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Road Traffic Pollution and Childhood Leukemia: A Nationwide Case-control Study in Italy

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Background. The association of childhood leukemia with traffic pollution was considered in a number of studies from 1989 onwards, with results not entirely consistent and little information regarding subtypes.

Aim of the study. We used the data of the Italian SETIL case-control on childhood leukemia to explore the risk by leukemia subtypes associated to exposure to vehicular traffic.

Methods. We included in the analyses 648 cases of childhood leukemia (565 Acute lymphoblastic−ALL and 80 Acute non lymphoblastic-AnLL) and 980 controls. Information on traffic exposure was collected from questionnaire interviews and from the geocoding of house addresses, for all periods of life of the children.

Results. We observed an increase in risk for AnLL, and at a lower extent for ALL, with indicators of exposure to traffic pollutants. In particular, the risk was associated to the report of closeness of the house to traffic lights and to the passage of trucks (OR: 1.76; 95% CI 1.03−3.01 for ALL and 6.35; 95% CI 2.59−15.6 for AnLL). The

Ethical Aspects: The SETIL study was authorized by the Ethical Review Board for the Piedmont Region (authorization n. 2886, on 15/2/1999; letter n. 1852/28.3 on 17/2/1999) and later by the corresponding board of each participating research unit. Parental informed consent was obtained before the interview.

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association was shown also in the analyses limited to AML and in the stratified analyses and in respect to the house in different period of life.

Conclusions. Results from the SETIL study provide some support to the association of traffic related exposure and risk for AnLL, but at a lesser extent for ALL. Our conclusion highlights the need for leukemia type specific analyses in future studies. Results support the need of controlling exposure from traffic pollution, even if knowledge is not complete.

Key Words: Childhood, Leukemia, Acute non Lymphoblastic Leukemia, Road Traffic, Environment.

Introduction

Leukemia is the most frequent neoplasm in childhood, with incidence rates of 35.9 per million children-year for Acute Lymphoblastic Leukemia (ALL) and of 6.5 for Acute non Lymphoblastic Leukemia (AnLL) in European countries (1). Analyses of incidence trends showed an increase, in particular in the EU and USA (1,2). Despite its relative frequency and the large number of studies, exposure to ionizing radiation is the only exposure unequivocally associated to childhood leukemia (3−5). A large number of putative risk factors has been studied, including among others: infectious agents and immune stimulation, parental and child exposure to: chemical agents, solvents, pesticides, tobacco smoking, Extremely Low Frequency Magnetic fields (ELF-MF) and Radiofrequency fields, and exhaust gases from traffic pollution (3,4,6−11). Traffic pollution causes exposure to a large number of chemicals, including some with known carcinogenic effect, such as benzene and polycyclic aromatic hydrocarbons (PAH). Diesel exhaust was classified in the IARC Monographs as Human Carcinogen (group 1), but only limited information was available on childhood leukemia (12). Benzene is a known carcinogen causing leukemia and lymphoma, but evidence for childhood leukemia is limited (13). Three recent metaanalyses observed an association of childhood leukemia and traffic related exposures (14−16).

Etiological factors for childhood leukemia were investigated in Italy in a large national population-based case-control study, including 683 cases of leukemia and 1044 matched controls (17). Exposure to traffic pollution was one of the main factors considered, with information based on the geocoding of all reported addresses and on questionnaire information on the area of residence and on the house characteristics. A pilot study was conducted including area and personal measurement of benzene exposure, showing that exposure was higher in wintertime, and it was not affected by gender, age or area of residence. The pilot study size was too limited to investigate association with leukemia and to conduct analyses by subtype (18). An analysis of SETIL main study focused on distance from main roads and estimates of exposure to pollutants from Land Use Regression (LUR) and dispersion models observed no association of traffic exposure indicators and leukemia status (19). The present study further investigates with further analyses on leukemia risk and traffic exposure, using both questionnaire information and geocoded home addresses to identify traffic related exposure variables. Present analyses were conducted separately for ALL and AnLL, in order to contribute information on etiological factors specific for leukemia type.

Material and Methods

Study Population

The SETIL study is a population based case-control study including the cases of acute childhood leukemia diagnosed in children aged 0−10 in 14 Italian regions in 1998−2001. Cases were identified from the national registry of the Italian Association of Pediatric Hematology and Oncology (AIEOP) (20), that provided descriptive and clinical information, including cytological diagnosis. For each case, two controls were randomly sampled from the rosters of the National Health Service, matched by birth date (+/−15 d), gender and region. Age range (0−10) corresponds to the primary (elementary) school in Italy. Parents of cases and controls were interviewed at home with a structured questionnaire administered by a trained interviewer. Interviews took place during 1999−2002. Subjects were invited after approval from the attending oncologist for cases, and after information of the GP for the controls. Details of the study design were presented elsewhere (17) and are only summarized here.

The study included 683 leukemia cases out of 745 eligible (participation rate 91.7%) and 1044 controls out of 1475 eligible (70.8%). Among controls, family refusal was the most common reason of non participation (70.3%); medical refusal was 6.2%, while the untraced proportion was 21.8%, and the remaining 1.6% included non-participants for other reasons (17). Subjects not participating for any reasons were not substituted.

Cases were classified using the ICCC-3 classification (21), according to the confirmed cytological diagnosis recorded at AIEOP registry (20). Cytological types of participant cases included: 601 (88%) Acute Lymphocytic Leukemia (ALL, ICCC I a), 82 cases (12%) of Acute non Lymphoblastic Leukemia (AnLL—ICCC I b-e). The ALL group included for the analyses 7 cases of Acute Hybrid Leukemia (1%). The frequency distribution of AnLL by cytological subtype was:

M1&M2: 37.8%, M3: 19.5%, M4: 12.2%, M5: 17.1%, M6: 1.2%, M7: 2.4, other and unclassified: 9.8%. Chronic leukemia was not eligible for the study.

Data Collection and Management

Data on road traffic exposure were collected using two different sources: the geocoding of addresses and the information from the interview. Information on the methodology and results of geocoding, dispersion models and Land Use Regression (LUR) analyses were provided in Badaloni et al. (19). All addresses reported at interview (from one year before birth to date of diagnosis of the index case) were considered for geocoding. The Geographical Information System (ArcEditor 10.0) software and the Tele Atlas/TomTom vector map (http://www.tomtom.com/) were used to assign the coordinate values (X,Y) to residential addresses. Geocoding of residential birth addresses was possible for 98.8% (n = 675) and 99.5% (n = 1039) of cases and controls, respectively. Similar proportions were obtained for the addresses at the other different periods of time (19). We classified the Italian roads in three groups according to traffic intensity on the basis of their importance in the road network, following the TeleAtlas/TomTom road classes: classes 1–2 (major roads, incl. highways), class 3 (secondary roads), and classes 4–5 (local connecting roads and local roads of high importance). Distance from Main Roads and Main Roads Length around the residence address were used as proxy indicators of traffic exposure. For the present analyses, we focused on the traffic intensity in the broad area, estimated using the cumulative Main Roads Length (in metres) within 500 m of the residence (500 m buffer). Main Roads Length distribution was stratified in three classes, based on the cumulative distribution of all the addresses: T1 below the median (2283 meters, including addresses with no Main Roads in the 500 m buffer), T2 above the median and up to the 90° percentile (4804 meters) and T3 above the 90° percentile. The higher value was 11313.

Besides the addresses, the questionnaire interview included also a description of the location of each house where the child and the mother used to live, from the year before birth to date of diagnosis. Information considered were: general evaluation of the traffic intensity in the area; for each road facing a side of the building (up to a maximum of four): road type and number of lanes, bus lines, occurrence of truck traffic, traffic lights within 100 m, number of windows facing on the road, floor number, petrol stations and surface parking areas nearby. Present analyses regard only road traffic indicators and characteristics of the house, while analyses of fixed structures, such as petrol stations or parking places will be considered for a separate presentation. If the building was surrounded by two or more roads (e.g.: a house at the junction of streets) the same information was collected for all the relevant roads, with an upper limit of four. Following the preliminary analyses, a variable was formed including both nearby (within 100 m, as reported in questionnaire) location of traffic lights and frequent truck traffic, under the 'a priori' hypothesis of an interaction of the two variables in originating high exposure conditions. Location of each address was defined as urban, rural or mixed according to the classification developed by the Italian National Institute of Statistics (ISTAT) on the basis of the municipal characteristics at the 1991 census (22). Agreement between these variables and objective measurements was assessed using the pilot study on area and personal benzene exposure (18). Supplementary Table 1 shows the results of the comparison: all questionnaires reporting 2 or more high traffic roads and 71% of questionnaires reporting traffic lights and trucks traffic were associated to benzene outdoor measurements over the median (2.37 $\mu g/m^3$). The pilot study results had also showed a strong association between outdoor and personal benzene measurements (18).

We focused analyses on the house where the child lived at birth and on the house contributing more to the exposure. Based on these criteria, the following sets of traffic related variables were constructed and analyzed: house at birth, house most exposed, house where the child lived the longest time, and house where the child lived for at least 50% of life.

From the houses reported at interview, we identified the most exposed as the one with the largest number of surrounding high traffic roads. In case of two or more buildings surrounded by the same number of high traffic roads, the one where the subject lived for a longer time was selected. In case of missing information from the questionnaire, the most exposed house was identified from the address location, according to the examination of the local map area. These evaluations were conducted blindly as regards the case or control status.

Consistently with previous analyses, we excluded 38 cases and 64 controls because they were living in areas where air pollution prediction could not be done, leaving for the analyses 645 cases (565 ALL and 80 AnLL) and 980 controls (19).

Statistical analyses were conducted with unconditional logistic regression (ULR) models, including the matching variables (age, sex and region) in all models. As described in previous papers, other potential confounders were included, such as parental occupational exposure to solvents, education and smoking (17,23–26). Based on the previous evidence we kept education and smoking (parental smoking and other sources of ETS interesting the child) in all analyses. The other exposures were tested and retained in the regression model only if actual confounding effect was observed.

Statistical Analyses

Analyses were separated by type of leukemia (ALL, AnLL), using a common set of controls formed of all

participating controls. Analyses separately considered each of the four sets of traffic related variables (house at birth, most exposed house, house where the child lived the longest time, and house where the child lived for at least 50% of life time). Sensitivity analyses were conducted limiting the sets of controls to those originally matched to ALL and AnLL cases. Stratified analyses by age, sex and other variables were also conducted.

The association between traffic related variables and ALL, AnLL occurrence was estimated computing the odds ratios (OR) and their 95% confidence interval (95% CI). The test for linear trend was computed using main roads length classes as a numerical variable. p-values <0.05 were considered as statistically significant.

Data elaboration and analyses were carried out using SAS v. 9.2 and Stata 11.

Results

Table 1 presents descriptive data of the study participants, parental education, exposure to smoking (both parental and ETS), and parental exposure to solvents. Age distribution was different for ALL and AnLL cases, reflecting the different age specific incidence rates. ALL were more frequent at age 2−3, while AnLL were distributed over the entire age range. Males were more frequent than females for both ALL and AnLL. The distribution by region of residence followed the population structure, as no regional differences in the incidence of childhood leukemia are observed in Italy (27). Parental education was higher for controls than for the cases. Cases were more frequently exposed to parental smoking than controls and case parents were more exposed to solvents (24−26).

Table 2 describes the house location and the indicators of traffic exposure, with reference to the house where the child lived at birth and to the house classified as the most exposed along child's life. However most children (70.9 of ALL, 69.6 of AnLL, and 77.6% of controls, data not tabulated) lived in the same house all life.

We did not observe differences in the distribution by Urban/Rural categories of ALL, AnLL and controls residences. The number of streets reported as surrounding the

Table 1. SETIL study on road traffic exposure and childhood leukemia. Descriptive data for the children included in the analyses, by leukemia type and controls

	ALL cases	**AnLL cases**	**Controls**
	***n* (%)**	***n* (%)**	***n* (%)**
Age at diagnosis (years)			
(0−1)	70 (12.4)	21 (26.3)	147 (15.0)
(2−3)	219 (38.8)	13 (16.3)	337 (34.4)
(4−5)	125 (22.1)	13 (16.3)	217 (22.1)
(6−10)	151 (26.7)	33 (41.3)	279 (28.5)
Total	565	80	980
Sex			
Male	310 (54.9)	41 (51.3)	533 (54.4)
Female	255 (45.1)	39 (48.8)	447 (45.6)
Region			
North, Lombardy only	153 (27.1)	16 (20.0)	260 (26.5)
North, other regions	144 (25.5)	22 (27.5)	250 (25.5)
Central Italy	156 (27.6)	17 (21.3)	257 (26.2)
South and Islands	112 (19.8)	25 (31.3)	213 (21.7)
Maternal educational level			
Primary and lower sec.	253 (44.8)	46 (57.5)	363 (37.1)
High school	249 (44.1)	25 (31.3)	481 (49.2)
University degree	63 (11.2)	9 (11.3)	134 (13.7)
Missing	0	0	2 (0.2)
Paternal educational level			
Primary and lower sec	271 (48.3)	46 (58.2)	423 (43.4)
High school	235 (41.9)	24 (30.4)	409 (42.0)
University degree	55 (9.8)	9 (11.4)	142 (14.6)
Missing	4 (0.6)	1 (0.1)	6 (0.6)
Index of smoking exposure[a]			
Exposed	287 (50.8)	42 (52.5)	427 (43.6)
Not exposed	276 (48.9)	38 (47.5)	547 (55.8)
Missing	2 (0.3)	0	6 (0.6)
Index of parental exposure to solvents			
Exposed	62 (11.0)	3 (3.8)	55 (5.6)
Not exposed	503 (89.0)	77 (96.3)	925 (94.4)

[a]Parental and ETS exposure interesting the child.

Table 2. SETIL study on road traffic exposure and childhood leukemia. Distribution of traffic related variables and of the duration of residence for the House at birth and the one identified as the most exposed, by leukemia type and controls. Proportions were computed excluding missing values

	ALL cases	AnLL cases	Controls
	n (%)	*n* (%)	*n* (%)
House at Birth			
Traffic intensity, as reported at interview			
No high traffic roads	446 (79.2)	61 (77.2)	764 (78.9)
One high traffic road	66 (11.7)	13 (16.5)	132 (13.6)
Two or more high traffic roads	12 (2.1)	2 (2.5)	21 (2.2)
Info. not reported, estimated from address	39 (6.9)	3 (3.8)	51 (5.3)
Missing	2	1	12
Main Roads length (metres in a 500 m radius)			
No main roads (incl in T1 for later analyses)	59 (10.5)	4 (5.1)	53 (5.5)
T1	264 (46.9)	35 (44.3)	455 (47.0)
T2	197 (35.0)	32 (40.5)	370 (38.2)
T3	43 (7.6)	8 (10.1)	90 (9.3)
Missing	2	1	12
Urban/rural location			
Urban	248 (44.8)	32 (41.6)	487 (50.6)
Mixed, urban	201 (36.3)	28 (36.4)	285 (29.6)
Mixed, rural	38 (6.9)	5 (6.5)	76 (7.9)
Rural	67 (12.1)	12 (15.6)	114 (11.9)
Missing	11	3	18
Proportion of life lived in the House at birth			
0−<0.25	50 (8.9)	9 (11.4)	78 (8.1)
0.25−<0.50	58 (10.3)	7 (8.9)	50 (5.2)
0.50−<0.75	56 (10.0)	8 (10.1)	89 (9.2)
0.75−1.00	399 (70.9)	55 (69.6)	751 (77.6)
Missing	2	1	12
Number of streets/roads reported in the questionnaire surrounding the House			
0	19 (3.4)	1 (1.3)	29 (3.0)
1	370 (65.7)	54 (68.4)	657 (67.9)
2	137 (24.3)	16 (20.3)	216 (22.3)
3	21 (3.7)	4 (5.1)	47 (4.9)
4	16 (2.8)	4 (5.1)	19 (2.0)
Missing	2	1	12
Local elements of traffic conditions			
Neither traffic lights nor trucks	435 (77.26)	51 (64.56)	742 (76.65)
Trucks	74 (13.14)	16 (20.25)	133 (13.74)
Traffic lights	34 (6.04)	4 (5.06)	64 (6.61)
Both traffic lights and trucks	20 (3.55)	8 (10.13)	29 (3.00)
Missing	2	1	12
House most exposed			
Traffic intensity, as reported at interview			
No high traffic roads	431 (76.6)	56 (70.9)	748 (76.6)
One high traffic road	93 (16.5)	16 (20.3)	166 (17.0)
Two or more high traffic roads	19 (3.4)	5 (6.3)	30 (3.1)
Info. not reported, estimated from address	20 (3.6)	2 (2.5)	32 (3.3)
Missing	2	1	4
Main Roads length (metres in a 500 m radius)			
No main roads (incl in T1 for later analyses)	47 (8.4)	3 (3.8)	54 (5.5)
T1	258 (45.8)	35 (44.3)	451 (46.2)
T2	211 (37.5)	32 (40.5)	381 (39.0)
T3	47 (8.4)	9 (11.4)	90 (9.2)
Missing	2	1	4
Urban/rural location			
Urban	256 (45.6)	33 (42.3)	486 (50.1)
Mixed, urban	200 (35.7)	27 (34.6)	292 (30.1)
Mixed, rural	39 (7.0)	5 (6.4)	78 (8.0)
Rural	66 (11.8)	13 (16.7)	114 (11.8)
Missing	4	2	10

(*continued on next page*)

Table 2 (*continued*)

	ALL cases	AnLL cases	Controls
	n **(%)**	***n*** **(%)**	***n*** **(%)**
Proportion of life lived in the House most exposed			
0−<0.25	18 (3.2)	4 (5.1)	27 (2.8)
0.25−<0.50	27 (4.8)	2 (2.5)	25 (2.6)
0.50−<0.75	89 (15.8)	13 (16.5)	123 (12.6)
0.75−1.00	429 (76.2)	60 (76.0)	801 (82.1)
Missing	2	1	4
Number of streets/roads reported in the questionnaire surrounding the house			
0	5 (0.9)	-	11 (1.1)
1	373 (66.3)	54 (68.4)	658 (67.4)
2	143 (25.4)	16 (20.3)	230 (23.6)
3	25 (4.4)	4 (5.1)	52 (5.3)
4	17 (3.0)	5 (6.3)	25 (2.6)
Missing	2	1	4
Local elements of traffic conditions			
Neither traffic lights nor trucks	422 (75.0)	46 (58.2)	734 (75.2)
Trucks	80 (14.2)	18 (22.8)	145 (14.9)
Traffic lights	32 (5.7)	6 (7.6)	66 (6.8)
Both traffic lights and trucks	29 (5.2)	9 (11.4)	31 (3.2)
Missing	2	1	4

building was also similar for cases and controls, with reference both to birth home addresses and to that most exposed. The occurrence of traffic lights and truck traffic was reported more often by families of AnLL cases.

Table 3 presents the estimated ORs for ALL and AnLL by road traffic exposure indicators regarding the 'most exposed' house. For ALL, no association was observed for Main Road Length in 500 m buffer nor for the urban/rural location of the house and the number of windows facing on the road. A statistically significant increase in ALL risk was only observed (OR:1.76; 95% CI 1.03−3.01) for the combined variable including traffic light within 100 m distance and the frequent occurrence of trucks. Similarly, for AnLL, a statistically significant increased risk was observed

Table 3. SETIL study on road traffic exposure and childhood leukemia. Risk of ALL and AnLL was analyzed using an Unconditional Logistic Regression model including a set of 'a priori' defined variables describing traffic exposure and confounders. The analysis was conducted with consideration of the house classified at highest exposure

	ALL	AnLL
House most exposed	**OR (95% CI);** ***p***	**OR (95% CI);** ***p***
Main Roads length in a 500 m radius		
T1	Ref.	Ref.
T2	0.94 (0.74−1.20); $p = 0.64$	1.32 (0.75−2.31); $p = 0.33$
T3	0.97 (0.63−1.48); $p = 0.88$	1.70 (0.69−4.17); $p = 0.25$
	Linear trend $p = 0.72$	Linear trend $p = 0.19$
Urban/rural location		
Urban	Ref.	Ref.
Mixed urban	1.22 (0.94−1.60); $p = 0.14$	1.57 (0.83−2.99); $p = 0.17$
Mixed rural	0.93 (0.60−1.45); $p = 0.75$	1.01 (0.35−2.92); $p = 0.99$
Rural	1.11 (0.71−1.72); $p = 0.65$	1.53 (0.62−3.75); $p = 0.36$
Number of windows facing on the road		
0	Ref.	Ref.
1	0.97 (0.74−1.28); $p = 0.84$	0.59 (0.30−1.13); $p = 0.11$
2	1.00 (0.75−1.34); $p = 0.99$	0.95 (0.50−1.82); $p = 0.88$
3+	0.91 (0.59−1.42); $p = 0.69$	1.58 (0.68−3.71); $p = 0.29$
Local elements of road traffic conditions		
Neither traffic lights nor trucks	Ref.	Ref.
Trucks	1.02 (0.75−1.39); $p = 0.91$	1.96 (1.05−3.65); $p = 0.03$
Traffic lights	0.91 (0.57−1.45); $p = 0.68$	1.82 (0.70−4.71); $p = 0.21$
Both traffic lights and trucks	1.76 (1.03−3.01); $p = 0.04$	6.35 (2.59−15.6); $p = 0.0001$

Analyses adjusted for: age, sex, region, parental education, parental smoking.

for the combined variable including traffic lights and frequent passage of trucks (OR: 6.35; 95% CI 2.59–15.60, based on 8 exposed cases). No statistically significant ORs for AnLL were observed for urban/rural location and number of windows facing the road, while a trend was suggested (but was not statistically significant) with increasing Main Roads Length categories. Floor level (basement and level 1 vs higher levels), the interviewee evaluation of traffic zone (high, intermediate, low), the road size, and the number of bus lines did not provide evidence of association for either ALL or AnLL and were not included in the final logistic regression models. Parental exposure to solvents showed an independent association, but it was not a confounder and, therefore, it was not included as a covariate in the logistic regression models.

Similar results were observed considering the house where the child lived at birth, that reflects environmental exposure experienced during foetal and early life. In particular, the borderline upward trend in AnLL risk with increasing main roads length and the association with the combination of traffic lights and truck traffic were confirmed (Table 4).

The additional analyses focused on the house where the child spent the longest part of life (Supplementary Table 2) and restricted to the house where children spent more than 50% of their life (Supplementary Table 3) confirmed the results.

For the house at birth and the house most exposed we also analyzed the association in the group of Myeloid leukemia (FAB: M1 and M2), that confirmed the results presented for the AnLL category and showed higher ORs for the category ''traffic lights & truck passage''. OR was 12.47 (3.42–45.40) for the house most exposed and 10.94 (2.79–42.88) for the house at birth.

Sensitivity evaluation analyses were conducted with stratification by sex, age at diagnosis (0–4 vs. 5 and older) and broad area of residence (Northern regions vs. other regions), as well as after the inclusion also of the areas excluded from our previous analyses (19): no relevant differences were observed (data not presented).

Discussion

The association of childhood leukemia with traffic pollution has been considered in a large number of studies from 1989 onwards (28), with results not entirely consistent and with little information regarding leukemia subtypes (14,29). We used the data of the Italian SETIL case-control study to explore the risk of childhood leukemia subtypes associated to exposure to vehicular traffic. An increase in risk was observed for AnLL with indicators of exposure to traffic pollutants; for ALL an increased risk was also observed for the same exposures, but of lower magnitude. In particular, the risk was associated to the report of closeness of the house to traffic lights and to the passage of trucks. The association was shown also in the analyses limited to AML. Stratified analyses and the analyses in respect to the house in different period of life did not show relevant variations.

Results of our study are consistent with the associations shown in recent meta-analyses on childhood leukemia and

Table 4. SETIL study on road traffic exposure and childhood leukemia. Risk of ALL and AnLL was analyzed using an Unconditional Logistic Regression model including a set of 'a priori' defined variables describing traffic exposure and confounders. The analysis was conducted with consideration of the house at birth

	ALL	AnLL
House at birth	**OR; *p***	**OR; *p***
Main Roads length in a 500 m radius		
T1	Ref.	Ref.
T2	0.92 (0.72–1.18); $p = 0.51$	1.57 (0.90–2.71); $p = 0.11$
T3	0.92 (0.60–1.42); $p = 0.70$	2.00 (0.78–4.88); $p = 0.15$
	Linear trend $p = 0.53$	Linear trend $p = 0.07$
Urban/rural location		
Urban	Ref.	Ref.
Mixed, urban	1.24 (0.95–1.63); $p = 0.12$	1.62 (0.89–3.10); $p = 0.11$
Mixed, rural	0.92 (0.59–1.44); $p = 0.72$	1.04 (0.36–2.96); $p = 0.95$
Rural	1.13 (0.72–1.77); $p = 0.58$	1.33 (0.54–3.25); $p = 0.54$
Number of windows facing on the road		
0	Ref.	Ref.
1	1.01 (0.76–1.33); $p = 0.97$	0.50 (0.25–0.97); $p = 0.04$
2	1.11 (0.83–1.49); $p = 0.49$	1.07 (0.57–2.01); $p = 0.83$
3+	0.89 (0.56–1.41); $p = 0.62$	1.51 (0.62–3.64); $p = 0.36$
Local elements of road traffic conditions		
Neither traffic lights nor trucks	Ref.	Ref.
Trucks	1.03 (0.75–1.41); $p = 0.87$	1.72 (0.91–3.25); $p = 0.10$
Traffic lights	1.03 (0.65–1.62); $p = 0.91$	1.00 (0.33–3.01); $p = 0.99$
Both traffic lights and trucks	1.34 (0.74–2.43); $p = 0.34$	5.18 (2.06–13.02); $p = 0.0005$

Adjusted for: age, sex, region, parental education, parental smoking.

traffic related exposure, albeit it must be noticed that published literature is not completely concordant. Boothe et al. (14) included 7 studies on childhood leukemia and exposure to residential traffic in the postnatal period published in 1989−2010, and estimated a meta-analytical OR of 1.53 (95% CI: 1.12−2.10) for postnatal exposure, not distinguishing by leukemia type. In their meta-analysis, Filippini et al. (15) included 11 different studies on childhood leukemia, of which 4 provided data for ALL and 2 for AnLL. They computed a meta-OR of 1.07 (95% CI 0.93−1.24) for all leukemias, with marginal differences by subtype (ALL: 1.25; 95% CI 0.92−1.69. AnLL: 1.08; 95% CI 0.53−2.19). The analysis for AnLL included two studies reporting results for traffic density: Amigou et al. (30) observed a non statistically significant increase of risk with increasing traffic density (OR = 2.10; 95% CI: 0.60−7.32), while Heck et al. (31) did not observe an excess (OR = 0.89; 95% CI 0.79−1.00). Carlos-Wallace et al. (16) included 12 studies in a meta-analysis on traffic related benzene exposure and childhood leukemia and estimated an OR = 1.48 (95% CI: 1.23−1.78) for all leukemia types. They observed a stronger association for Acute Myeloid Leukemia (4 studies; OR = 2.07; 95% CI: 1.34−3.20) than for Acute Lymphoblastic Leukemia (7 studies; OR = 1.49; 95% CI 1.20−1.84).

A few recent studies were not included in those metanalyses. Houot et al. (32) in the GEOCAP study in France, analyzed risk of leukemia in relation to proximity to heavy traffic roads and to model-based benzene exposure, using a geocoded estimation of exposure of all leukemia cases and of a sample of controls. They observed little evidence of association for ALL. On the contrary, the analysis of AML risk showed a significant upward trend in relation to major roads length in the surroundings and to benzene concentration in environmental air. In a Swiss cohort, Spycher et al. (33) observed a significant increase in the risk of childhood leukemia (all types and ALL) with proximity to highways, but they did not conduct a separate analysis of AnLL. No association of childhood leukemia with road density was observed by Janitz et al. (34), while an increasing risk was observed by Symanski et al. (35) in Texas.

Although the residential stability of the majority of subjects precluded more detailed analyses, our analyses suggest that postnatal exposures might convey a higher risk than those associated with residence at birth, in agreement with the results of the metaanalysis by Carlos-Wallace et al. (16).

We cannot disentangle from our study data the effect of the different components of traffic exposure. The interview questions aimed at describing the area around the house in respect to traffic pollution. In particular the question regarding the frequent observation of trucks aimed at obtaining a general indication of heavy traffic but cannot be taken as a direct indication of association with Diesel exhaust rather than with benzene or other pollutants. Benzene is of special interest, however, because of the known leukemogenic effect (13). Clear indication exists of personal exposure to benzene following road traffic exposure, also from studies carried out in Italy. In a population based study, urinary benzene concentration was found to be significantly elevated among adult urban residents in relation to traffic emissions (36). Time for commuting to work by car and residence in urban areas were significant predictors of urinary benzene excretion, more than self reported traffic density around the residence (37). A strong correlation was observed between benzene biomarkers and airborne benzene levels among children in a pilot study conducted within the framework of the SETIL project (18).

Strength of the SETIL study include the large size, the population based case-control study including a large section of Italian population (recruitment in 14 out of 20 Italian regions), the collection of incident cases by a clinical-based national registry of childhood neoplasm with complete coverage for the diseases and age of interest (20). Cases were confirmed at the central AIEOP laboratory. Age range (0−10) was chosen under the assumption that until 10 years of age parents are better informed about child exposure, while in age 11−14, corresponding to the intermediate school and early adolescence, child's social life may cause exposures the parents don't know. Participation rate was almost complete for the leukemia cases. For the controls the population-based design was pursued sampling subjects from the official rosters of the National Health Service, that covers the entire Italian population. Albeit participation of families of controls was not complete (70.8%), it was similar or higher than the results observed in other population based studies on the topic (17). The information was based on interview of parents. The timing of the interview was decided with the contribution of attending clinicians, to avoid the most stressful periods after diagnosis. Great attention was put in the preparation of interviewers, as interviews had to take place always at home because of the interest in conducting ELF-MF measurements. This precluded the possibility of conducting blind interviews but gave the interviewer the opportunity to interact with the interviewee and avoid misclassification of the house characteristics. All the activities following the interview, in particular coding and geocoding were conducted blindly. The information consistency between questionnaire results and objective information on exposure was tested in the pilot study. Analyses of the prediction of questionnaire answers stating high exposure conditions showed a positive predictive value of about 100% for benzene outdoor concentration over the median exposure. Moreover, the study focus was more on the ELF-EMF, a topic that was hotly debated at the time of the study, while less attention was put in the media on traffic exposure, making information (recall) bias less likely. Recall bias cannot be excluded, however the results show a difference by type of leukemia and the association was specific for AnLL and

AML in particular, while recall bias is expected to act uniformly. Participation in the study was different for cases and controls making participation bias possible: it was evaluated by Lagorio et al. (18) observing that outdoor benzene levels were lower among participant controls compared with non-participants, but did not differ between participant and non-participant cases; the direction of the bias depended on the cut-point chosen to distinguish exposed and unexposed.

The SETIL study size was more limited for analyses by leukemia type, in particular when AnLL or AML cases were considered. Therefore, a chance finding cannot be discarded, but we notice the consistency with numerous reports in the literature, the internal consistency of different analyses and specificity of the effect that increases for AML. Even if the number of exposed subjects is not large, it will contribute to future meta-analyses and pooled studies.

The final statistical model was kept redundant as we wanted to keep in the analysis not only the house characteristics but also an objective evaluation of the road traffic in the area, given by the Main Roads Length in a 500 m radius. However, some of the information collected at interview were selected out because no association was observed: in particular the interviewee evaluation of road traffic in the area of residence or possible source of pollution in the area and the number of bus lines. Indirectly the null association with these variables collected at the interview is a confirmation that recall bias was not a major cause of the observed results.

Several sensitivity analyses were conducted, in particular the role of exposure in different periods of life was tested, with analyses focused on the house at birth, on the house most exposed and on the house where the child spent most part of life. Additional analyses (not shown in detail) evaluated the possible differences of effects after stratification by child or residential characteristics. None of these analyses showed relevant differences. However it must be remembered that most children lived all life in the same house and therefore the power to analyze the effect of exposure in different periods of life was limited.

The relation of childhood leukemia and traffic pollution had been investigated in the SETIL study with special reference to traffic indicators and estimates of pollutants, with little evidence of association (19). The two analyses used different methodologies and different data. The first study focused on model estimates of exposure and used questionnaire data on house characteristics only to a limited extent. Here we aimed to investigate in greater details the local conditions of the residence area and of the house, together with a broad description of the area provided as the Main Roads Length in a 500 metres radius. Moreover the first study did not investigate on AnLL. It is not unexpected therefore that the investigation of more specific exposure conditions and leukemia type provide a different insight.

Conclusion

Our results from the SETIL study provide some support to the association of traffic related exposure and risk for AnLL, but at a lesser extent for ALL. Our conclusion highlight the need for leukemia type specific analyses, as the pool of different leukemia types may mask type specific associations.

Results support the need of controlling exposure from traffic pollution, even if knowledge is not complete, under the framework of a precautionary attitude (38). SETIL study period was before the more stringent regulations of vehicle emissions, leading to likely levels of exposure higher than current ones in EU countries but not in the countries with less stringent regulations.

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Supplementary Data

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.arcmed.2017.02.001.

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