			1.45 (1.08, 1.95)	100.00
.				

.9 1   2   6

D

Reference	Region		RR (95% CI)	Weight
North America				
Heck 2014 (ALL)	California		1.73 (0.97, 3.08)	20.10
Heck 2014 (AML)	California		2.35 (1.02, 5.40)	10.95
Symanski 2016 (ALL)	Texas		1.28 (1.08, 1.52)	68.95
Subtotal (I-squared = 28.0% - tau-squared = 0.025)			1.45 (1.08, 1.95)	100.00
.				

.9 1   2   6

Figure S6. Risk ratio (RR) of childhood leukemia and leukemia subtype from 1,3-butadiene exposure for all children (all pre-school, i.e. <6 years): all studies (A); by leukemia subtype (B); by exposure window, i.e. residence at birth vs. at diagnosis (C); by region/continent (D). The area of each gray square is proportional to the inverse of the variance of the estimated log RR. Black diamonds represent point estimates of RR and horizontal lines represent their 95% confidence intervals (CIs). The open diamonds represent the combined RR for each subgroup and the overall RR for all studies. The solid line represents RR=1. The dash line represents the point estimate of overall RR for all studies.
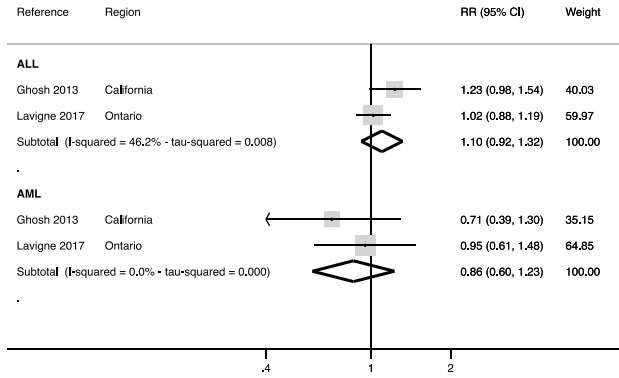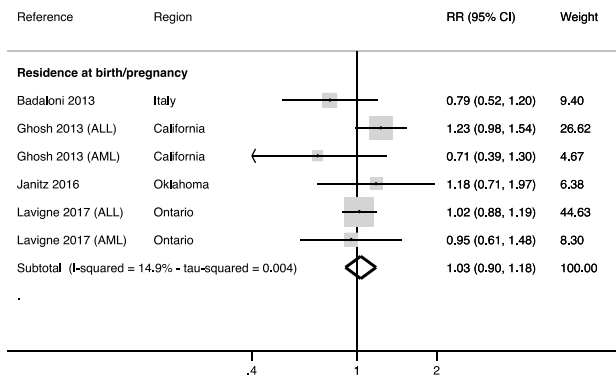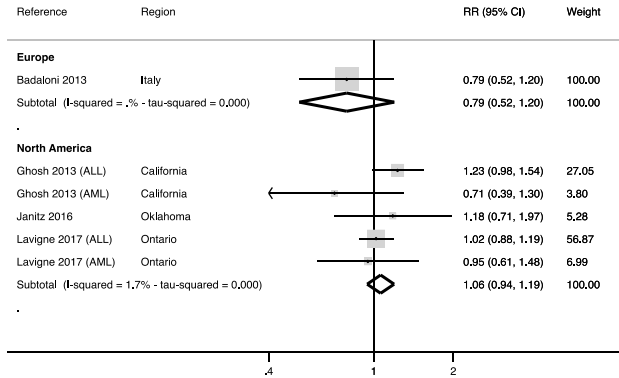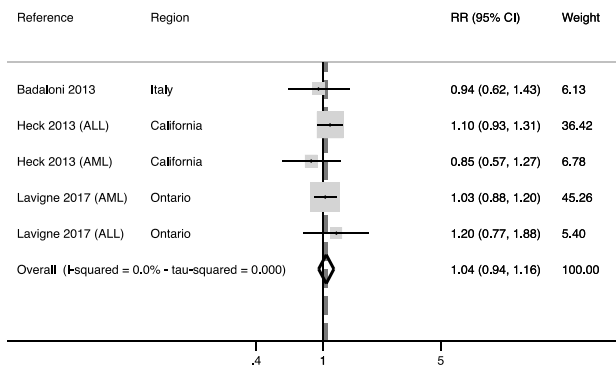
Figure S7. Risk ratio (RR) of childhood leukemia from indicators of traffic exposure restricted to pre-school children: all studies (A); by leukemia subtype (B); by exposure window, i.e. residence at birth vs. at diagnosis (C); by region/continent (D). The area of each gray square is proportional to the inverse of the variance of the estimated log RR. Black diamonds represent point estimates of RR and horizontal lines represent their 95% confidence intervals (CIs). The open diamonds represent the combined RR for each subgroup and the overall RR for all studies. The solid line represents RR=1. The dash line represents the point estimate of overall RR for all studies.
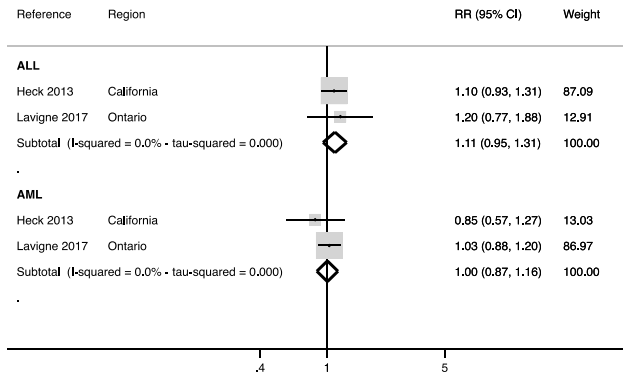
Figure S8. Risk ratio (RR) of childhood leukemia and leukemia subtype from benzene exposure restricted to pre-school children: all studies (A); by leukemia subtype (B); by exposure window, i.e. residence at birth vs. at diagnosis (C); by region/continent (D). The area of each gray square is proportional to the inverse of the variance of the estimated log RR. Black diamonds represent point estimates of RR and horizontal lines represent their 95% confidence intervals (CIs). The open diamonds represent the combined RR for each subgroup and the overall RR for all studies. The solid line represents RR=1. The dash line represents the point estimate of overall RR for all studies.
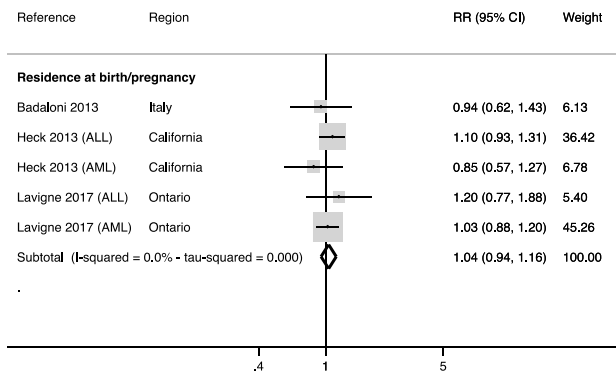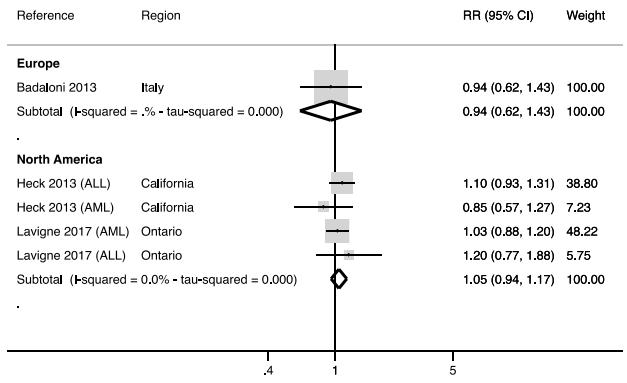
Figure S9. Risk ratio (RR) of childhood leukemia and leukemia subtype from air NO_2 exposure restricted to pre-school children: all studies (A); by leukemia subtype (B); by exposure window, i.e. residence at birth vs. at diagnosis (C); by region/continent (D). The area of each gray square is proportional to the inverse of the variance of the estimated log RR. Black diamonds represent point estimates of RR and horizontal lines represent their 95% confidence intervals (CIs). The open diamonds represent the combined RR for each subgroup and the overall RR for all studies. The solid line represents RR=1. The dash line represents the point estimate of overall RR for all studies.
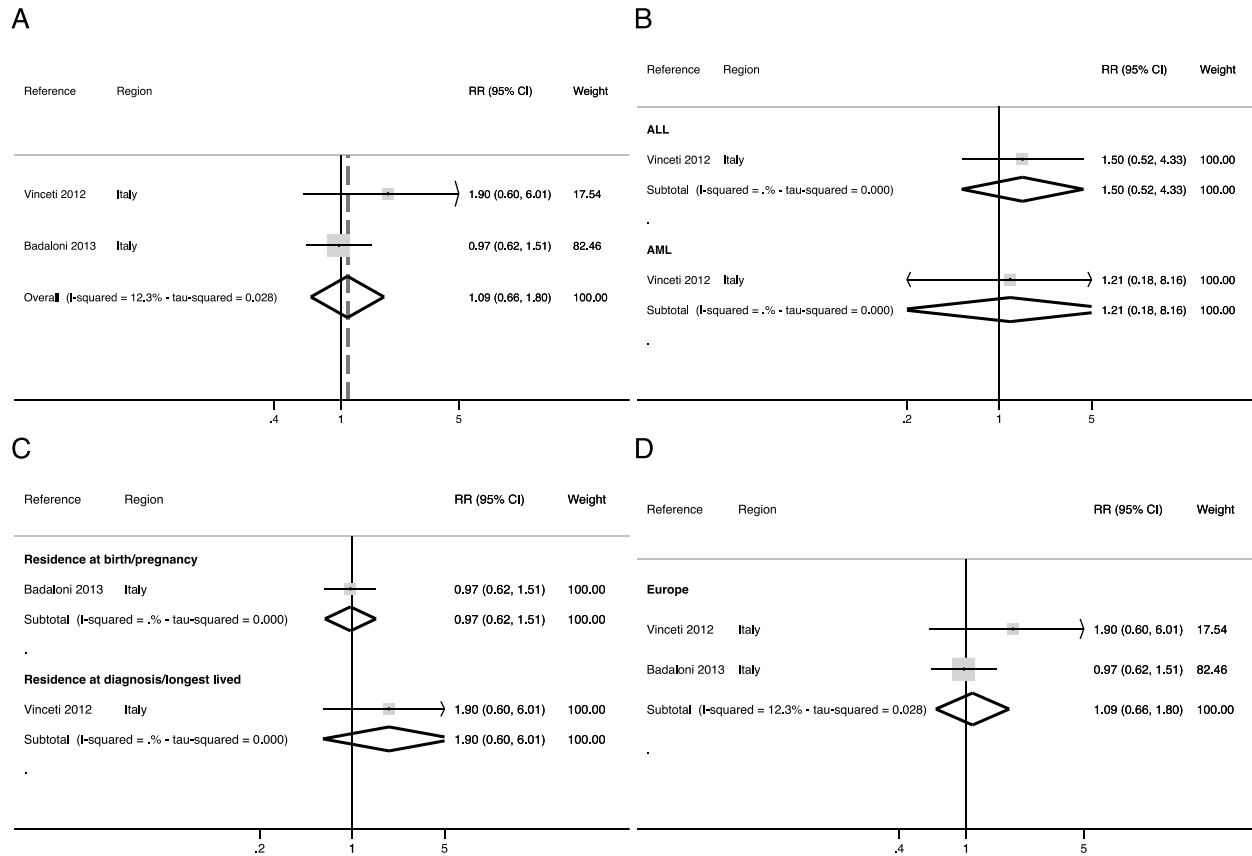
Figure S10. Risk ratio (RR) with 95% confidence interval (CI) of childhood leukemia from particulate matter (PM$_{2.5}$) restricted to pre-school children: all studies (A); by leukemia subtype (B); by exposure window, i.e. residence at birth vs. at diagnosis (C); by region/continent (D). The area of each gray square is proportional to the inverse of the variance of the estimated log RR. Black diamonds represent point estimates of RR and horizontal lines represent their 95% confidence intervals (CIs). The open diamonds represent the combined RR for each subgroup and the overall RR for all studies. The solid line represents RR=1. The dash line represents the point estimate of overall RR for all studies.

Figure S11. Risk ratio (RR) with 95% confidence interval (CI) of childhood leukemia from particulate matter (PM$_{10}$) restricted to pre-school children: all studies (A); by leukemia subtype (B); by exposure window, i.e. residence at birth vs. at diagnosis (C); by region/continent (D). The area of each gray square is proportional to the inverse of the variance of the estimated log RR. Black diamonds represent point estimates of RR and horizontal lines represent their 95% confidence intervals (CIs). The open diamonds represent the combined RR for each subgroup and the overall RR for all studies. The solid line represents RR=1. The dash line represents the point estimate of overall RR for all studies.
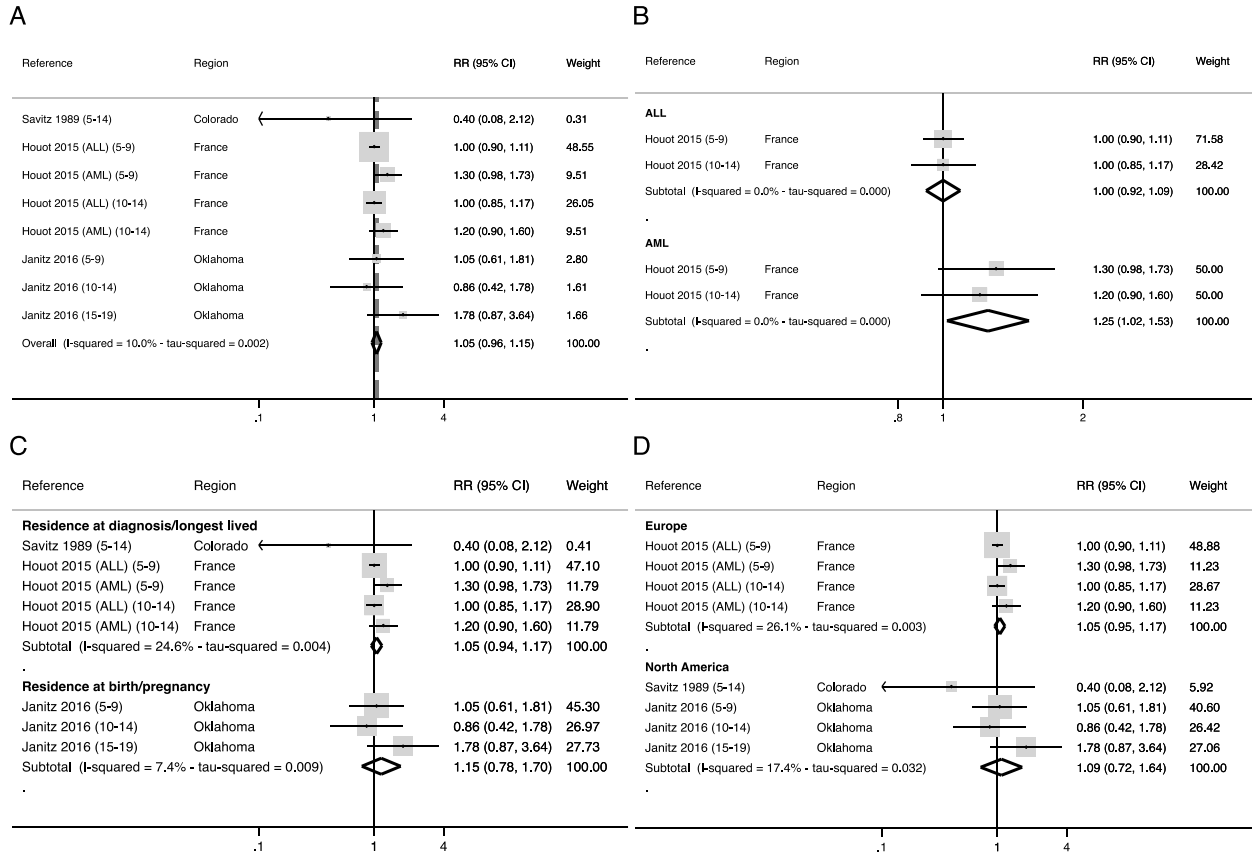
Figure S12. Risk ratio (RR) of childhood leukemia from indicators of traffic exposure restricted to older (>6 years) children: all studies (A); by leukemia subtype (B); by exposure window, i.e. residence at birth vs. at diagnosis (C); by region/continent (D). The area of each gray square is proportional to the inverse of the variance of the estimated log RR. Black diamonds represent point estimates of RR and horizontal lines represent their 95% confidence intervals (CIs). The open diamonds represent the combined RR for each subgroup and the overall RR for all studies. The solid line represents RR=1. The dash line represents the point estimate of overall RR for all studies.
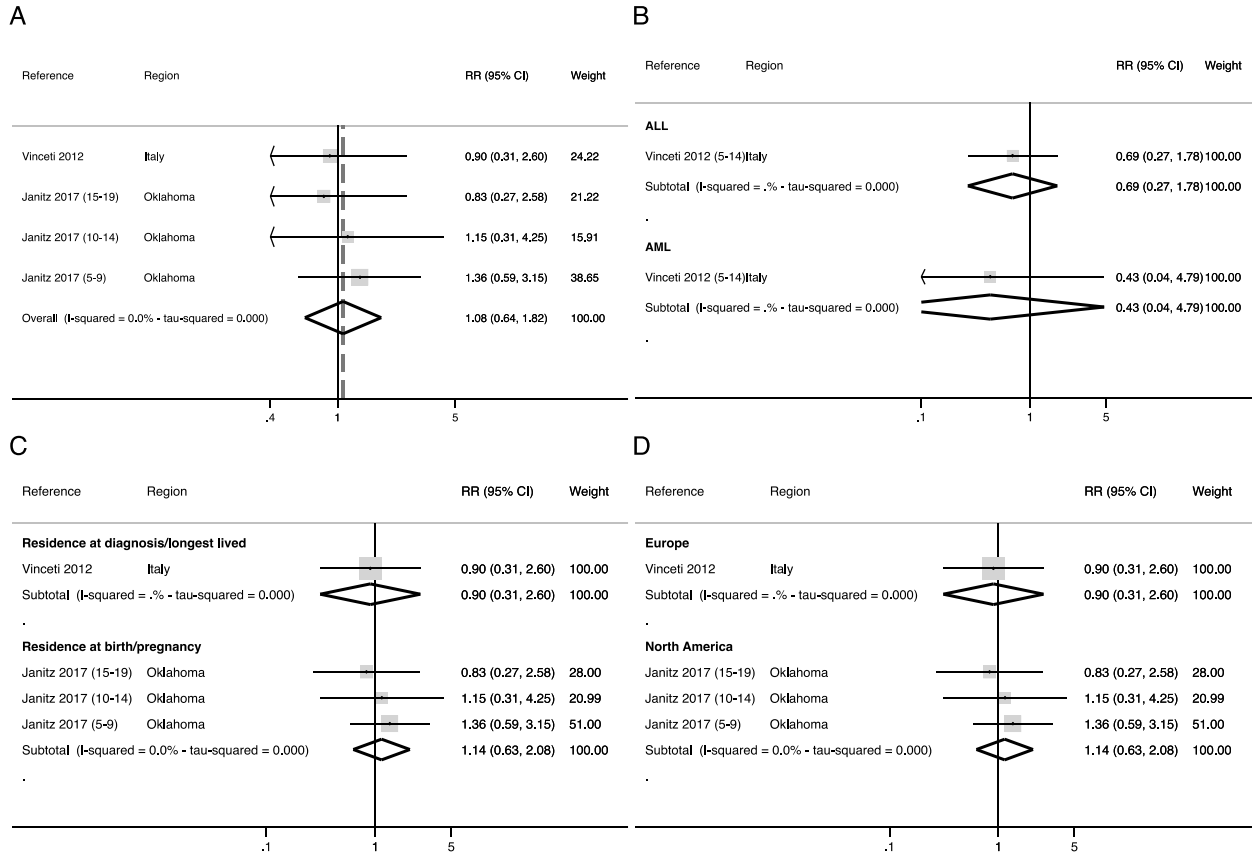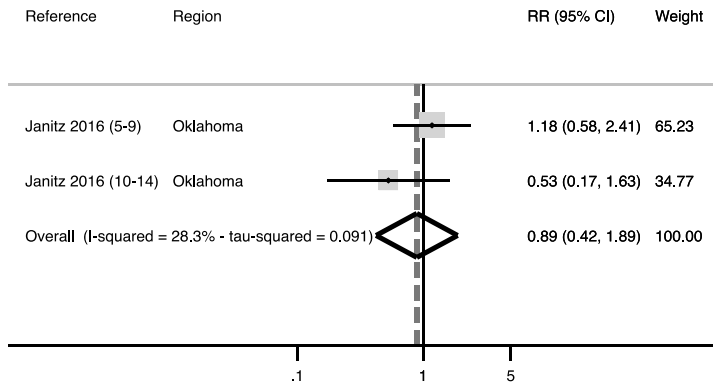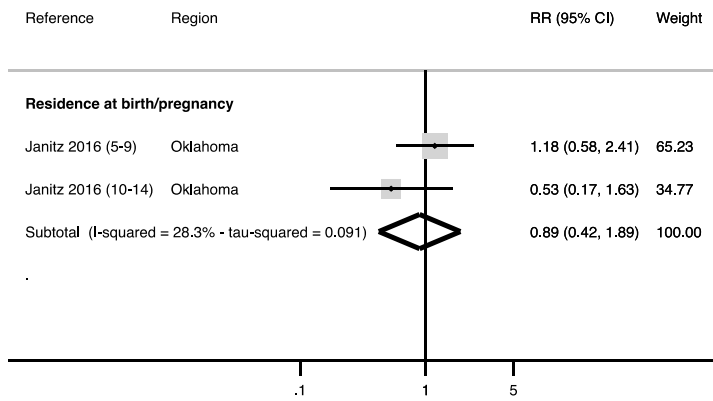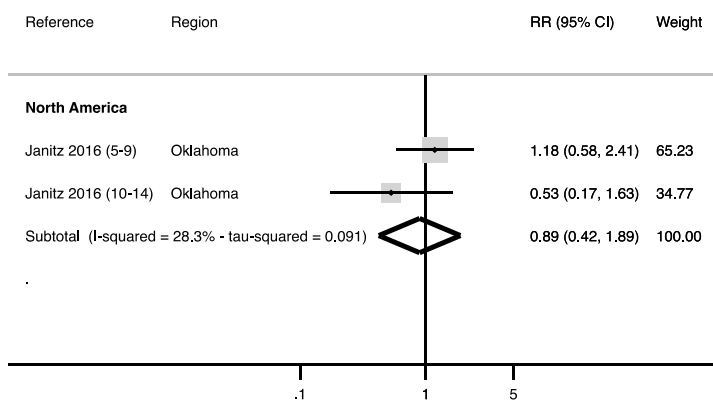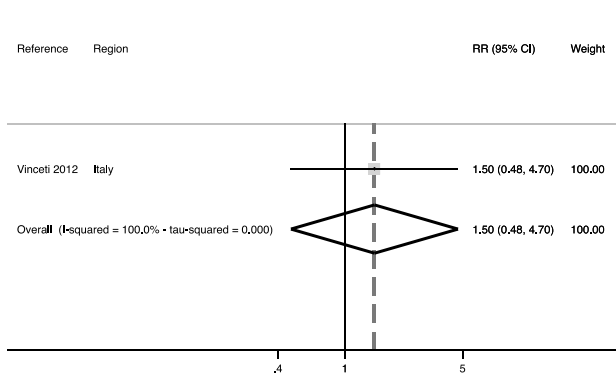
A

Reference	Region		RR (95% CI)	Weight
Vinceti 2012	Italy		0.90 (0.31, 2.60)	24.22
Janitz 2017 (15-19)	Oklahoma		0.83 (0.27, 2.58)	21.22
Janitz 2017 (10-14)	Oklahoma		1.15 (0.31, 4.25)	15.91
Janitz 2017 (5-9)	Oklahoma		1.36 (0.59, 3.15)	38.65
Overall (I-squared = 0.0% - tau-squared = 0.000)			1.08 (0.64, 1.82)	100.00

B

Reference	Region		RR (95% CI)	Weight
ALL				
Vinceti 2012 (5-14)	Italy		0.69 (0.27, 1.78)	100.00
Subtotal (I-squared = .% - tau-squared = 0.000)			0.69 (0.27, 1.78)	100.00
AML				
Vinceti 2012 (5-14)	Italy		0.43 (0.04, 4.79)	100.00
Subtotal (I-squared = .% - tau-squared = 0.000)			0.43 (0.04, 4.79)	100.00

C

Reference	Region		RR (95% CI)	Weight
Residence at diagnosis/longest lived				
Vinceti 2012	Italy		0.90 (0.31, 2.60)	100.00
Subtotal (I-squared = .% - tau-squared = 0.000)			0.90 (0.31, 2.60)	100.00
Residence at birth/pregnancy				
Janitz 2017 (15-19)	Oklahoma		0.83 (0.27, 2.58)	28.00
Janitz 2017 (10-14)	Oklahoma		1.15 (0.31, 4.25)	20.99
Janitz 2017 (5-9)	Oklahoma		1.36 (0.59, 3.15)	51.00
Subtotal (I-squared = 0.0% - tau-squared = 0.000)			1.14 (0.63, 2.08)	100.00

D

Reference	Region		RR (95% CI)	Weight
Europe				
Vinceti 2012	Italy		0.90 (0.31, 2.60)	100.00
Subtotal (I-squared = .% - tau-squared = 0.000)			0.90 (0.31, 2.60)	100.00
North America				
Janitz 2017 (15-19)	Oklahoma		0.83 (0.27, 2.58)	28.00
Janitz 2017 (10-14)	Oklahoma		1.15 (0.31, 4.25)	20.99
Janitz 2017 (5-9)	Oklahoma		1.36 (0.59, 3.15)	51.00
Subtotal (I-squared = 0.0% - tau-squared = 0.000)			1.14 (0.63, 2.08)	100.00

Figure S13. Risk ratio (RR) of childhood leukemia and leukemia subtype from benzene exposure restricted to older (>6 years) children: all studies (A); by leukemia subtype (B); by exposure window, i.e. residence at birth vs. at diagnosis (C); by region/continent (D). The area of each gray square is proportional to the inverse of the variance of the estimated log RR. Black diamonds represent point estimates of RR and horizontal lines represent their 95% confidence intervals (CIs). The open diamonds represent the combined RR for each subgroup and the overall RR for all studies. The solid line represents RR=1. The dash line represents the point estimate of overall RR for all studies.
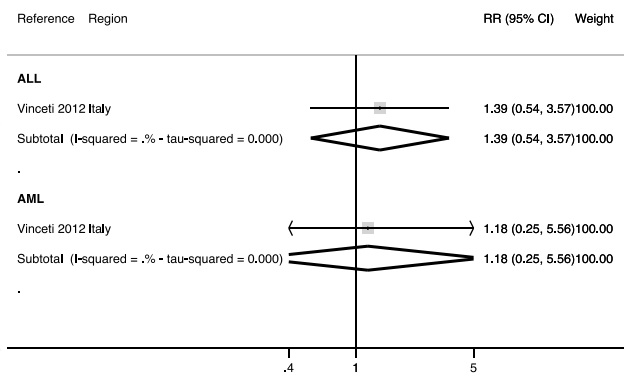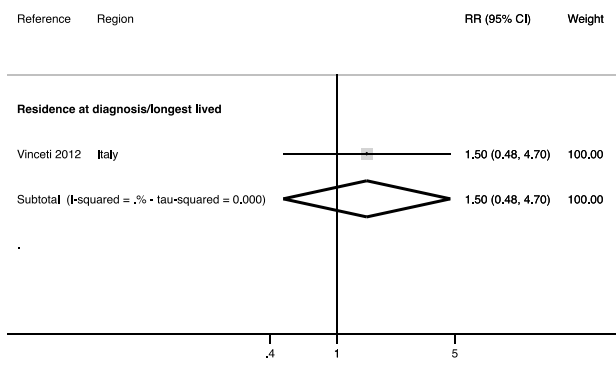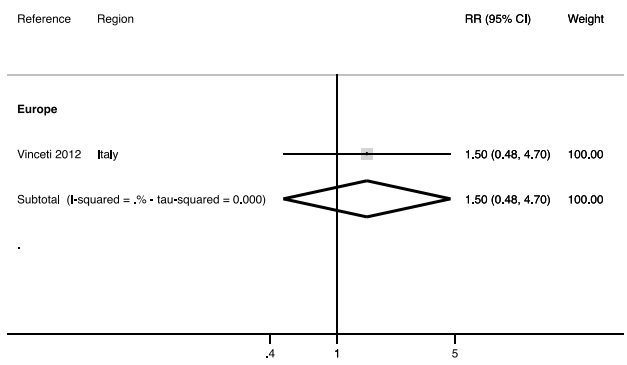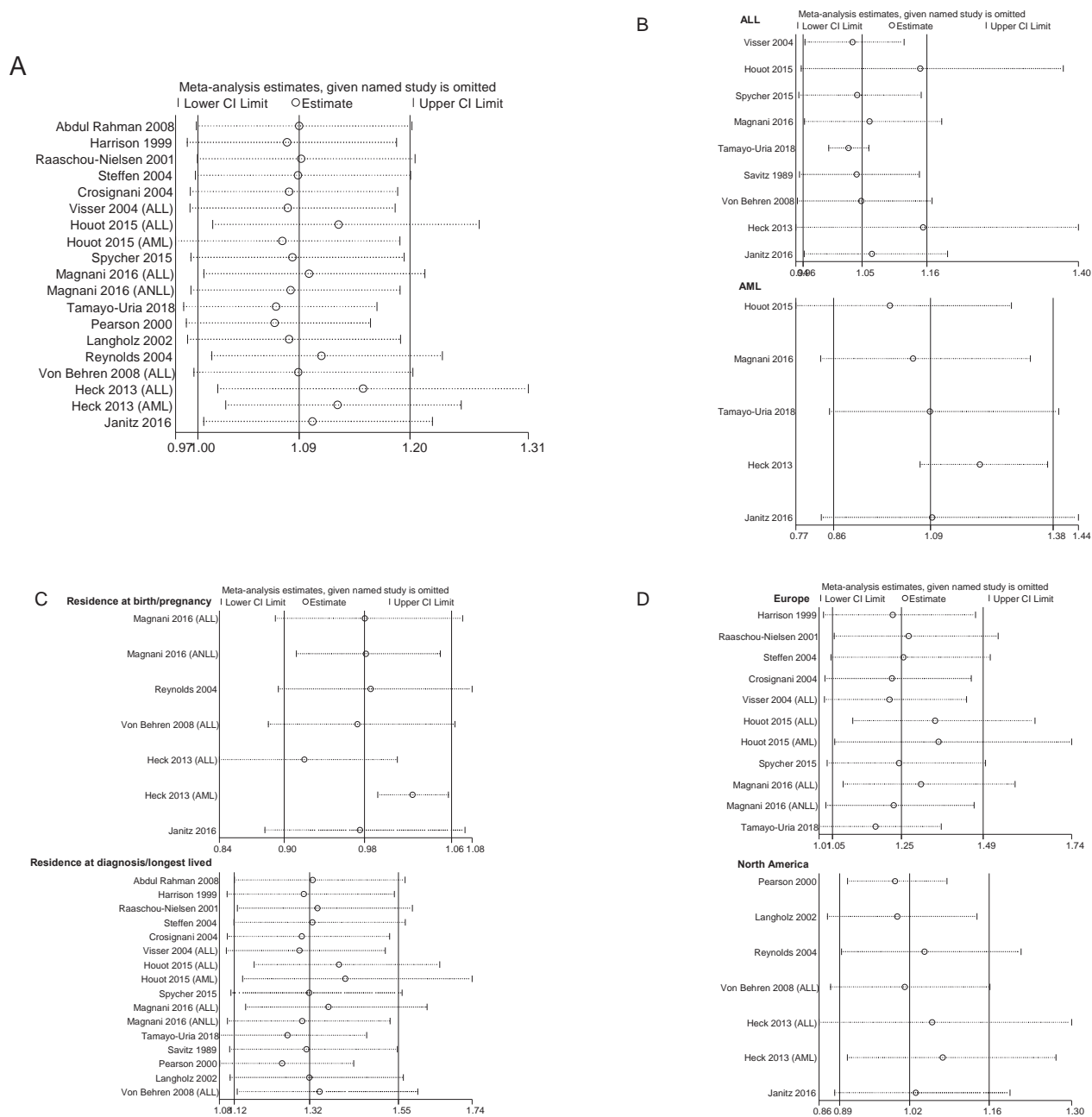
A

Reference	Region		RR (95% CI)	Weight
Janitz 2016 (5-9)	Oklahoma		1.18 (0.58, 2.41)	65.23
Janitz 2016 (10-14)	Oklahoma		0.53 (0.17, 1.63)	34.77
Overall (I-squared = 28.3% - tau-squared = 0.091)			0.89 (0.42, 1.89)	100.00

.1   1   5

B

Reference	Region		RR (95% CI)	Weight
Residence at birth/pregnancy				
Janitz 2016 (5-9)	Oklahoma		1.18 (0.58, 2.41)	65.23
Janitz 2016 (10-14)	Oklahoma		0.53 (0.17, 1.63)	34.77
Subtotal (I-squared = 28.3% - tau-squared = 0.091)			0.89 (0.42, 1.89)	100.00

.1   1   5

C

Reference	Region		RR (95% CI)	Weight
North America				
Janitz 2016 (5-9)	Oklahoma		1.18 (0.58, 2.41)	65.23
Janitz 2016 (10-14)	Oklahoma		0.53 (0.17, 1.63)	34.77
Subtotal (I-squared = 28.3% - tau-squared = 0.091)			0.89 (0.42, 1.89)	100.00

.1   1   5

Figure S14. Risk ratio (RR) of childhood leukemia from NO$_2$ exposure restricted to older (>6 years) children: all studies (A); by exposure window, i.e. residence at birth vs. at diagnosis (C); by region/continent (C). The area of each gray square is proportional to the inverse of the variance of the estimated log RR. Black diamonds represent point estimates of RR and horizontal lines represent their 95% confidence intervals (CIs). The open diamonds represent the combined RR for each subgroup and the overall RR for all studies. The solid line represents RR=1. The dash line represents the point estimate of overall RR for all studies.

Figure S15. Risk ratio (RR) with 95% confidence interval (CI) of childhood leukemia from particulate matter (PM$_{10}$) restricted to pre-school children: all studies (A); by leukemia subtype (B); by exposure window, i.e. residence at birth vs. at diagnosis (C); by region/continent (D). The area of each gray square is proportional to the inverse of the variance of the estimated log RR. Black diamonds represent point estimates of RR and horizontal lines represent their 95% confidence intervals (CIs). The open diamonds represent the combined RR for each subgroup and the overall RR for all studies. The solid line represents RR=1. The dash line represents the point estimate of overall RR for all studies.
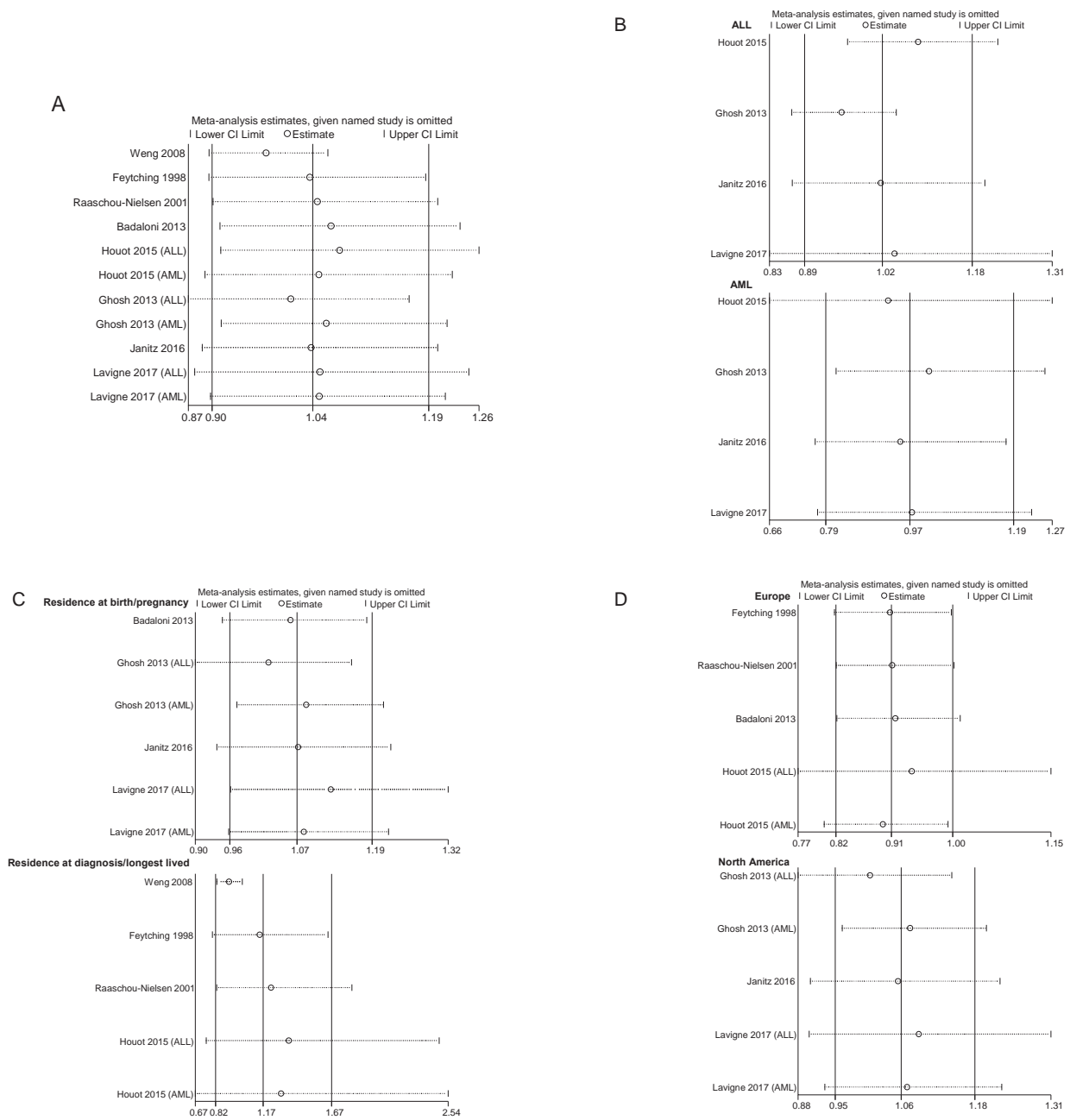
Figure S16. Sensitivity analysis with summary estimate with 95% confidence interval (CI) of childhood leukemia from indicators of traffic exposure for all children after removal of single study result (leave-one-out analysis): all studies (A); by leukemia subtype (B); by exposure window, i.e. residence at birth vs. at diagnosis (C); by region/continent (D). Each given named study is omitted when computing the overall meta-analysis summary estimate. Hollow circles represent point estimates of RR and horizontal dotted lines represent their 95% confidence intervals (CIs). The solid lines represent the point estimate of overall RR for all studies with its 95% CI.
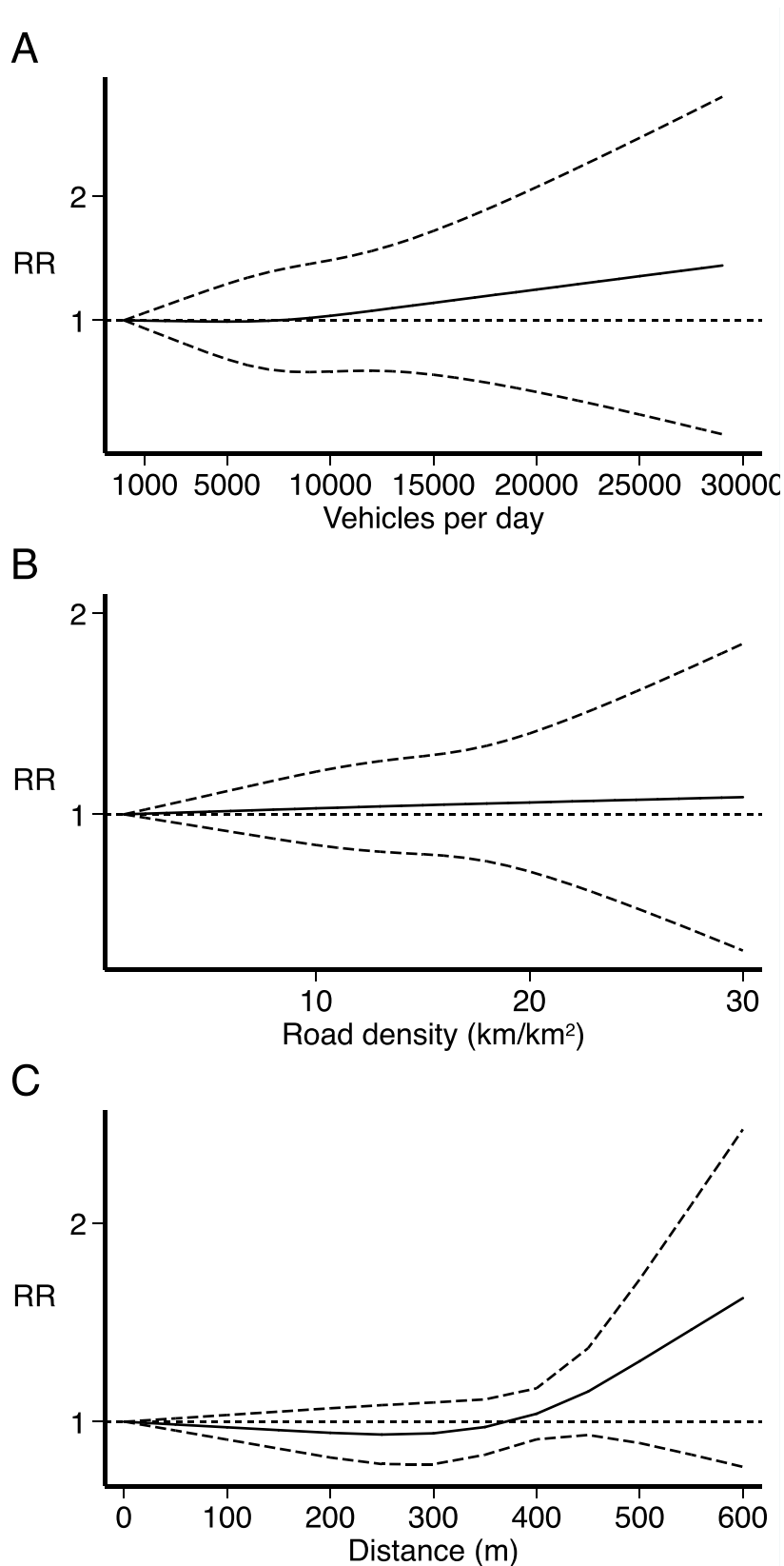
Figure S17. Sensitivity analysis with summary estimate with 95% confidence interval (CI) of childhood leukemia from benzene exposure for all children after removal of single study result (leave-one-out analysis): all studies (A); by leukemia subtype (B); by exposure window, i.e. residence at birth vs. at diagnosis (C); by region/continent (D). Each given named study is omitted when computing the overall meta-analysis summary estimate. Hollow circles represent point estimates of RR and horizontal dotted lines represent their 95% confidence intervals (CIs). The solid lines represent the point estimate of overall RR for all studies with its 95% CI.

Figure S18. Sensitivity analysis with summary estimate with 95% confidence interval (CI) of childhood leukemia from nitrogen dioxide exposure for all children after removal of single study result (leave-one-out analysis): all studies (A); by leukemia subtype (B); by exposure window, i.e. residence at birth vs. at diagnosis (C); by region/continent (D). Each given named study is omitted when computing the overall meta-analysis summary estimate. Hollow circles represent point estimates of RR and horizontal dotted lines represent their 95% confidence intervals (CIs). The solid lines represent the point estimate of overall RR for all studies with its 95% CI.
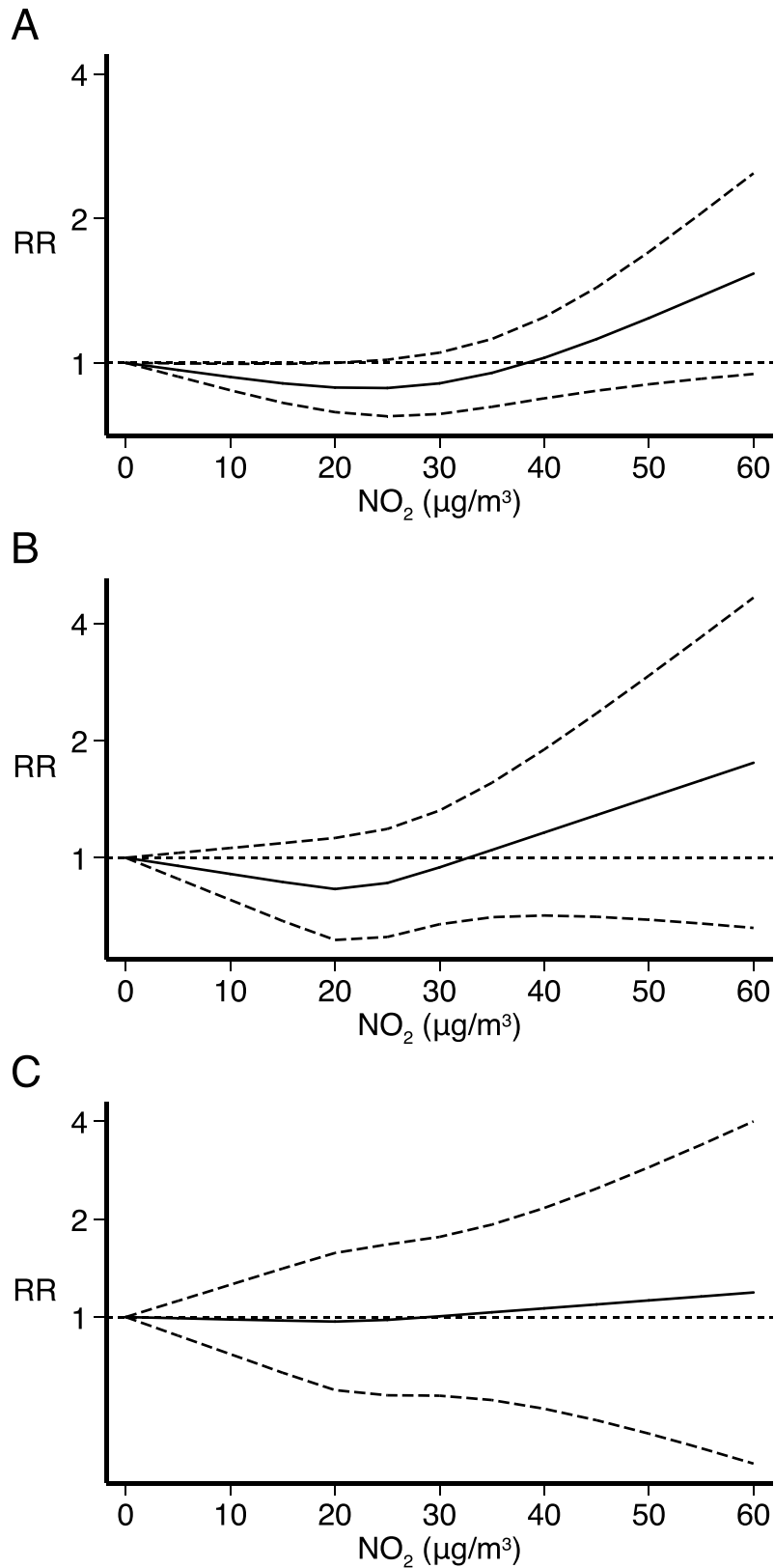
Figure S19. Sensitivity analysis entering a ±15% value instead of ±20 in the dose-response meta-analysis of childhood leukemia risk from traffic indicators using vehicles per day count (A), road density in km/km^2 (B), and distance from a major road in meters (C). Overall spline curve (black solid line) with 95% confidence limits (black dashed lines). RR: risk ratio.

Figure S20. Sensitivity analysis entering a ±15% value instead of ±20 in the dose-response meta-analysis of childhood leukemia risk from benzene exposure of all leukemia (A), acute lymphoblastic leukemia only (B), and acute myeloid leukemia only (C). Overall spline curve (black solid line) with 95% confidence limits (black dashed lines). RR: risk ratio.
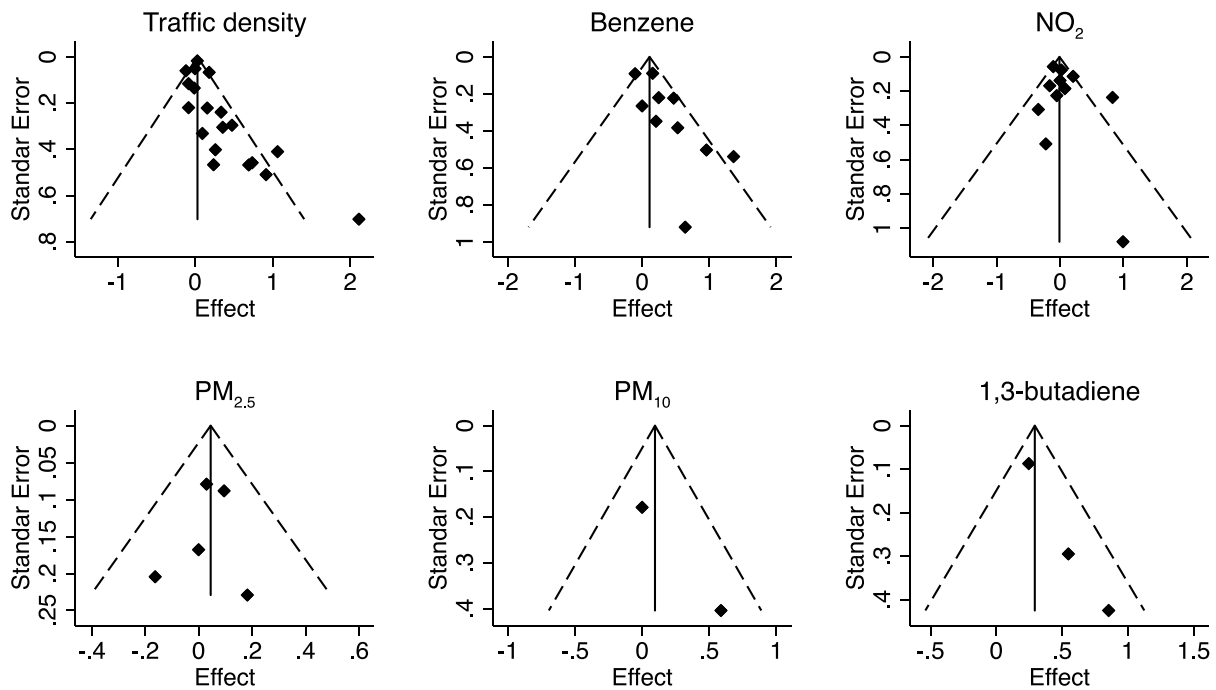
Figure S21. Sensitivity analysis entering a ±15% value instead of ±20 in the dose-response meta-analysis of childhood leukemia risk from nitrogen dioxide exposure of all leukemia (A), acute lymphoblastic leukemia only (B), and acute myeloid leukemia only (C). Overall spline curve (black solid line) with 95% confidence limits (black dashed lines). RR: risk ratio.

Figure S22. Funnel plots for publication bias for traffic density, benzene, nitrogen dioxide (NO_2), particulate matter ($PM_{2.5}/PM_{10}$), and 1,3-butadiene indicators. Black diamonds represent studies included in each analysis, the x-axis indicates the study effect/results through its risk ratio (RR), and the y-axis indicates study precision through its standard error. The outer dashed lines indicate the triangular region within which 95% of studies are expected to lie in the absence of both biases and heterogeneity. The solid vertical line corresponds to overall summary RR from meta-analysis of included studies.

Figure S23. Dose-response meta-analysis of childhood leukemia risk from traffic indicators using vehicles per day count (A), road density in km/km^2 (B), and distance from a major road in meters (C). Overall spline curve (black solid line) with 95% confidence limits (black dashed lines) and the study-specific trends showing the influence of variation across studies (gray solid lines). RR: risk ratio.
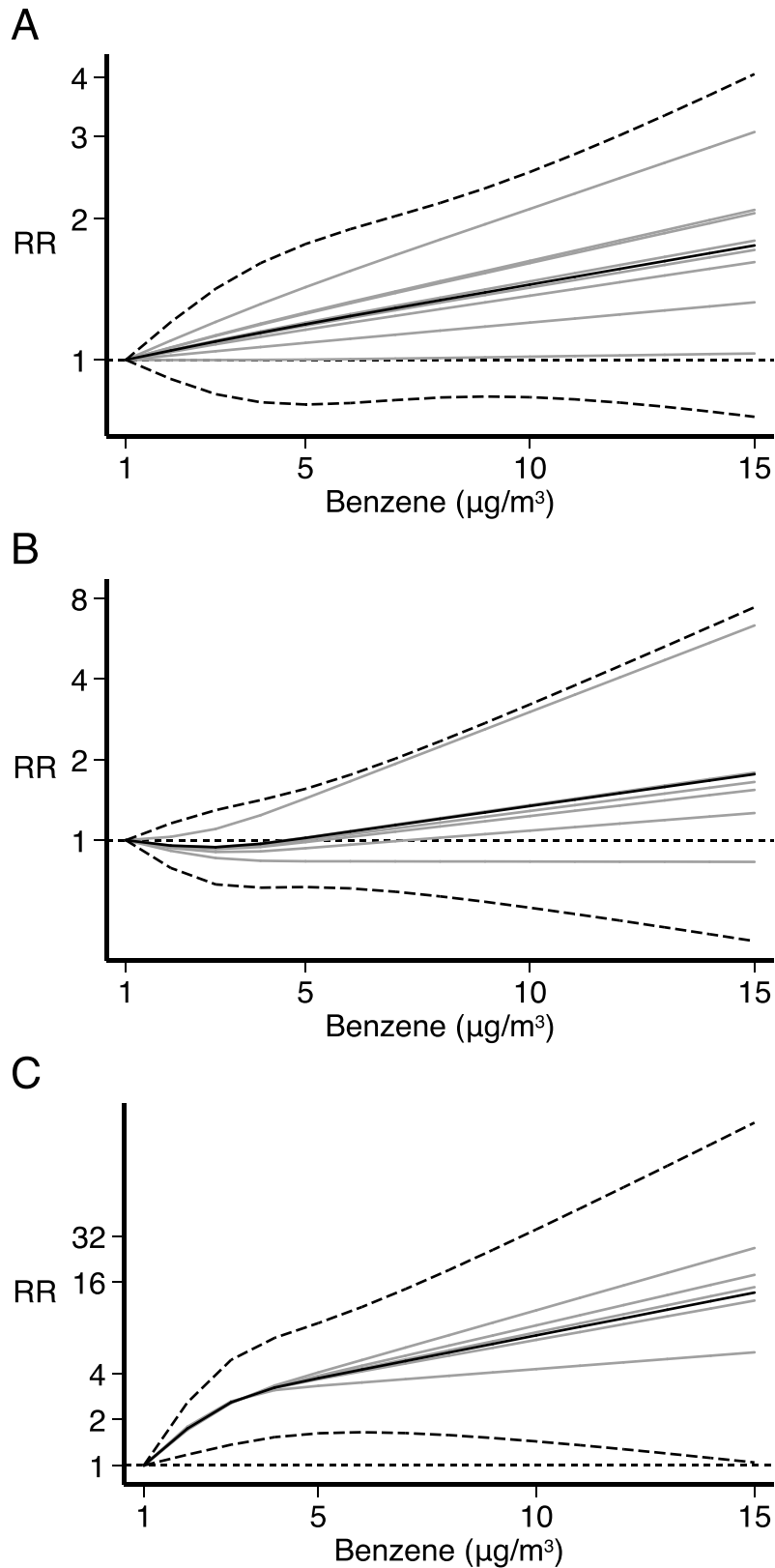
Figure S24. Dose-response meta-analysis of childhood leukemia risk from benzene exposure of all leukemia (A), acute lymphoblastic leukemia only (B), and acute myeloid leukemia only (C). Overall spline curve (black solid line) with 95% confidence limits (black dashed lines) and the study-specific trends showing the influence of variation across studies (gray solid lines). RR: risk ratio.
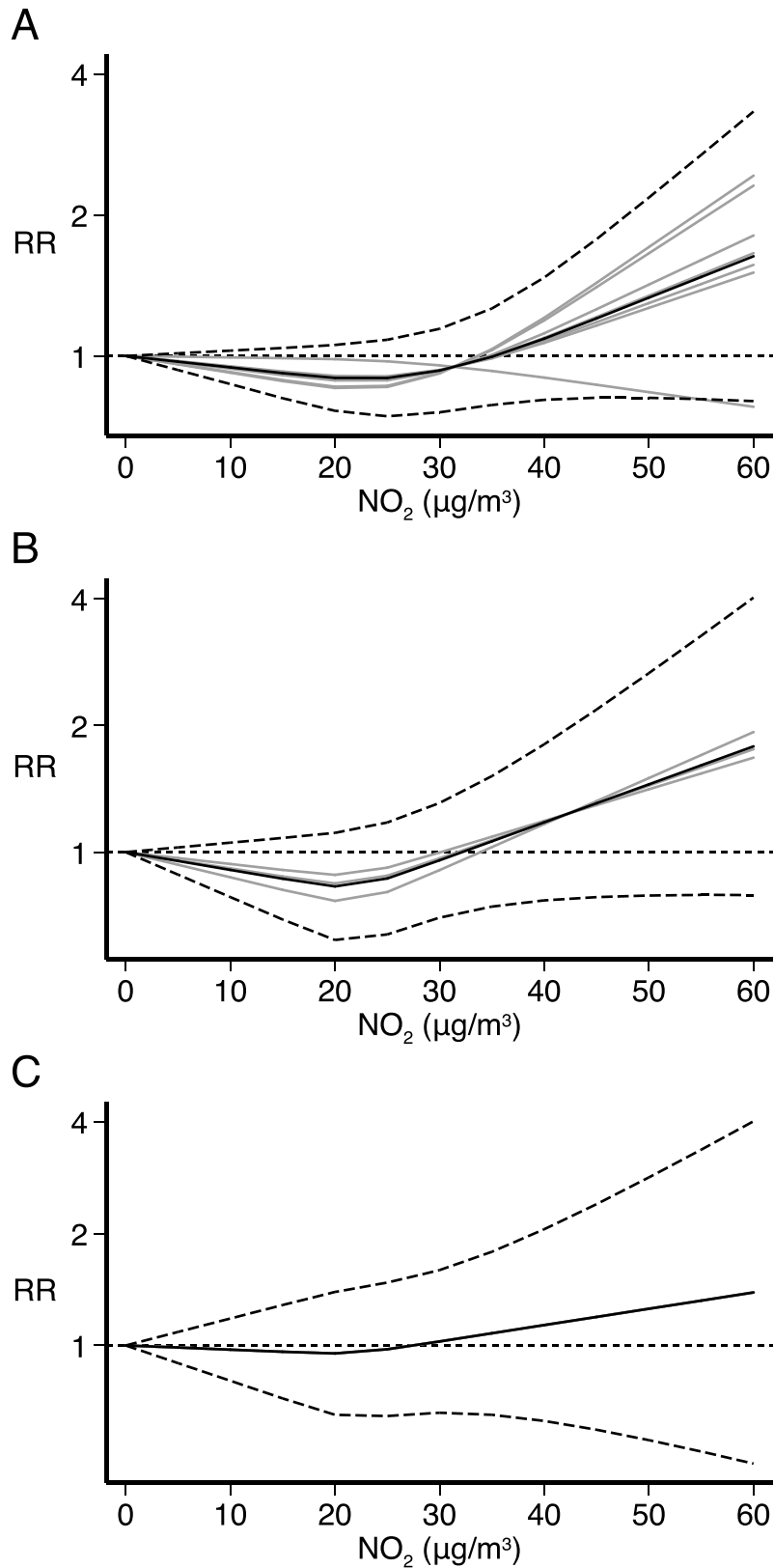
Figure S25. Dose-response meta-analysis of childhood leukemia risk from NO_2 exposure of all leukemia (A), acute lymphoblastic leukemia only (B), and acute myeloid leukemia only (C). Overall spline curve (black solid line) with 95% confidence limits (black dashed lines) and the study-specific trends showing the influence of variation across studies (gray solid lines). RR: risk ratio.

References for Supplemental Material:

Abdul Rahman HI, Shah SA, Alias H, Ibrahim HM. 2008. A case-control study on the association between environmental factors and the occurrence of acute leukemia among children in Klang Valley, Malaysia. Asian Pac J Cancer Prev 9(4):649-652, PMID: 19256754.

Amigou A, Sermage-Faure C, Orsi L, Leverger G, Baruchel A, Bertrand Y, et al. 2011. Road traffic and childhood leukemia: the ESCALE study (SFCE). Environ Health Perspect 119(4):566-572, PMID: 21147599, https://doi.org/10.1289/ehp.1002429.

Badaloni C, Ranucci A, Cesaroni G, Zanini G, Vienneau D, Al-Aidrous F, et al. 2013. Air pollution and childhood leukaemia: a nationwide case-control study in Italy. Occup Environ Med 70(12):876-883, PMID: 24142970, https://doi.org/10.1136/oemed-2013-101604.

Crosignani P, Tittarelli A, Borgini A, Codazzi T, Rovelli A, Porro E, et al. 2004. Childhood leukemia and road traffic: A population-based case-control study. Int J Cancer 108(4):596-599, PMID: 14696126, https://doi.org/10.1002/ijc.11597.

Feychting M, Svensson D, Ahlbom A. 1998. Exposure to motor vehicle exhaust and childhood cancer. Scand J Work Environ Health 24(1):8-11, PMID: 9562395, https://doi.org/10.5271/sjweh.272.

Ghosh JK, Heck JE, Cockburn M, Su J, Jerrett M, Ritz B. 2013. Prenatal exposure to traffic-related air pollution and risk of early childhood cancers. Am J Epidemiol 178(8):1233-1239, PMID: 23989198, https://doi.org/10.1093/aje/kwt129.

Harrison RM, Leung PL, Somervaille L, Smith R, Gilman E. 1999. 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(11):774-780, PMID: 10658564.

Heck JE, Wu J, Lombardi C, Qiu J, Meyers TJ, Wilhelm M, et al. 2013. Childhood cancer and traffic-related air pollution exposure in pregnancy and early life. Environ Health Perspect 121(11-12):1385-1391, PMID: 24021746, https://doi.org/10.1289/ehp.1306761.

Heck JE, Park AS, Qiu J, Cockburn M, Ritz B. 2014. Risk of leukemia in relation to exposure to ambient air toxics in pregnancy and early childhood. Int J Hyg Environ Health 217(6):662-668, PMID: 24472648, https://doi.org/10.1016/j.ijheh.2013.12.003.

Houot J, Marquant F, Goujon S, Faure L, Honore C, Roth MH, et al. 2015. Residential proximity to heavy-traffic roads, benzene exposure, and childhood leukemia-The GEOCAP Study, 2002-2007. Am J Epidemiol 182(8):685-693, PMID: 26377958, https://doi.org/10.1093/aje/kwv111.

Janitz AE, Campbell JE, Magzamen S, Pate A, Stoner JA, Peck JD. 2016. Traffic-related air pollution and childhood acute leukemia in Oklahoma. Environ Res 148:102-111, PMID: 27038831, https://doi.org/10.1016/j.envres.2016.03.036.

Janitz AE, Campbell JE, Magzamen S, Pate A, Stoner JA, Peck JD. 2017. Benzene and childhood acute leukemia in Oklahoma. Environ Res 158:167-173, PMID: 28645022, https://doi.org/10.1016/j.envres.2017.06.015.

Langholz B, Ebi KL, Thomas DC, Peters JM, London SJ. 2002. Traffic density and the risk of childhood leukemia in a Los Angeles case-control study. Ann Epidemiol 12(7):482-487, PMID: 12377426, https://doi.org/10.1016/S1047-2797(01)00317-9.

Lavigne E, Belair MA, Do MT, Stieb DM, Hystad P, van Donkelaar A, et al. 2017. Maternal exposure to ambient air pollution and risk of early childhood cancers: A population-based study in Ontario, Canada. Environ Int 100:139-147, PMID: 28108116, https://doi.org/10.1016/j.envint.2017.01.004.

Magnani C, Ranucci A, Badaloni C, Cesaroni G, Ferrante D, Miligi L, et al. 2016. Road traffic pollution and childhood leukemia: a nationwide case-controlstudy in Italy. Arch Med Res 47(8):694-705, PMID: 28476197, https://doi.org/10.1016/j.arcmed.2017.02.001.

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(2):175-180, PMID: 10680346, https://doi.org/10.1080/10473289.2000.10463998.

Raaschou-Nielsen O, Hertel O, Thomsen BL, Olsen JH. 2001. Air pollution from traffic at the residence of children with cancer. Am J Epidemiol 153(5):433-443, PMID: 11226975, https://doi.org/10.1093/aje/153.5.433.

Raaschou-Nielsen O, Hvidtfeldt UA, Roswall N, Hertel O, Poulsen AH, Sorensen M. 2018. Ambient benzene at the residence and risk for subtypes of childhood leukemia, lymphoma and CNS tumor. Int J Cancer 143(6):1367-1373, PMID: 29633247, https://doi.org/10.1002/ijc.31421.

Reynolds P, Elkin E, Scalf R, Von Behren J, Neutra RR. 2001. A case-control pilot study of traffic exposures and early childhood leukemia using a geographic information system. Bioelectromagnetics Suppl 5:S58-68, PMID: 11170118.

Reynolds P, Von Behren J, Gunier RB, Goldberg DE, Hertz A. 2004. Residential exposure to traffic in California and childhood cancer. Epidemiology 15(1):6-12, PMID: 14712141, https://doi.org/10.1097/01.ede.0000101749.28283.de.

Savitz DA, Feingold L. 1989. Association of childhood cancer with residential traffic density. Scand J Work Environ Health 15(5):360-363, PMID: 2477895, https://doi.org/10.5271/sjweh.1848.

Spycher BD, Feller M, Roosli M, Ammann RA, Diezi M, Egger M, et al. 2015. Childhood cancer and residential exposure to highways: a nationwide cohort study. Eur J Epidemiol 30(12):1263-1275, PMID: 26520639, https://doi.org/10.1007/s10654-015-0091-9.

Steffen C, Auclerc MF, Auvrignon A, Baruchel A, Kebaili K, Lambilliotte 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(9):773-778, PMID: 15317919, https://doi.org/10.1136/oem.2003.010868.

Symanski E, Tee Lewis PG, Chen TY, Chan W, Lai D, Ma X. 2016. Air toxics and early childhood acute lymphocytic leukemia in Texas, a population based case control study. Environ Health 15(1):70, PMID: 27301866, https://doi.org/10.1186/s12940-016-0154-8.

Tamayo-Uria I, Boldo E, Garcia-Perez J, Gomez-Barroso D, Romaguera EP, Cirach M, et al. 2018. Childhood leukaemia risk and residential proximity to busy roads. Environ Int 121(Pt 1):332-339, PMID: 30241021, https://doi.org/10.1016/j.envint.2018.08.056.

Vinceti M, Rothman KJ, Crespi CM, Sterni A, Cherubini A, Guerra L, 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(10):781-790, PMID: 22892901, https://doi.org/10.1007/s10654-012-9727-1.

Visser O, van Wijnen JH, van Leeuwen FE. 2004. Residential traffic density and cancer incidence in Amsterdam, 1989-1997. Cancer Causes Control 15(4):331-339, PMID: 15141134, https://doi.org/10.1023/B:CACO.0000027480.32494.a3.

Von Behren J, Reynolds P, Gunier RB, Rull RP, Hertz A, Urayama KY, et al. 2008. Residential traffic density and childhood leukemia risk. Cancer Epidemiol Biomarkers Prev 17(9):2298-2301, PMID: 18768496, https://doi.org/10.1158/1055-9965.EPI-08-0338.

Weng HH, Tsai SS, Chen CC, Chiu HF, Wu TN, Yang CY. 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(7):434-438, PMID: 18306090, https://doi.org/10.1080/15287390701839042.