Traffic-related air pollution exposure at birth and risk of childhood leukemia: results from the GEOCAP-Birth case–control study

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Abstract

Background Air pollution, in particular due to traffic, is suspected of increasing the risk of childhood acute leukemia (AL), most of the evidence coming from epidemiological studies and literature reviews that focused on the time around diagnosis. Using data on the national scale, we tested the hypothesis that prenatal exposure to traffic-related air pollution increases the risk of childhood AL.

Methods This case–control study included 581 cases of acute lymphoblastic leukemia (ALL) and 136 cases of acute myeloid leukemia (AML), registered in the French national registry of childhood cancer and born and diagnosed between 2010 and 2015, and 11,908 controls. Exposure indicators were evaluated at the addresses at birth and included major road length in 500 m buffers, and modeled exposures of nitrogen dioxide (NO_2), fine particulate matter ($PM_{2.5}$) and black carbon (BC). Odds ratios (OR) and 95% confidence intervals (CI) were estimated using logistic regression models. Exposures were considered in categories using tertiles' cut offs or continuously for increments of ½ interquartile range.

Results Both ALL and AML risks increased with $PM_{2.5}$ exposure (OR ALL = 1.14, 95%CI = 1.08–1.20 and OR AML = 1.12, 95%CI = 1.00–1.25 for an increment of 2 µg/m^3, respectively). The risk of ALL was associated with BC exposure in urban units of < 5,000 inhabitants and of 5,000–99,999 inhabitants (OR = 1.90, 95%CI = 1.22–2.97 and OR = 1.58, 95%CI = 1.16–2.17 for an increment of 0.5 10^{-5}/m, respectively), and not in more urban municipalities. An elevated OR for AML was observed for NO_2 exposure (OR = 1.4, 95%CI = 0.9–2.1 for the highest *versus* lowest category). There was no association with the length of major roads.

Conclusion The results support a role of exposure to air pollution at time of birth in the risk of childhood AL.

Keywords Childhood leukemia, Air pollution, Nitrogen dioxide, Particulate matter, Black carbon, Traffic, Roads

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Background

Leukemia derives from the uncontrolled proliferation of hematopoietic stem cells in the bone marrow, leading to large numbers of abnormal immature white blood cells entering the bloodstream. Acute leukemia (AL) represents the most common cancer in children under 15 years old worldwide, and comprises several cytological and molecular subtypes that may differ by age distribution, clinical outcome and aetiology [1, 2].

The two main types of AL are acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML), which account respectively for around 80% and 15% of childhood AL cases. In France over the period 2014–2020, around 485 new cases of acute leukemia were diagnosed each year in children aged less than 15 years old and the average annual age-standardized incidence rates were estimated at 36.8 cases and 6.7 cases per one million children for ALL and AML, respectively. The incidence of ALL peaks at 1 to 5 years old and a higher incidence of AML is observed under 2 years old [3, 4].

While high dose ionizing radiation, some genetic factors and some chemotherapies are well established risk factors for AL, the potential role of other environmental factors in prenatal and childhood periods, in particular residential exposure to background ionizing radiation, parental domestic use of pesticides and residential exposure to air pollutants, remains debated [5, 6]. Outdoor air pollution, particulate matter from outdoor air pollution and exhaust fumes from diesel engines have been classified as carcinogenic to humans (group 1), but evidence was rather limited for childhood AL [7, 8]. Benzene, a component of gasoline and vehicle exhaust, is known to cause AML in adults [9].

Road traffic is the leading emitter of several air pollutants especially in urban areas, in particular nitrogen dioxide (NO_2) and particulate matter with a diameter less than 2.5 μm ($PM_{2.5}$), which have been used as markers of traffic-related air pollution. A significant number of epidemiological studies, and several reviews and meta-analyses have been carried out on traffic-related air pollution and childhood AL. The comprehensive meta-analysis published by Carlos-Wallace et al. has concluded to evidence of positive associations between childhood AL and several indicators of benzene exposure, including parental occupation and domestic uses, as well as residential exposure to traffic-related air-pollution and residential proximity to gas stations, although with a limited number of studies for the latter exposure [10]. The meta-analysis by Filippini et al. focused on metrics of exposure to air pollutants and concluded to an increased risk of AL with metrics of benzene exposure and of traffic density, but not with indicators of NO_2 and $PM_{2.5}$ exposures; the number of studies for $PM_{2.5}$ was low [11]. Studies published thereafter showed positive associations with NO_2 [12], and both positive association [13] and no association [14] with $PM_{2.5}$. Only one study investigated exposure to black carbon (BC), which is a constituent of $PM_{2.5}$, and showed no association for both types of childhood acute leukemia [14].

In our previous study GEOCAP-Diag conducted in France on the national scale, we found increased risk of childhood AML associated with major road length within 150 m of residence at diagnostic but not with an indicator of NO_2 exposure [15]. In this new study, we focused on exposures at the residence at birth, which are more likely to reflect prenatal exposures than residence at diagnosis/inclusion. We used data from our national registry-based case–control study GEOCAP-Birth to estimate the risk of childhood acute leukemia associated with residential proximity to heavy-traffic roads and model-based estimates of exposure to traffic-related air pollutants.

Methods

Study design

GEOCAP-birth is a case–control study with prospective recruitment within birth cohorts in mainland France. Cases were identified and documented by the French National Registry of Childhood Cancer (RNCE). They were all children aged less than 6 years old diagnosed with AL (ICCC-3 subgroups 1.a, 1.b and 1.e) according to the International Classification of Childhood Cancer third edition [16], born and diagnosed between 1 January 2010 and 31 December 2015 and living in Mainland France at the time of birth and diagnosis. Controls were children born between 1 January 2010 and 31 December 2015, living in mainland France at the time of birth, and randomly selected each year (1 birth every 400 births) from the birth certificates by the French National Institute of Statistics and Economic Studies (INSEE) [17]. They were representative of the French birth cohorts in terms of month of birth, sex and *département* of birth.

Data collection

Data extracted from the RNCE were the date of birth, the municipality of birth (where the maternity was located), detailed information related to the diagnosis (date of diagnosis, cytological, cytogenetic and molecular AL subtypes) and the presence of a Down syndrome. Data obtained for controls were sex, birth year and municipality of birth. The precise addresses of residence at birth were directly obtained from INSEE for the controls born in 2013–2015. For the other controls and for the cases, addresses were obtained from their municipality of birth, after consent from the High Court's prosecutors of the corresponding *départements*. All addresses were digitized in a standardized format for geocoding.

Study population

We were able to obtain the addresses at birth for 717 (97%) of the 739 eligible AL cases (581 ALL cases and 136 AML) and for 11,908 (98%) of the 11,985 controls.

Exposure assessment

All addresses collected were Geocoded in Lambert 93 by an external partner, blind to the case–control status, using the database BD Adresses® (version 2.2) from the French National Institute of Geographic and Forest Information (IGN, Saint Mandé, France). Overall, 73% of the addresses were geocoded with an imprecision estimated to be less than 120 m (Table 1). In controls, the addresses obtained from the municipalities of birth (births of 2010–2012) were more complete than those obtained directly from the INSEE (births of 2013–2015), therefore geocoding was of higher quality among controls born in 2010–2012 than those born in 2013–2015 (85.1% *versus* 59.0%), and among cases than controls overall (86.8% *versus* 72.3%). For both cases and controls, addresses were better geocoded in urban areas than in rural areas (81.1% *versus* 68.8% of addresses with a high-quality geocoding).

The French roads network is digitally mapped by the American HERE® system for the design of global positioning system (GPS). Roads are classified by HERE® into 5 functional groups according to traffic intensity and their importance in the road network: class 1 represents high volume and maximum speed traffic roads between and through metropolitan areas, with very little or no speed change; class 2 roads are used to smooth traffic of class 1 roads between and through cities in the shortest amount of time; class 3 roads are secondary interconnected to class 2 roads with high volume and lower speed traffic; and class 4 and 5 roads consist of municipal roads with moderated traffic speed and remaining roads with near to zero traffic. The mapping of the road network was available for the year of birth of all cases and controls (2010–2015).

We defined *major roads* as roads of HERE® classes 1 to 3. *Major road length* was defined as the cumulative length of major roads within 500 m of the geocoded addresses at birth; a 150 m radius was also used in sensitivity analysis. Buffer sizes of 500 m and 150 m were defined *a priori* based on studies showing that levels of pollutants tended to decrease exponentially beyond 100–400 m from roads depending on the pollutant, meteorological conditions and topography [18, 19]. These buffer sizes were also used in our previous studies [15, 20]. *Major road length* in 500 m buffer was coded into a 4-category variable: no major road within 500 m of the address (reference group), and 3 categories based on the tertiles of the distribution among controls (cut offs: 1030.4 m and 1965.6 m), and also considered as continuous for a variation of 500 m length.

Pollutant concentration maps produced for Europe were used to assess air pollutant exposure at the geocoded addresses. The methodology has been described previously [21]. Briefly, annual mean concentrations in NO_2 and $PM_{2.5}$ (µg/m³) for the year 2010 were calculated based on the daily concentration data from the Air-Base V8 dataset [22]. Annual mean concentration of BC (10^{-5}/m) were obtained from the ESCAPE project (European Study of Cohorts for Air Pollution Effects) and calculated as $PM_{2.5}$ absorbance; $PM_{2.5}$ reflectance of filters were measured during three 14-day sampling campaigns conducted over the year 2010 [23]. For each pollutant, a validated hybrid land use regression (LUR) model was used to estimate the annual mean concentrations in Western Europe for the year 2010, with a 100×100 m resolution [21]. The models included satellite-derived and chemical transport modelled air pollutant data, land cover, road density and altitude as predictor variables. All models were shown to be robust through a five-fold hold-out validation process and comparison with measurements [21]. For each pollutant (NO_2, $PM_{2.5}$ and BC) and for each of the 8 French territorial units for statistics (NUTS1, *i.e.* European Union-defined administrative regions within countries), annual pollutant concentration data from monitoring stations were used to estimate the annual ratios of 2011–2015 concentrations to 2010 concentrations. Annual mean concentrations of NO_2, $PM_{2.5}$ and BC at the geocoded addresses for the years 2011 to 2015 were then obtained by multiplying the NUTS-specific ratio by the 2010 concentration estimates. Cases and controls' addresses at birth were assigned annual mean concentrations of NO_2, $PM_{2.5}$ and BC corresponding to the child birth year. Exposures were categorized in 3 groups based on the tertiles of the distribution among controls (cut offs: 17.5 and 26.4 µg/m³ for NO_2, 14.3 and 16.8 µg/m³ for $PM_{2.5}$ and 1.3 and 1.7 10^{-5}/m for BC) and considered continuous for increments of 5 µg/m³, 2 µg/m³ and 0.5 10^{-5}/m, respectively (corresponding to ½ interquartile range (IQR) among controls, allowing to use these increments in all strata of analyses). We also defined two composite exposure indicators by crossing categorical NO_2 exposure with categorical $PM_{2.5}$ and BC exposures. The low-exposed category consisted in both air pollutant exposures below the second tertile (used as reference); the high-exposed category in both air pollutant exposures greater than the second tertile; and the intermediate-exposed categories of the remaining exposure combinations.

Statistical analysis

Odds ratios (OR) and 95% confidence intervals (CI) for the associations between major road length and pollutant (NO_2, $PM_{2.5}$ and BC) exposures and risk of childhood ALL and AML were estimated using polytomous logistic

Table 1 Characteristics of childhood leukemia cases and controls, GEOCAP-Birth study, France, 2010–2015

	Controls (N = 11,908)		ALL (N = 581)		AML (N = 136)	
	N	(%)	N	(%)	N	(%)
Sex						
Female	5821	(48.9)	254	(43.7)	62	(45.6)
Male	6087	(51.1)	327	(56.3)	74	(54.4)
Age at diagnosis, years						
< 1	-	-	60	(10.3)	65	(47.8)
1	-	-	122	(21.0)	46	(33.8)
2	-	-	177	(30.5)	14	(10.3)
3	-	-	133	(22.9)	6	(4.4)
4	-	-	70	(12.0)	3	(2.2)
5	-	-	19	(3.3)	2	(1.5)
Geocoding quality						
Imprecision < 120 m	*8609*	*(72.3)*	*507*	*(87.3)*	*115*	*(84.6)*
Entrance of the plot	6345	(53.3)	384	(66.1)	91	(66.9)
Projected toward the plot*	825	(6.9)	44	(7.6)	10	(7.4)
Interpolated between two neighboring numbers	1439	(12.1)	79	(13.6)	14	(10.3)
Imprecision ≥ 120 m	*3299*	*(27.7)*	*74*	*(12.7)*	*21*	*(15.4)*
Street segment	2317	(19.5)	24	(4.1)	8	(5.9)
Urban hamlet (center)	69	(0.6)	2	(0.3)	0	(0.0)
Rural hamet (center)	708	(5.9)	40	(6.9)	9	(6.6)
Townhall of the municipality	205	(1.7)	8	(1.4)	4	(2.9)
Territorial units within France NUTS1						
Ile de France *(Région parisienne)*	2716	(22.8)	124	(21.3)	33	(24.3)
Surrounding Ile de France *(Bassin parisien)*	1930	(16.2)	106	(18.2)	15	(11.0)
North *(Nord)*	863	(7.2)	47	(8.1)	13	(9.6)
East *(Est)*	904	(7.6)	37	(6.4)	8	(5.9)
West *(Ouest)*	1527	(12.8)	80	(13.8)	20	(14.7)
South-West *(Sud-Ouest)*	1090	(9.2)	45	(7.7)	10	(7.4)
Center East *(Centre-Est)*	1407	(11.8)	76	(13.1)	21	(15.4)
South-East *(Méditerranée)*	1471	(12.4)	66	(11.4)	16	(11.8)
Size of urban unit						
< 5,000 inhabitants	2950	(24.8)	154	(26.5)	31	(22.8)
5,000 to 99,999 inhabitants	2774	(23.3)	144	(24.8)	30	(22.1)
≥ 100,000 inhabitants	6184	(51.9)	283	(48.7)	75	(55.1)
Social deprivation index of the municipality of birth**						
Q1	2440	(20.5)	113	(19.4)	30	(22.1)
Q2	2358	(19.8)	119	(20.5)	18	(13.2)
Q3	2375	(19.9)	121	(20.8)	32	(23.5)
Q4	2366	(19.9)	117	(20.1)	32	(23.5)
Q5	2369	(19.9)	111	(19.1)	24	(17.6)
Presence of viticulture in the municipality of birth						
No	8436	(70.8)	409	(70.4)	103	(75.7)
Yes	3472	(29.2)	172	(29.6)	33	(24.3)
Municipal density of viticulture (%)**						
Median (Q1-Q3)	0.3	(0.0–3.5)	0.2	(0.0–3.0)	0.2	(0.0–2.4)
Average daily UV A + B in the municipality of birth (J/cm^3)						
Median (Q1-Q3)	100.2	(96.7-107.2)	100.0	(96.5-106.9)	100.2	(97.5-106.9)

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; NUTS1, territorial units for statistics level 1

* projection from the middle of the road to the plot

** defined as the first component of a principal component analysis of four census variables (median income of the households, proportion of blue-collar workers, proportion of unemployed and proportion of high school graduates; Q1-Q5 are quintiles of the distribution among controls, Q1 representing the least deprived quintile, Q5 representing the most deprived quintile

*** defined as the surface area in viticulture in the municipality compared to the total surface area of the municipality, expressed as %; among children with viticulture in the municipality

regression models. We used the likelihood ratio test to test the heterogeneity between the two AL types . P-for-trend were estimated for the categorical variables using partial t-test.

To test for nonlinearity, cubic spline functions were performed for all continuous variables, using a smoothing parameter estimated by restricted maximum likelihood (REML) (R package *mgcv*), with a number of knots automatically determined. Linearity was assessed using the likelihood ratio test comparing the linear and the spline models. When no deviation from linearity was observed in the exposure–response associations, we estimated OR and 95% CI using continuous exposure variables.

Additional stratified analyses were conducted for ALL (numbers of AML were too small), using logistic regression models. First, since the sources of pollution, their contribution to air pollutant concentrations and finally the difference in air pollutant exposures between rural and urban locations [24], we conducted stratified analyses by size of urban units (< 5,000 inhabitants, 5,000 to 99,999 inhabitants, ≥ 100,000 inhabitants). In mainland France, an urban unit is defined by INSEE as a municipality or group of municipalities with at least 2,000 inhabitants and a distance between buildings of less than 200 m [25]. Second, we stratified the analyses of air pollutants exposures by categories of major road length. Third, analyses were stratified for sex. For these stratified analyses, tertiles of exposure were redefined within each stratum. Effect modifications between continuous exposure variables and stratification variables were tested with likelihood ratio tests comparing models with and without interaction terms.

Several sensitivity analyses were performed. We adjusted the models for three potential confounding factors that were found to be associated with childhood acute leukemia risk in our previous ecological studies at the municipality level: the French deprivation index of 2006 (continuous) that was defined as the first component of a principal component analysis of four census variables (median income of the households, proportion of blue-collar workers, proportion of unemployed and proportion of high school graduates) [26, 27]; the density of viticulture in the municipality of residence at birth (%, continuous) defined from the French agricultural census of 2010 [28]; and the annual average of daily UV residential exposure in the municipality of residence at birth (J/cm2, continuous) estimated from the EURO-SUN database on a 5×5 km grid [29]. We also ran the models in the subgroup of children with high-quality geocoded addresses (N = 9242). We excluded cases of childhood leukemia with Down syndrome (N = 15 AML cases excluded), as Down syndrome patients are highly susceptible to develop AL [30]. Finally, we investigated the association with major road length estimated within a 150 m radius around residence at birth (cut offs 267.3 m and 330.6 m; variation of 100 m for the continuous variable).

P-values were two-sided and the significance level was set at 0.05. R statistical software version 4.0.4 was used for statistical analyses [31].

Results

Cases were more often males than controls (56.3% and 54.4% for ALL and AML, respectively, *vs* 51.1% for controls) (Table 1). The number of ALL cases peaked at 2 years old at diagnosis (30.5%), while most of AML cases were less than 1 year old (47.8%) at diagnosis. Around 25% of cases and controls lived in municipalities of less than 5,000 inhabitants and around 50% lived in municipalities of 100,000 and more inhabitants.

For participants with a non-zero major road length (67.9%, 65.2% and 63.2% of controls, ALL and AML cases, respectively), the median (IQR) length of major roads within 500 m of the residence at birth was 1449.8 m (1364.7 m) among controls, 1329.5 m (1390.0 m) among ALL cases and 1304.9 m (1377.3 m) among AML cases (Table 2). In controls, medians ranged from 1001.3 m in the least populated areas to 1772.5 m in the most populated urban areas. There were also strong contrasts in median NO_2 exposure which doubled among controls from least to most populated urban units (from 13.7 to 29.1 μg/mO^3), and lower variations for $PM_{2.5}$ (from 13.6 to 17.2 μg/m^3) and BC (from 1.1 to 1.8 10^{-5}/m). The Spearman correlation coefficients between length of major roads and air pollutants exposures were less elevated in urban units of < 5,000 inhabitants than in urban units of ≥ 100,000 inhabitants (from 0.28 to 0.48 for NO_2; from 0.09 to 0.25 for $PM_{2.5}$; from 0.23 to 0.50 for BC) (supplementary Table 1, Additional file 1). NO_2, $PM_{2.5}$ and BC exposures also tended to be more correlated in the most urban areas.

Major road length within 500 m of residence at birth was not associated with ALL and AML (Table 3). AML risk tended to increase with NO_2 exposure, although not statistically significantly (p-for-trend = 0.12, with OR = 1.4, CI = 0.9–2.1 for the third category *versus* the first), whereas the ORs did not deviate from one for ALL. Positive associations were observed between risk of ALL and $PM_{2.5}$ exposure, with OR = 1.5 (CI = 1.2–1.8) and OR = 1.7 (CI = 1.3–2.1) for the second and third exposure categories *versus* the first respectively (p-trend < 0.001), and the OR for a 2 μg/m^3 increment in $PM_{2.5}$ exposure was 1.14 (CI = 1.08–1.20). Our results also suggested an increased risk of AML in the highest $PM_{2.5}$ exposure category *versus* the first (OR = 1.4, CI = 0.9–2.1), with a slight exposure–response association (OR = 1.12, CI = 1.00–1.25 for a 2 μg/m^3 increase). There was no heterogeneity

Table 2 Distribution of air pollution indicators at the address of residence at birth (major road length and exposures to NO_2, $PM_{2.5}$ and BC) in cases and controls, GEOCAP birth study, France, 2010–2015

	Mainland France			Size of urban unit					
				< 5,000 inhabitants		5,000–99,999 inhabitants		≥ 100,000 inhabitants	
	Controls (N = 11,908)	ALL (N = 581)	AML (N = 136)	Controls (N = 2950)	ALL (N = 154)	Controls (N = 2774)	ALL (N = 144)	Controls (N = 6184)	ALL (N = 283)
Major road length within 500 of residence at birth (m)									
Length = 0, N (%)	3818 (32.1)	202 (34.8)	50 (36.8)	1574 (53.4)	88 (57.1)	863 (31.1)	41 (28.5)	1381 (22.3)	73 (25.8)
Length > 0, N (%)	8090 (67.9)	379 (65.2)	86 (63.2)	1376 (46.6)	66 (42.9)	1911 (68.9)	103 (71.5)	4803 (77.7)	210 (74.2)
Median	1449.8	1329.5	1304.9	1001.3	1008.9	1337.4	1077.6	1772.5	1828.9
IQR	1364.7	1390.0	1377.3	427.9	386.1	1011.1	1307.1	1809.2	1847.0
Major road length within 150 of residence at birth (m)									
Length = 0, N (%)	8029 (67.4)	403 (69.4)	92 (67.6)	2244 (76.1)	115 (74.7)	1853 (66.8)	100 (69.4)	3932 (63.6)	188 (66.4)
Length > 0, N (%)	3879 (32.6)	178 (30.6)	44 (32.4)	706 (23.9)	39 (23.4)	921 (33.2)	44 (30.6)	2252 (36.4)	95 (33.6)
Median	298.6	298.1	298.2	292.4	297.0	296.2	290.1	298.9	298.9
IQR	181.0	193.8	128.7	67.1	60.9	120.4	197.4	249.8	229.5
NO_2 exposure (µg/m³)									
Median	21.6	21.7	23.5	13.7	14.0	18.2	18.5	29.1	29.6
IQR	14.3	14.1	15.5	5.9	6.4	7.0	8.3	13.2	12.4
$PM_{2.5}$ exposure (µg/m³)									
Median	15.4	16.0	16.2	13.6	14.3	14.4	15.3	17.2	18.2
IQR	4.1	4.1	4.8	2.8	3.0	2.7	3.3	4.2	4.1
BC exposure (10^{-5}/m)									
Median	1.5	1.5	1.5	1.1	1.2	1.3	1.4	1.8	1.9
IQR	0.7	0.7	0.7	0.2	0.2	0.3	0.3	0.6	0.6

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; IQR, interquartile range

between ALL and AML (p-het = 0.79). Elevated ORs were observed for BC exposure and ALL, with however no statistically significant association overall, and no exposure–response association.

The association between ALL and $PM_{2.5}$ exposure was similar in the three categories of urban units, all showing increased risks (Table 4). Using the composite variable, no particular interaction was observed between $PM_{2.5}$ and NO_2 exposures (supplementary Table 2, Additional file 1). BC exposure was associated with ALL in urban units < 5,000 inhabitants and urban units between 5,000 and 99,999 inhabitants (OR = 1.8, CI = 1.2–2.7 in both strata for the most exposed category), with marked trends (OR = 1.90, CI = 1.22–2.97 and OR = 1.58, CI = 1.16–2.17 for a 0.5 10^{-5}/m increase, respectively), while no clear association was observed in the stratum of most urban units (*p*-value for interaction = 0.06). For the three pollutants, the results for ALL were quite stable across strata of major road length (Table 5). The results observed in the strata of male and female participants did not differ from those of the main analysis (Table 6).

The results were unchanged when density of viticulture, UV radiation level and deprivation index were included in the models (supplementary Tables 3 and 4, Additional file 1). Analyses restricted to cases and controls with high-quality geocoded addresses led to similar results for ALL and attenuated results for AML. Excluding AML cases with Down syndrome did not change the results. There was no association with major road length within 150 m of address of residence at birth.

Discussion

This study examined the relationship between indicators of air pollution at the place of residence at birth and subsequent risk of childhood leukemia. Its main findings were the association between $PM_{2.5}$ exposure and AL, clearer for ALL than for AML. For ALL, the association was reinforced by stratifying the analyses on size of urban unit, which also revealed an association with BC exposure, particularly in units < 100,000 inhabitants. An increase in risk of childhood AML was also suggested with NO_2 exposure but overall, the analyses for AML were limited by small numbers. Major road length was not associated with childhood acute leukemia.

The study benefitted from the exhaustive inclusion of cases by the French national registry of childhood cancer, and the random sampling of controls from birth databases avoiding selection and participation biases that an active involvement of cases and controls could have resulted in. We were able to assess exposure for all study participants, at the residential address, blinded to the case–control status, using accurate cartographic tools and modelling. Numbers were limited for AML, but not for ALL.

The prenatal period is a critical exposure period for pediatric carcinogenesis. Although we were not able to

Table 3 Childhood acute leukemia and air pollution indicators at the address of residence at birth—association with major road length in 500 m buffer and exposures to NO_2, $PM_{2.5}$ and BC, GEOCAP birth study, France, 2010–2015

	Controls		ALL					AML					p-HET[b]
	N	(%)	N	%	OR	95% CI	p[a]	N	(%)	OR	95% CI	p[a]	
Major road length within 500 m of residence at birth (m)													
0, nearest major road 500 m away	3818	(32.1)	202	(34.8)	1.0	Ref	0.14	50	(36.8)	1.0	Ref	0.20	0.92
Nearest major road less than 500 m away													
length <=1030.4 m	2697	(22.6)	139	(23.9)	1.0	(0.8–1.2)		32	(23.5)	0.9	(0.6–1.4)		
length]1030.4;1965.6]	2696	(22.6)	112	(19.3)	0.8	(0.6–1.0)		27	(19.9)	0.8	(0.5–1.2)		
length >1965.6	2697	(22.6)	128	(22.0)	0.9	(0.7–1.1)		27	(19.9)	0.8	(0.5–1.2)		
Per 500 m increase	11,908	(100.0)	581	(100.0)	0.98	(0.95–1.01)	0.20	136	(100.0)	0.98	(0.92–1.05)	0.60	0.92
NO_2 exposure (µg/m³)													
[1.7;17.5]	3970	(33.3)	193	(33.2)	1.0	Ref	0.88	39	(28.7)	1.0	Ref	0.12	0.39
]17.5;26.4]	3969	(33.3)	192	(33.0)	1.0	(0.8–1.2)		43	(31.6)	1.1	(0.7–1.7)		
]26.4;77.4]	3969	(33.3)	196	(33.7)	1.0	(0.8–1.3)		54	(39.7)	1.4	(0.9–2.1)		
Per 5 µg/m³ increase[c]	11,908	(100.0)	581	(100.0)	1.00	(0.96–1.04)	0.89	136	(100.0)	1.05	(0.97–1.14)	0.19	0.27
$PM_{2.5}$ exposure (µg/m³)													
[2.1;14.3]	3970	(33.3)	141	(24.3)	1.0	Ref	<0.001	39	(28.7)	1.0	Ref	0.10	0.48
]14.3;16.8]	3969	(33.3)	205	(35.3)	1.5	(1.2–1.8)		42	(30.9)	1.1	(0.7–1.7)		
]16.8;26.0]	3969	(33.3)	234	(40.3)	1.7	(1.3–2.1)		55	(40.4)	1.4	(0.9–2.1)		
Per 2 µg/m³ increase[c]	11,908	(100.0)	581	(100.0)	1.14	(1.08–1.2)	<0.001	136	(100.0)	1.12	(1.00–1.25)	0.05	0.79
BC exposure (10^{-5}/m)													
[0.7;1.3]	3970	(33.3)	178	(30.6)	1.0	Ref	0.29	39	(28.7)	1.0	Ref	0.25	0.84
]1.3;1.7]	3969	(33.3)	204	(35.1)	1.2	(0.9–1.4)		47	(34.6)	1.2	(0.8–1.9)		
]1.7;4.3]	3969	(33.3)	198	(34.1)	1.1	(0.9–1.4)		50	(36.8)	1.3	(0.8–2.0)		
Per 0.5 10^{-5}/m increase[c]	11,908	(100.0)	581	(100.0)	1.05	(0.96–1.14)	0.31	136	(100.0)	1.06	(0.89–1.26)	0.51	0.89

ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; OR, odds ratio and 95% CI, 95% confidence interval obtained by polytomous logistic regression models

[a] p-value for trend derived from partial t-test for the categorical variables, and from the likelihood ratio test for the continuous variables

[b] p-value for heterogeneity between ALL and AML derived from the Likelihood Ratio Test

[c] increase of 1/2 interquartile range of the distribution among controls

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assess the exposure during pregnancy nor during a specific trimester during pregnancy, we considered that the address at birth was an appropriate proxy of the prenatal period of exposure. However, the exposure at birth may not represent the exposure during mothers' pregnancy if the mother changed residence before birth, so that the address at birth may rather reflect the perinatal period. Residential history was not available in the study, and the extent to which this may have impacted exposure estimates depends on the residential mobility before birth. In a previous case–control study based on the RNCE (ESTELLE study, 2010–2011, including 1733 childhood leukemia cases and 1421 controls from the general population [32]), in which residential history was collected for 97%, 84% of mothers had not moved during pregnancy and the median distance between addresses was 5.1 km among mothers who moved (unpublished data). In two American studies assessing maternal residential mobility during pregnancy, no difference in air pollution exposures (ozone, PM_{10} and benzene) was found between address at birth and address during pregnancy or at conception, mostly because of low mobility (16% and 21% of mothers moved in [33] and [34], respectively) and short distances moved (median of 4.1 km in [33] and 6.0 km in [34]) in these study populations. Here, if a significant number of mothers had moved during pregnancy, and over large distances, it may have led to exposure misclassification, although not differential.

Although imprecisions in geocoding were higher in rural areas than in urban areas, the associations we observed with $PM_{2.5}$ and BC exposures, overall and by rural/urban locations, were stable when restricted to the addresses with high-quality geocoding. Geocoding was performed blinded to the case–control status, but imprecisions were higher in controls than in cases, leading to possible differential exposure misclassification.

Length of major roads and the modeled concentrations of three different pollutants have been used as indicators of traffic-related air pollution exposures. However, vehicle exhaust is a complex mixture of chemicals, and there may have been some confounding due to other unmeasured pollutants, should traffic-related air pollution be a risk factors for childhood AL. Benzene exposure, which is an established risk factor for leukemia in adults, could be a good candidate. Besides, we cannot be ruled out the possibility that the associations we found with $PM_{2.5}$ and BC exposures were due to another factor, both associated with pollutant exposures and childhood AL risk.

Our results were not altered when taking into account other environmental risk factors (UV residential exposure, density in viticulture and deprivation) that had been associated with leukemia in previous analyses. Other factors that could be relevant to consider include ambient temperature, as some studies have shown a link between air pollution and temperature [35], and between temperature and risk of childhood ALL [36]. This question is currently being investigated by our team. No individual data was available on perinatal characteristics, breastfeeding, or parental habits for instance that could be related to AL risk. However, there are no strong associations between these factors and air pollution exposure that could explain the observed associations, and in the French ESCALE interview-based case–control study, results remained unchanged after adjustment for factors related to AL (birth order, early common infections in childhood, maternal use of pesticides during pregnancy and paternal smoking before conception) [20].

Concentrations of air pollutants were estimated with a land use regression model and extrapolation of 2010 concentrations to other years, assuming the spatial variations in concentrations remained stable over the 6 years of the study within French NUTS regions. BC concentrations in particular were estimated from measurement data collected within the ESCAPE project, taken over the area of Paris and its suburb for France. Although measurements were made in 20 sites in Paris area, including rural sites, urban sites and street sites, BC concentration estimates may be imprecise in other regions. Thus, our results on BC exposure should be carefully interpreted.

Studies on childhood leukemia have used various metrics to assess children residential exposure to traffic, such as traffic density [37–42], and distance to [15, 20, 43–48] or density of [15, 20, 41, 44, 47, 49, 50] heavy traffic roads, with proximity ranging from < 20 m to ≤ 1500 m. They more often considered exposure around time of diagnosis [15, 20, 37–39, 42, 43, 45, 46, 50–53] than that of birth [40, 41, 44, 47, 49]. A few of them provided distinct estimates for ALL and AML [15, 47, 49]. The two most recent meta-analyses were in favor of positive associations between indicators of traffic density and residential exposure to benzene due to traffic proximity and childhood AL risk [10, 11]. Filippini et al. showed however limited association with NO_2, PM_{10} and $PM_{2.5}$, and in particular no association for exposures at the time of birth, for which the number of studies was again very limited [11]. Our previous studies focused on exposures at the time of diagnosis. In the ESCALE case–control study carried out in 2003–2004, which was taken into account in the two meta-analyses, the length of major roads within 500 m of the residence was associated with both ALL and AML [20]. In the GEOCAP-Diag study, included in the second meta-analysis, the length of l. 2major roads within 150 m was associated with AML over 2002–2007 [15]. In our study, which is completely distinct from GEOCAP-Diag and has been set to complementary investigate perinatal exposures with a different recruitment of controls, we used the same definition of major roads as previously but the period of exposure was much more recent (births

Table 4 Childhood acute lymphoblastic leukemia and air pollution indicators at the address of residence at birth in strata of size of urban unit—association with major road length in 500 m buffer and exposures to NO_2, $PM_{2.5}$ and BC, GEOCAP birth study, France, 2010–2015

	Size of urban unit															p-INT[b]
	<5,000 inhabitants					5,000 to 99,999 inhabitants					≥100,000 inhabitants					
	N controls	N ALL	OR	95% CI	p[a]	N controls	N ALL	OR	95% CI	p[a]	N controls	N ALL	OR	95% CI	p[a]	
Major road length within 500 m of residence at birth (m) [c]																
0, nearest major road 500 m away	1574	88	1.0	Ref	0.91	863	41	1.0	Ref	0.73	1381	73	1.0	Ref	0.32	
Nearest major road less than 500 m away																
length <=T1	459	19	0.7	(0.5–1.2)		637	43	1.4	(0.9–2.2)		1601	70	0.8	(0.6–1.2)		
length]T1;T2]	458	24	0.9	(0.6–1.5)		637	28	0.9	(0.6–1.5)		1601	69	0.8	(0.6–1.1)		
length >T2	459	23	0.9	(0.6–1.4)		637	32	1.1	(0.7–1.7)		1601	71	0.8	(0.6–1.2)		
Per 500 m increase [g]	2950	154	0.95	(0.84–1.08)	0.47	2774	144	1.00	(0.92–1.09)	0.95	6184	283	0.99	(0.95–1.02)	0.43	0.32
NO_2 exposure (µg/m³) [d]																
<=T1	984	50	1.0	Ref	0.27	925	45	1.0	Ref	0.29	2062	84	1.0	Ref	0.51	
]T1;T2]	983	42	0.8	(0.6–1.3)		924	43	1.0	(0.6–1.5)		2061	106	1.3	(0.9–1.7)		
>T2	983	62	1.2	(0.9–1.8)		925	56	1.2	(0.8–1.9)		2061	93	1.1	(0.8–1.5)		
Per 5 µg/m³ increase [g]	2950	154	1.12	(0.93–1.35)	0.25	2774	144	1.12	(0.96–1.31)	0.16	6184	283	1.03	(0.97–1.1)	0.35	0.53
$PM_{2.5}$ exposure (µg/m³) [e]																
<=T1	984	38	1.0	Ref	0.01	925	36	1.0	Ref	0.01	2062	69	1.0	Ref	<0.001	
]T1;T2]	983	46	1.2	(0.8–1.9)		924	35	1.0	(0.6–1.6)		2061	92	1.3	(1.0–1.8)		
>T2	983	70	1.8	(1.2–2.8)		925	73	2.0	(1.4–3.1)		2061	122	1.8	(1.3–2.4)		
Per 2 µg/m³ increase [g]	2950	154	1.30	(1.12–1.51)	0.01	2774	144	1.40	(1.20–1.63)	<0.001	6184	283	1.20	(1.10–1.31)	<0.001	0.51
BC exposure (10^{-5}/m) [f]																
<=T1	984	36	1.0	Ref	0.01	925	36	1.0	Ref	0.01	2062	82	1.0	Ref	0.37	
]T1;T2]	983	54	1.5	(1.0–2.3)		924	45	1.3	(0.8–2.0)		2061	107	1.3	(1.0–1.8)		
>T2	983	64	1.8	(1.2–2.7)		925	63	1.8	(1.2–2.7)		2061	94	1.2	(0.9–1.6)		
Per 0.5 10^{-5}/m increase [g]	2950	154	1.90	(1.22–2.97)	0.01	2774	144	1.58	(1.16–2.17)	0.01	6184	283	1.09	(0.95–1.24)	0.22	0.06

ALL, acute lymphoblastic leukemia; OR, odds ratio and 95% CI, 95% confidence interval obtained by logistic regression models; T, tertile

[a] p-value for trend derived from the partial t-test for the categorical variables, and from the likelihood ratio test for the continuous variables

[b] p-value for interaction between exposures and size of urban unit derived from the Likelihood Ratio Test comparing the models with and without interaction terms

[c] cut offs at 935.5 and 1089.7 m in stratum of <5,000 inhabitants; 1022.8 and 1761.4 m in stratum of 5,000 to 99,999 inhabitants; 1242.5 and 2396.9 m in stratum of ≥ 100,000 inhabitants

[d] cut offs at 11.8 and 15.6 µg/m³ in stratum of <5,000 inhabitants; 15.9 and 20.3 µg/m³ in stratum of 5,000 to 99,999 inhabitants; 25.2 and 33.8 µg/m³ in stratum of ≥ 100,000 inhabitants

[e] cut offs at 12.8 and 14.5 µg/m³ in stratum of <5,000 inhabitants; 13.5 and 15.2 µg/m³ in stratum of 5,000 to 99,999 inhabitants; 15.8 and 18.6 µg/m³ in stratum of ≥ 100,000 inhabitants

[f] cut offs at 1.0 and 1.2 10^{-5}/m in stratum of <5,000 inhabitants; 1.2 and 1.4 10^{-5}/m in stratum of 5,000 and 99,999 inhabitants; 1.6 and 2.1 10^{-5}/m in stratum of ≥ 100,000 inhabitants

[g] increase of 1/2 interquartile range of the distribution among controls

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in 2010–2015) and significant progress have been made in recent years in the road transport sector to reduce air pollution, for instance renewal of the vehicle fleet, establishment of low-emission zones, development of air pollutants reduction technologies such as catalytic converters, compensating for the increase in traffic and number of vehicles [54]. In this context, major road length within 500 m may be a weaker proxy of exposures to air pollutants than in the past. The correlations we observed between major road length and exposures to air pollutants were also weak, especially for $PM_{2.5}$.

The absence of association with NO_2 exposure in the main analysis is consistent with the meta-analysis by Filippini et al. and other studies published thereafter, regardless of the window of exposure [11, 12, 14]. One recent study reported no association for ALL but showed increased risks for AML for a 10 μg/m^3 increment in NO_2 exposure over the period 1990–2015 [12]. Our analyses yielded OR above the null for AML in the highest NO_2 exposure category, but we may have lacked statistical power to actually show an association.

Our study found associations for the risks of childhood ALL and AML with exposure to $PM_{2.5}$ at time of birth. Similarly, one recently published case–control study reported an increased risk of childhood ALL for $PM_{2.5}$ modeled exposure at time of birth, combining satellite-derived data, chemical transport modeling and ground-based measurements [13]. However, a previous cohort [55] and two case–control studies [44, 56], summarized in the meta-analysis [11], reported no association between childhood acute leukemia and perinatal $PM_{2.5}$ exposure, while also using exposure modelling. In the recent Danish case–control study, the time-weighted average concentration of $PM_{2.5}$ calculated from birth to inclusion, also taking into account traffic intensity, was not associated with childhood ALL and AML risks either [14].

BC is a constituent of $PM_{2.5}$ formed from the incomplete fuel combustion generated mainly from domestic heating and road traffic, and not yet routinely measured in Europe. This can explain the lack of epidemiological studies investigating the relationship between BC concentrations and risk of childhood leukemia. The main analyses showed no association with BC concentration, however, increased risk of ALL were observed in rural areas and urban units < 99,999 inhabitants. So far, one Danish case–control study reported elevated but imprecise OR for ALL [14]. In this study, no association was found for AML, which is in agreement with our results.

The association of childhood ALL with $PM_{2.5}$ exposure that we reported was observed in both rural and urban areas and there was no greater effect when the degree of urbanization increased. In France, $PM_{2.5}$ concentrations are on average higher in large urban units (located mainly in the Ile de France region, in the North-East and in the South-East of France). However, some rural municipalities highly industrial can experience elevated concentrations, for instance in the East of France [57]. Moreover, $PM_{2.5}$ exposure was not correlated with major road length, whether in rural or urban birthplaces. Positive associations were observed in all strata of major road length, including in the first stratum in which traffic was considered not to influence background air pollution, and the strength of association did not increase with increasing traffic density. $PM_{2.5}$ originate from different sources depending on the settings, in particular from domestic heating in rural areas and mainly but not exclusively from road transport in urban areas, while the main source of BC is road traffic [54, 58]. Therefore, our results suggest that there may be an effect of $PM_{2.5}$ on childhood ALL, possibly due to traffic but not only. Other combustion-related chemical constituents of $PM_{2.5}$ (*e.g.* trace metals and hydrocarbons) may also explain part of the observed associations, in rural areas particularly [59, 60]. The absence of a clear association with BC concentrations in the most populated urban places remains to be elucidated.

The biological mechanisms linking air pollutants and childhood leukemia remain poorly understood. $PM_{2.5}$ can be absorbed from the respiratory tract, reach the alveoli and interact with blood. An *ex vivo* study showed that they can cross the human placental barrier and expose the developing fetus [61]. $PM_{2.5}$ may induce hematopoietic toxicity by increasing oxidative stress and DNA damage, inhibiting DNA repair, reducing the expression of hematopoietic growth factors and decreasing the number of blood cells and myeloid progenitor cells [62]. DNA methylation has been shown to be sensitive to $PM_{2.5}$ exposure and induce the inhibition of gene expression and cellular differentiation [63–65]. In an *in vitro* study, the prolonged exposure to $PM_{2.5}$ led to the progression of leukemic cells through reactive oxygen species-mediated pathways [66]. $PM_{2.5}$ may also weaken the immune system by stimulating a pro-inflammatory immune response through cytokine expression [67–69].

Conclusion

Our findings suggest a role of perinatal exposure to air pollution, as reflected by $PM_{2.5}$ and BC exposures, in the development of childhood acute leukemia, particularly ALL, stressing the importance of air pollution regulations. They call for increasing sample sizes to provide more robust results for AML, and highlight the need to better understand which sources of pollution and which other pollutants could be behind the observed association with $PM_{2.5}$.

Table 5 Childhood acute lymphoblastic leukemia and air pollution indicators at the address of residence at birth in strata of major road length in 500 m buffer—association with exposures to NO₂, PM₂.₅ and BC, GEeOCAP birth study, France, 2010–2015

| | Major road length in 500 m buffer | | | | | | | | | | | | | | | | | | | | p-INT^b |
| | No major road within 500 m | | | | | Major road length ≤1030.4 m | | | | | Major road length in]1030.4;1965.6] m | | | | | Major road length >1965.6 m | | | | | |
	N controls	N ALL	OR	95% CI	p^a	N controls	N ALL	OR	95% CI	p^a	N controls	N ALL	OR	95% CI	p^a	N controls	N ALL	OR	95% CI	p^a	
NO₂ exposure (μg/m³) ^c																					
<=T1	1273	64	1.0	Ref	0.45	899	45	1.0	Ref	0.62	899	35	1.0	Ref	0.91	899	36	1.0	Ref	0.47	
]T1;T2]	1272	65	1.0	(0.7–1.5)		899	44	1.0	(0.6–1.5)		899	43	1.2	(0.8–1.9)		899	52	1.4	(0.9–2.2)		
>T2	1273	73	1.1	(0.8–1.6)		899	50	1.1	(0.7–1.7)		899	34	1.0	(0.6–1.6)		899	40	1.1	(0.7–1.8)		
Per 5 μg/m³ increase ^f	3818	202	1.04	(0.95–1.14)	0.42	2697	139	1.02	(0.92–1.12)	0.75	2697	112	1.00	(0.90–1.11)	1.00	2697	128	1.03	(0.94–1.12)	0.55	0.70
PM₂.₅ exposure (μg/m³) ^d																					
<=T1	1273	45	1.0	Ref	0.001	899	36	1.0	Ref	0.03	899	23	1.0	Ref	0.04	899	27	1.0	Ref	0.27	
]T1;T2]	1272	71	1.6	(1.1–2.3)		899	45	1.3	(0.8–2.0)		899	49	2.1	(1.3–3.5)		899	55	2.0	(1.3–3.3)		
>T2	1273	86	1.9	(1.3–2.8)		899	58	1.6	(1.1–2.5)		899	40	1.7	(1.0–2.9)		899	46	1.7	(1.1–2.8)		
Per 2 μg/m³ increase ^f	3818	202	1.22	(1.10–1.35)	<0.001	2697	139	1.17	(1.05–1.32)	0.01	2696	112	1.15	(1.01–1.32)	0.03	2697	128	1.12	(1.00–1.26)	0.06	0.96
BC exposure (10⁻⁵/m) ^e																					
<=T1	1273	55	1.0	Ref	0.08	899	40	1.0	Ref	0.53	899	36	1.0	Ref	0.99	899	38	1.0	Ref	0.63	
]T1;T2]	1272	71	1.3	(0.9–1.9)		899	53	1.3	(0.9–2.0)		899	40	1.1	(0.7–1.8)		899	41	1.1	(0.7–1.7)		
>T2	1273	76	1.4	(1.0–2.0)		899	46	1.2	(0.8–1.8)		899	36	1.0	(0.6–1.6)		899	49	1.3	(0.8–2.0)		
Per 0.5 10⁻⁵/m increase ^f	3818	202	1.19	(0.97–1.45)	0.09	2697	139	1.09	(0.88–1.34)	0.44	2696	112	1.00	(0.80–1.25)	0.97	2697	128	1.13	(0.95–1.35)	0.17	0.86

ALL, acute lymphoblastic leukemia; OR, odds ratio and 95% CI, 95% confidence interval obtained by logistic regression models; T, tertile

^a p-value for interaction between air pollutant exposures and major road length in 500 m buffer, derived from the Likelihood Ratio Test comparing the models with and without interaction terms

^b p-value for interaction between air pollutant exposures and major road length in 500 m buffer, derived from the Likelihood Ratio Test comparing the models with and without interaction terms

^c cut offs at 13.6 and 20.1 μg/m in stratum of no major road within 500 m; 16.0 and 23.7 μg/m in stratum of major road length ≤ 1030.4 m; 19.6 and 27.0 μg/m in stratum of major road length in]1030.4;1965.6] m; 26.2 and 37.8 μg/m³ in stratum of major road length >1965.6 m

^d cut offs at 13.4 and 15.6 μg/m in stratum of no major road within 500 m; 14.0 and 16.3 μg/m in stratum of major road length ≤1030.4 m; 19.6 and 27.0 μg/m in stratum of major road length in]103 0.4;1965.6] m; 15.7 and 18.9 μg/m³ in stratum of major road length >1965.6 m

^e cut offs at 1.1 and 1.4 10⁻⁵/m in stratum of no major road within 500 m; 1.2 and 1.6 10⁻⁵/m in stratum of major road length ≤ 1030.4 m; 1.4 and 1.8 10⁻⁵ /m in stratum of major road length in]1030.4; 1965.6] m; 1.7 and 2.2 10⁻⁵ /m in stratum of major road length >1965.6 m

^f increase of 1/2 interquartile range of the distribution among controls

Table 6 Childhood acute lymphoblastic leukemia and air pollution indicators at the address of residence at birth in strata of sex—association with major road length in 500 m buffer and exposures to NO_2, $PM_{2.5}$ and BC, GEOCAP birth study, France, 2010–2015

	Sex											p-INT[b]
	Male participants					Female participants						
	N controls	N ALL	OR	95% CI	p[a]	N controls	N ALL	OR	95% CI	p[a]	
Major road length within 500 m of residence at birth (m) [c]											
0, nearest major road 500 m away	1925	108	Ref		0.10	1893	94	Ref		0.02	
Nearest major road less than 500 m away											
length < =T1	1388	89	1.1	(0.9–1.5)		1360	50	0.8	(0.5–1.1)		
length]T1;T2]	1387	71	0.9	(0.7–1.2)		1350	41	0.6	(0.4–0.9)		
length >T2	1387	59	0.8	(0.6–1.1)		1378	69	1.1	(0.8–1.5)		
Per 500 m increase [g]	6087	327	0.99	(0.98–1.00)	0.04	5981	254	0.99	(1.01–0.76)	0.77	0.10
NO_2 exposure (µg/m^3) [d]											
< =T1	2029	111	Ref		0.97	1941	81	Ref		0.87	
]T1;T2]	2029	108	1.0	(0.7–1.3)		1940	85	1.1	(0.8–1.4)		
>T2	2029	108	1.0	(0.7–1.3)		1940	88	1.1	(0.8–1.5)		
Per 5 µg/m^3 increase [g]	6087	327	0.99	(0.93–1.04)	0.61	5821	254	1.02	(0.96–1.09)	0.45	0.37
$PM_{2.5}$ exposure (µg/m^3) [e]											
< =T1	2029	80	Ref		0.002	1941	61	Ref		0.003	
]T1;T2]	2029	117	1.5	(1.1–2.0)		1940	87	1.4	(1.0–2.0)		
>T2	2029	130	1.6	(1.2–2.2)		1940	106	1.7	(1.3–2.4)		
Per 2 µg/m^3 increase [g]	6087	327	1.13	(1.05–1.21)	0.001	5821	254	1.15	(1.06–1.25)	0.001	0.70
BC exposure (10^{-5}/m) [f]											
< =T1	2029	103	Ref		0.76	1941	74	Ref		0.36	
]T1;T2]	2029	114	1.1	(0.8–1.5)		1940	92	1.2	(0.9–1.7)		
>T2	2029	110	1.1	(0.8–1.4)		1940	88	1.2	(0.9–1.6)		
Per 0.5 10^{-5}/m increase [g]	6087	327	0.99	(0.88–1.11)	0.83	5821	254	1.12	(0.99–1.27)	0.08	0.15

ALL, acute lymphoblastic leukemia; OR, odds ratio and 95% CI, 95% confidence interval obtained by logistic regression models; T, tertile

[a] *p*-value for trend derived from the partial t-test for the categorical variables, and from the likelihood ratio test for the continuous variables

[b] *p*-value for interaction between exposures and size of urban unit derived from the Likelihood Ratio Test comparing the models with and without interaction terms

[c] cut offs at 1031.0 and 1970.3 m in stratum of male participants; 1030.2 and 1958.2 m in stratum of female participants

[d] cut offs at 17.7 and 26.4 µg/m^3 in stratum of male participants; 17.3 and 26.4 µg/m^3 in stratum of female participants

[e] cut offs at 14.3 and 16.8 µg/m^3 in stratum of male participants; 14.3 and 16.8 µg/m^3 in stratum of female participants

[f] cut offs at 1.28 and 1.71 10^{-5}/m in stratum of male participants; 1.27 and 1.71 10^{-5}/m in stratum of female participants

[g] increase of 1/2 interquartile range of the distribution among controls

Abbreviations

AL	Acute leukemia
ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
BC	Black carbon;
CI	Confidence interval
DNA	Deoxyribonucleic acid
ESCAPE	European study of cohorts for air pollution effects
GEOCAP	*Geolocalisation des cancers pédiatriques*
GPS	Global positioning system
ICCC-3	International classification of childhood cancer – 3rd edition
IGN	National institute of geographic and forest information
INSEE	National institute of statistics and economic studies
IQR	Interquartile range
LUR	Land use regression
NO2	Nitrogen dioxide
NUTS-1	Nomenclature of territorial units for statistics geography—Level 1
OR	Odds ratio
PM2.5	Particulate matter
REML	Restricted maximum likelihood
UV	Ultraviolet

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12940-025-01227-x.

Supplementary Material 1.

Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The research undertaken with the French National Registry of Childhood Haematological Malignancies data is covered by agreements on the ethical use of data and the protection of personal data, and have been approved by French national authorities: *Commission national Informatique et Libertés* (CNIL N°998198 v8).

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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