



## Childhood leukaemia risk and residential proximity to busy roads

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### ABSTRACT

**Background:** Current evidence suggests that childhood leukaemia can be associated with residential traffic exposure; nevertheless, more results are needed to support this conclusion.

**Objectives:** To ascertain the possible effects of residential proximity to road traffic on childhood leukaemia, taking into account traffic density, road proximity and the type of leukaemia (acute lymphoid leukaemia or acute myeloid leukaemia).

**Methods:** We conducted a population-based case-control study of childhood leukaemia in Spain, covering the period 1990–2011. It included 1061 incidence cases gathered from the Spanish National Childhood Cancer Registry and those Autonomous Regions with 100% coverage, and 6447 controls, individually matched by year of birth, sex and autonomous region of residence. Distances were computed from the respective participant's residential locations to the different types of roads and four different buffers. Using logistic regression, odds ratios (ORs) and 95% confidence intervals (95% CIs), were calculated for four different categories of distance to roads.

**Results:** Cases of childhood leukaemia had more than three-fold increased odds of living at < 50 m of the busiest motorways compared to controls (OR = 2.90; 95%CI = 1.30–6.49). The estimates for acute lymphoid leukaemia (ALL) were slightly higher (OR = 2.95; 95%CI = 1.22–7.14), while estimates for cases with the same address at birth and at diagnosis were lower (OR = 2.40; 95%CI = 0.70–8.30).

**Conclusions:** Our study agrees with the literature and furnishes some evidence that living near a busy motorway could be a risk factor for childhood leukaemia.

### 1. Background

Air pollution is a significant threat to human health, and children are at increased risk because of their immature lungs and immune systems. Traffic emissions are a major source of urban air pollution, mainly in cities, producing particulate matter, metals, and gaseous pollutants, including carbon monoxide, ozone, nitrogen dioxide, aldehydes, benzene, 1,3 – butadiene, and polycyclic aromatic hydrocarbons (Jacobson, 2002; Martins et al., 2012). Many of these substances are listed as carcinogenic by The International Agency for Research on

Cancer (IARC); for instance PM<sub>2.5</sub>, benzene, diesel exhaust, benzo[a]pyrene (B[a]P) and polycyclic aromatic hydrocarbon [PAH]) are classified as Group 1 carcinogenic agents; and petrol/gasoline engine exhaust as Group 2B (International Agency for Research on Cancer, 2013). Benzene merits special mention as it is already classified as carcinogenic for leukaemia in adults by the IARC (International Agency for Research on Cancer, 1982).

Concern about the effect of exposure to traffic emissions on childhood health has motivated numerous studies in various countries in Europe, North America and Asia, among them many have focused on

**Abbreviations:** ALL, acute lymphoid leukaemia; AML, acute myeloid leukaemia; RETI-SEHOP, Spanish Registry of Childhood Tumours; FC, Navteq cartography Functional Class; ORs, odds ratios; 95% CIs, 95% confidence intervals; IARC, International Agency for Research on Cancer; PM<sub>2.5</sub>, ambient concentrations of particulate matter of < 2.5 μm aerodynamic diameter; IPPC, Integrated Pollution Prevention and Control; E-PRTR, European Pollutant Release and Transfer Register

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cancer outcomes, including a number of systematic reviews and meta-analyses (Boothe et al., 2014; Carlos-Wallace et al., 2016; Filippini et al., 2015; Raaschou-Nielsen and Reynolds, 2006). The main conclusion of these reviews is that the literature supports a link between ambient exposure to traffic pollution and childhood leukaemia risk. After the publication of the more recent review (2015) three more studies from Switzerland, Italy and France have been published supporting this hypothesis (Houot et al., 2015; Magnani et al., 2016; Spycher et al., 2015).

Among childhood cancers, leukaemia is the main group with around a third of all diagnosed cases worldwide (Peris-Bonet et al., 2010; Steliarova-Foucher et al., 2017). In Spain, the overall age-adjusted incidence rate (ASRw) of leukaemia was 47.9 cases per million children in children and 23.8 in adolescents (Marcos-Gragera et al., 2017). Within leukaemia subtypes, acute lymphoid leukaemia (ALL) is the most common type of leukaemia in young children and accounts for three-quarters of the cases. The second most frequent is acute myeloid leukaemia (AML) with > 15% of the cases and the remaining cases are distributed between minor causes (Marcos-Gragera et al., 2017). Most of the risk factors remain unknown (Inaba et al., 2013) and only a few risk factors are suspected, such as exposure to ionizing radiation (Richardson et al., 2005) or inheriting cancer-predisposing genes (Stieglitz and Loh, 2013), the hypothesis of delayed infections has also been proposed (Greaves, 2006). With respect to environmental risk factors, as we just mentioned, different meta-analyses and individual studies suggest that traffic-related air pollution exposure could be an important factor (Boothe et al., 2014; Carlos-Wallace et al., 2016; Filippini et al., 2015; Houot et al., 2015; Magnani et al., 2016; Raaschou-Nielsen and Reynolds, 2006; Spycher et al., 2015).

In our previous studies, we analyzed the influence of residing in urban areas, residential proximity to industries and residential proximity to crops on childhood leukaemia incidence (García-Pérez et al., 2015; Gómez-Barroso et al., 2016). We think that the influence of residential traffic exposure could be one of the missing pieces that help us to explain part of the variability in the distribution of leukaemia incidence. The aim of this project was to assess the possible effects of residential proximity to road traffic on childhood leukaemia, taking into account traffic density, road proximity and the type of leukaemia: ALL or AML.

## 2. Methods

### 2.1. Data

This paper is part of a population-based case-control study which aims to analyse the effect of environmental risk factors on childhood cancer using the geographic locations of the cases and controls in Spain. Specific details of the design of the study can be found in the previous papers from the project (García-Pérez et al., 2015; Ramis et al., 2015). For the reader's convenience, a summary of the design can be found below.

For the study we used data from children aged 0 to 14 with diagnoses of leukaemia – covering 1061 cases. Incidence cases were registered by the Spanish Registry of Childhood Tumours (RETI-SEHOP). RETI-SEHOP collects information from cases of childhood cancer from hospitals' paediatric oncology units over all Spain (Peris-Bonet et al., 2017). The estimated national coverage of the childhood cancer cases in this register is over 90%; however, this coverage is estimated to be 100% for the regions included in the study. The period studied went from 1996 to 2011 and the area under study covered five autonomous regions: the Autonomous Region of Madrid, the Basque country, Aragon, Navarre, and Catalonia. Fig. 1 shows the exact location of these regions within Spain.

As a control group (6447 children), we used a random incidence-density sample from the at-risk population extracted from the complete Birth Registry of the Spanish Statistical Office (Instituto Nacional de

Estadística, INE). Controls were individually matched to cases by sex, year of birth and autonomous region of residence, in a ratio of 6:1. These matching conditions were quite open and allowed for the interchange of controls between different cases.

We geocoded the home addresses of the cases at the moment of diagnosis; these addresses were included in the RETI-SEHOP database. For the controls we geocoded the mother's home address as listed on the birth certificate (included in the Birth Registry of the INE). We successfully geocoded 87% of addresses for the cases. The remaining 13% were fairly uniformly distributed across the different regions and, therefore, we did not think the data were biased in this sense. We only selected controls for the georeferenced cases. From the initial sample we were able to get valid coordinates for 98% of the controls. Given that the number of failures was very small, we decided to select more controls to replace this 2%, and we geocoded and validated this last group to match 6 controls with valid coordinates to each case. As we had all the entries from the Birth Registry, we used a matching strategy to find cases with the same address at the time of birth (birth certificate) and diagnosis (included in the RETI-SEHOP register) to perform a sensitivity analysis to evaluate the potential for misclassification due to residential mobility.

#### 2.1.1. Traffic density

Annual average daily traffic, abbreviated AADT, is a measure used primarily in transportation planning and transportation engineering. Traditionally, it is the total volume of vehicle traffic of a highway or road for a year divided by 365 days (expressed in vehicles per day). AADT is a simple useful measurement of how busy a road is. To be able to explore the effect of exposure to traffic density on childhood leukaemia incidence, we calculated the AADT for all roads within our studied regions. To compute the AADT we merged Navteq cartography, the official cartography of the Spanish Ministry of Public Works and Transport (Fomento, 2016). We considered the road classification of Navteq cartography and the traffic-density measurements provided by the Ministry of Public Works' cartography. Navteq cartography was also used to estimate effect of exposure to road traffic exhaust fumes on childhood leukaemia in the French study ESCALE (Amigou et al., 2011). The cartography classifies the roads into 5 Functional Classes (FC) that define a hierarchical network used to determine a logical and efficient route for travellers (Table 1). For this paper we named the five FCs as follow; FC1 and FC2 for motorways, FC3 for arterial roads, FC4 for main streets and FC5 for streets in neighbourhoods, or those with less traffic still. This approximation was also used in the multicentre ESCAPE project (Beelen et al., 2013).

To assign a measurement of exposure to traffic density to every child in the study, we built four buffers around each home address and computed the traffic density within the buffers. To take account of the different scenarios, we combined the road types (FC) into three groups: FC12 included FC1 and FC2 (motorways); FC123 included FC1, FC2 and FC3 (motorways and arterial roads); and, finally, FC1234 which included FC1, FC2, FC3 and FC4 (motorways, arterial roads and main streets). We defined buffer zones' radii in reference to each participant's home – and at the following distances (D): 50 m, 100 m (Fig. 2), 200 m and 500 m. We used FC5 to define the reference areas. Therefore, we ended up with 12 variables, 3 groups of road type (FC) and 4 distances (D), each accounting for the traffic density of a specific road type group (FC) within a buffer of a defined distance (D) centred on the home address of the child.

We could not assume that the effects of traffic density on cancer incidence are linear; thus we categorized the variables to allow for non-linear effects. To begin with, we defined the reference group (Category = 0) as those children living in areas with only FC5 roads within buffers of 200 m from their home addresses. This definition of a reference area guaranteed a constant reference group through the different variables. Then, to create each of the 12 categorical variables of traffic density we followed the following steps:

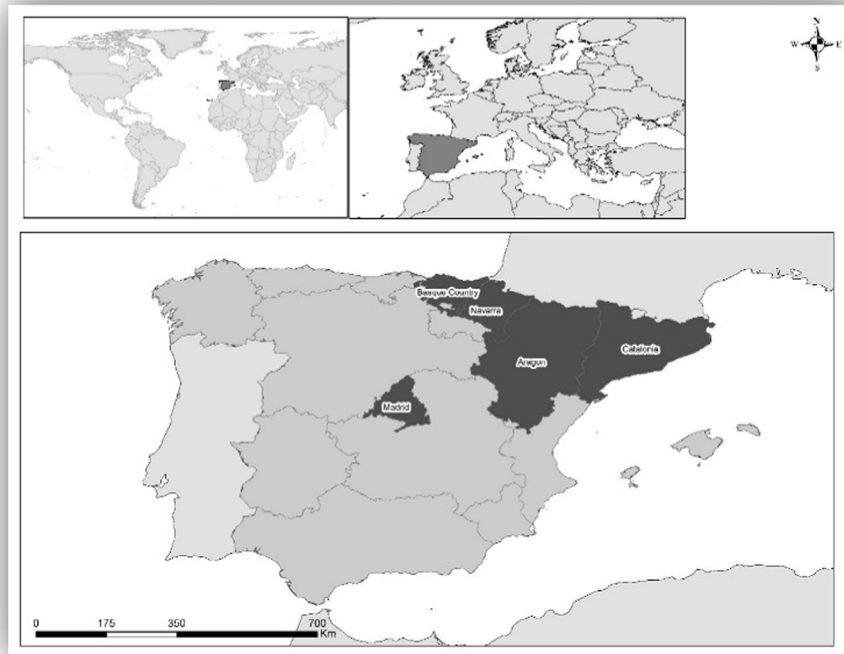


Fig. 1. Studied regions in dark grey.

1. We calculated the quartiles of the variable using only the controls that were outside of the reference category. Categories = 1, 2, 3 and 4.
2. We classified every children (cases and controls) that were outside of the reference category between the four categories defined in the previous step.
3. When studying 50 and 100 m distances, children not exposed to FC1234 at those distances but exposed to roads at up to 200 m were classified in Category = 5, as an intermediate group.

In summary, each variable was defined as categorical with 5 or 6 levels. Q0 = reference group, Q1 = first quartile group (lowest traffic density), Q2 = second quartile group, Q3 = third quartile group, Q4 = fourth quartile group (highest traffic density) and, for distances from 50 to 200 m, Q5 = intermediate group.

According to the literature, our previous analyses and the availability of data, we decided to include three covariates in the models which were not related strictly to traffic-related air pollution:

### 2.1.2. Crop exposure

In another previous study we found a positive association between exposure to crops and childhood leukaemia. To be able to assess this

effect, we built a specific index of exposure to crops, Global Crop Index (Gómez-Barroso et al., 2016). The Global Crop Index accounts for the percentage of cultivated land in a 1-km buffer around each child's residence. We used the CORINE Land Cover (European Environment Agency, 15ADb) to obtain the land use data and we computed the index for all the participants.

### 2.1.3. Socio-economic status

Socio-economic status is an important factor related to childhood cancer (Kehm et al., 2017). Although we did not have individual information about socio-economic status, we still decided to include it in the model. We took the data at census-tract level from the 2001 Census and we assigned the socio-economic status of the corresponding census tract of residence to each child (Ramis et al., 2017). The used variable was denominated “socioeconomic condition” (SES) and it was based on the occupation of the head of the family. This variable ranged from 0.46 to 1.57; lower values were assigned to worse socio-economic status and higher values to better socioeconomic status.

### 2.1.4. Industrial pollution

In a previous study, we found a positive association between exposure to industrial pollution and childhood leukaemia (García-Pérez

Table 1

Definition of the 5 FCs by Navteq and the corresponding traffic counts per day in each area.

Functional class	Description	Traffic counts per day		
		Rural area	Urban area	Highly dense urban area
FC1	Roads that allow for high volume, maximum speed traffics movement between and through mayor metropolitan areas	10,000	30,000	100,000
FC2	Roads that are used to channel traffic to FC1 road for travel between and through cities in the shortest amount of time	6000	20,000	50,000
FC3	Roads which interconnect FC2 roads and provide a high volume of traffic movement at a lower level of mobility FC2	4000	15,000	30,000
FC4	Roads that provide a high volume of traffic movement at moderate speeds between neighbourhoods	2000	6539	15,000
FC5	Roads with the lowest level of traffic	50	300	2500

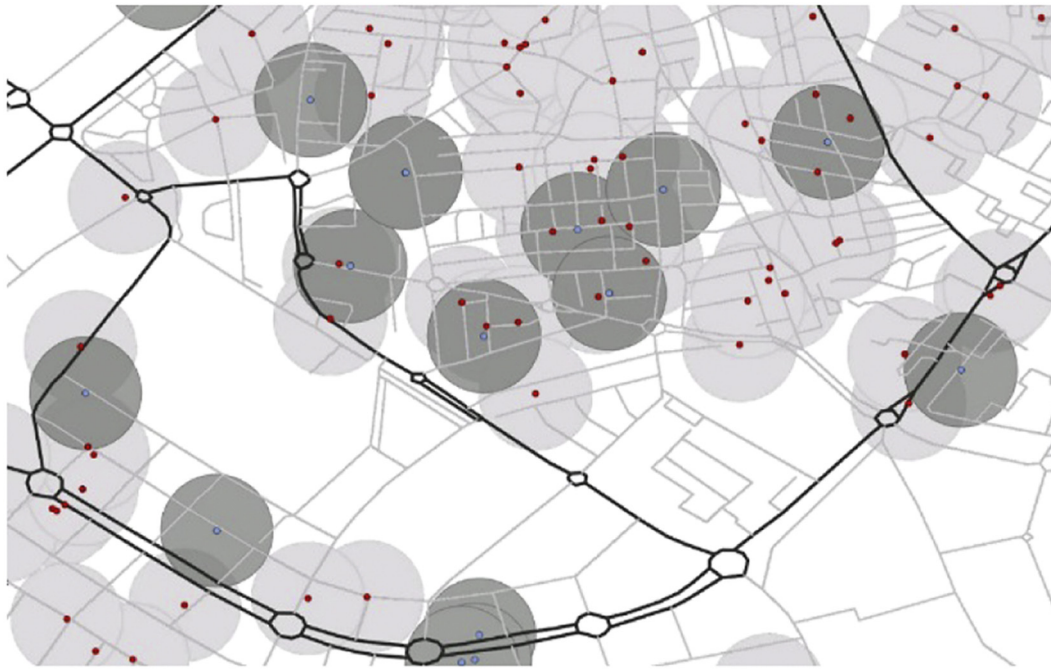


Fig. 2. An example of the 100-metre buffers; controls (red dot and light grey buffer) and cases (blue dot and dark grey buffer). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

et al., 2015). Industrial pollution and traffic pollution share many substances. In order to control the effects of industrial pollution, we included a specific variable in the model. Data for the exposure to industrial pollution was extracted from the industrial database (industries governed by IPPC and facilities pertaining to industrial activities not subject to IPPC but included in the E-PRTR) provided by the Spanish Ministry for Agriculture, Food & Environment in 2009, which includes information on the geographic location and industrial pollution emissions of all industrial plants in Spain. We defined a 2.5 km buffer around the industry to calculate cases' and controls' exposure.

## 2.2. Statistical analysis

In order to estimate the odds ratio and 95% confidence intervals (95% CIs) associated with exposure to traffic density, we fitted mixed multiple unconditional logistic regression models, including the crop exposure, socio-economic status and industrial pollution covariates and the region as a random effect. We fitted an initial unadjusted model that included only the random effect, then a second model including also crop exposure and a final model with all covariates. We used unconditional logistic regression rather than conditional logistic regression because sex and year of birth were simple matching factors and we had a large studied population (1061 cases and 6447 controls) that hindered sparse data problems (Pearce, 2016). We did not adjust for multiple testing in order to avoid an increase of the type II error that would hamper the finding of true associations (Rothman et al., 2012). We used the Akaike information criterion (AIC) for model selection.

We used R library lmer4 (Bates et al., 2015) for statistical analysis, and ArcGIS 10.0 to estimate the distance from each participant's home to any roads and to build the indexes.

## 3. Results

The analysis covered 1061 cases and 6447 controls. Table 2 shows the distribution of the characteristics of the studied children; among them, 58% were boys and 42% were girls. The distribution by autonomous region of residence was the following: Aragon (5.6%), Catalonia (40%), Basque Country (11%), Madrid (40%) and Navarre (4%). There

were 238 cases exposed to crops (22%) and 823 controls (13%). The percentage of children with at least one industrial factory within 2.5 km was 59% for cases and 61% for controls. Regarding the histologic type, 79.7% of the cases were lymphoid leukaemia, 16.4% were acute myeloid leukaemia and remaining subtypes account for 4%. The mean age at diagnosis was 4.5 years old, with cases at all ages, from 0 to 14.

We were able to identify 473 cases with exactly the same address at birth and at diagnosis, the 45% of the cases. For the remaining 55% we did not find exactly the same address. Nonetheless, the identify cases had fairly similar characteristics to the full group of cases as it can be seen in Table 2.

We fitted a total of 12 models by group of cases to estimate the ORs for each of the traffic density and distance variables. Tables 3, 4 and Tables S1, S2, S3 and S4 of the Supplementary material present the resulting ORs and 95% CIs. Each OR estimates the odds of exposure between the cases compared to controls for the quartile Q of road type FC at distance D and children in the reference group (children who did not have roads of type FC1234 in the buffer of 200 m around their home address).

Table 3 shows the ORs for total leukaemia and exposure to motorways (FC<sub>12</sub>). Estimations from the three models were very similar and according to the AIC the best models were those adjusted by crop exposure only. We observed that the ORs for exposure to motorways showed increased odds for cases in Q4 and Q3 at any distance and that these odds increased with decreasing distance for both Q4 and Q3 (Fig. S1, Supplementary material). However, only the OR associated to D<sub>50</sub>Q4 was statistically significant. We did not observe differences in motorway exposure for the less busy motorways (Q1) between cases and controls. The same occurred with exposure to FC<sub>123</sub> and FC<sub>1234</sub> where we did not observe differences either (Table S1, Supplementary material).

Looking at individual results, the highest OR, and the only statistically significant, was that associated to residence at < 50 m of the busiest motorways (Q4 of FC<sub>12</sub> at D<sub>50</sub>), with odds of exposure 2.90 times higher for cases than for controls.

The crop-index OR for the second model was 1.13 (95%CI = 1.06,1.19), meaning that an increase of 10% in crop surface around the home address of the child produces a 13% increase in the



**Table 2**  
Characteristics of childhood leukaemia – cases, controls and the sensitivity group\* (cases with the same address at birth and at diagnosis).

Characteristics	Cases		Controls		Cases = address*	
	(n = 1061)		(n = 6447)		(n = 473)	
	n	%	n	%	n	%
Sex						
Male	615	58	3742	58	255	54
Female	446	42	2705	42	218	46
Age at diagnosis, mean (SD)	4.5	3.1	x	x	3.9	
Autonomous region						
Catalonia	418	39	2586	40	156	34
Basque Country	118	11	709	11	68	14
Aragon	60	6	358	6	40	8
Navarre	41	3	245	3	21	4
Madrid	424	40	2549	40	188	40
Socio-economic status (mean)	1.08		1.08		1.08	
Industrial pollution exposed	628	60	3937	61	291	62
Crop exposed (Crop Global Index > 0)	238	22	823	13	104	22
Reference category	247	23	1420	22	100	21
Histologic type						
Lymphoid Leukaemia	846	80			363	77
Acute myeloid leukaemia	174	16			95	20
Chronic myeloproliferative diseases	12	1			3	1
Myelodysplastic syndrome and other Myeloproliferative diseases	16	2			7	1
Unspecified and other specified Leukaemia	14	1			5	1

**Table 3**  
For total leukaemia cases and motorways (FC\_12). Number of cases and controls in the category. OR and 95% CI for quartiles (Q) compare to the reference group, for the four distances (D): 50, 100, 200 and 500 m. Unadjusted and adjusted models.

Dist_Quantil	Cases/ controls	Unadjusted	Adjusted for crops exposure	Adjusted for crops, socio- economic status and industrial pollution exposure
		OR(95%CI)	OR(95%CI)	OR(95%CI)
Reference	247/ 1420	–	–	–
D.50_Q4	9/19	2.86(1.27,6.40)	2.90(1.30,6.49)	2.72(1.22,6.09)
D.100_Q4	13/62	1.26(0.68,2.33)	1.27(0.69,2.36)	1.21(0.65,2.23)
D.200_Q4	30/154	1.18(0.78,1.79)	1.19(0.79,1.80)	1.12(0.74,1.69)
D.500_Q4	58/344	1.03(0.75,1.40)	1.03(0.76,1.41)	0.97(0.71,1.32)
D.50_Q3	5/24	1.27(0.48,3.36)	1.27(0.48,3.37)	1.20(0.45,3.17)
D.100_Q3	9/47	1.17(0.56,2.41)	1.17(0.57,2.42)	1.10(0.53,2.27)
D.200_Q3	24/120	1.22(0.77,1.94)	1.22(0.77,1.94)	1.15(0.73,1.82)
D.500_Q3	58/290	1.22(0.89,1.67)	1.22(0.89,1.67)	1.15(0.84,1.57)
D.50_Q2	58/290	0.62(0.14,2.67)	0.62(0.14,2.67)	0.61(0.14,2.62)
D.100_Q2	11/50	1.32(0.68,2.58)	1.32(0.68,2.57)	1.26(0.65,2.46)
D.200_Q2	24/117	1.24(0.78,1.97)	1.24(0.78,1.96)	1.18(0.74,1.87)
D.500_Q2	38/299	0.77(0.53,1.11)	0.76(0.53,1.10)	0.73(0.51,1.05)
D.50_Q1	2/16	0.63(0.14,2.80)	0.63(0.14,2.80)	0.72(0.16,3.14)
D.100_Q1	2/350	0.32(0.08,1.33)	0.32(0.08,1.33)	0.33(0.08,1.37)
D.200_Q1	16/114	0.79(0.46,1.36)	0.79(0.46,1.35)	0.81(0.47,1.39)
D.500_Q1	43/276	0.89(0.63,1.27)	0.89(0.63,1.26)	0.90(0.63,1.27)

odds for cases compared to the controls. Estimated ORs from the full adjusted model for the covariates socio-economic status and industrial pollution exposure did not show differences between cases and controls.

We repeated the same analyses by leukaemia subtype and for the group of cases with the same address at birth and at diagnosis. Table 4 shows the results regarding exposure to motorways (FC\_12) for the adjusted for crop models. The results for FC\_123 and FC\_1234 are included in the supplementary material tables S2, S3 and S4.

The ORs for ALL were very similar to those for the total leukaemia cases, this was expected since this subtype accounted for the 80% of the cases, and nevertheless these ORs were slightly higher. For AML the number of cases in most categories was too low to obtain reliable estimations. Finally, results for the sensitivity analysis group show increased OR for most of the categories and for Q4 estimates increased with decreasing distance. However only the OR for D.50\_Q3 was statistically significant with a value of 3.28 (95%CI = 1.21,8.86).

#### 4. Discussion

In this study we investigated the effects of exposure to traffic-related air pollution on childhood leukaemia risk in several Spanish regions, taking into account different road types and different distances. Our findings support the hypothesis of association between proximity to major roads and childhood leukaemia incidence. In particular, our results showed increased ORs for cases resident in the proximity of heavily trafficked motorways compared to controls and those ORs increased at decreasing distances, suggesting a potential dose-response relationship. Our results did not show significant differences between cases and controls for proximity to arterial roads and main streets. We also found elevated ORs for cases with the same address at birth and at diagnosis. And regarding leukaemia subtype, we found high ORs for ALL but we could not obtain reliable estimates for AML due to low numbers of cases.

In our study we used type of road to define the density of vehicles per day and to assess the risk of each of these roads, and the buffers as a proxy for the concentration of traffic-related air pollution. We used different buffer distances as exposure metrics to explore potential dose-response effects. In other studies they used the concentration of NO<sub>2</sub> or benzene (Boothe et al., 2014; Carlos-Wallace et al., 2016; Filippini et al., 2015) as measure of traffic-related air pollution.

An early study from 1989 already suggested a strong association between traffic density and childhood leukemias (Savitz and Feingold, 1989). The authors reported an OR of 2.70 for children with high-traffic-density addresses in contrast with low-density addresses. In 2014 Boothe et al. published a meta-analysis that analyzed fifteen studies (Boothe et al., 2014), suggesting that leukaemia in children was

**Table 4**

Number of cases and controls in the category. OR and 95% CI for quartiles (Q) compare to the reference group, for the four distances (D): 50, 100, 200 and 500 m. Adjusted for crops exposure models.

Dist_Quantil	ALL (846)			AML (174 cases)		Cases with the same address at birth and at diagnosis (330 cases)	
	Controls	Cases	OR(95%CI)	Cases	OR(95%CI)	Cases	OR(95%CI)
Reference	1420	191	–	46	–	100	–
D.50_Q4	19	1	2.95(1.22,7.14)	0	0(0,0)	3	2.40(0.70,8.30)
D.100_Q4	58	9	1.24(0.60,2.54)	1	0.55(0.07,4.05)	8	2.05(0.95,4.42)
D.200_Q4	152	26	1.36(0.87,2.12)	1	0.21(0.03,1.53)	12	1.18(0.63,2.20)
D.500_Q4	346	49	1.12(0.80,1.57)	6	0.55(0.23,1.31)	21	0.89(0.54,1.45)
D.50_Q3	22	5	1.80(0.67,4.81)	1	1.48(0.20,11.26)	5	3.28(1.21,8.86)
D.100_Q3	48	9	1.47(0.71,3.05)	0	0(0,0)	3	0.92(0.28,2.99)
D.200_Q3	121	17	1.12(0.66,1.90)	5	1.37(0.53,3.53)	10	1.22(0.62,2.41)
D.500_Q3	286	48	1.33(0.95,1.88)	7	0.81(0.36,1.81)	23	1.26(0.78,2.03)
D.50_Q2	21	2	0.73(0.17,3.13)	0	0(0,0)	3	1.87(0.54,6.44)
D.100_Q2	79	10	1.59(0.79,3.19)	1	0.67(0.09,4.94)	7	1.93(0.85,4.41)
D.200_Q2	116	21	1.42(0.87,2.31)	3	0.85(0.26,2.78)	13	1.54(0.83,2.86)
D.500_Q2	299	27	0.70(0.46,1.07)	9	1.00(0.48,2.06)	20	0.93(0.56,1.54)
D.50_Q1	16	2	0.82(0.18,3.63)	0	0(0,0)	0	0.00(0.00,inf)
D.100_Q1	39	2	0.37(0.09,1.55)	0	0(0,0)	0	0.00(0.00,inf)
D.200_Q1	116	12	0.75(0.40,1.38)	3	0.80(0.24,2.61)	8	0.88(0.41,1.86)
D.500_Q1	278	35	0.93(0.63,1.37)	8	0.91(0.42,1.94)	25	1.18(0.74,1.88)

associated with residential traffic exposure during the postnatal period, but not during the prenatal. For the postnatal period, they reported that the weighted summary OR was 1.53 (95%CI = 1.12, 2.10), while for the prenatal period it was 0.92 (95%CI = 0.78, 1.09). Our results show fairly similar ORs for the group of children with the same address at diagnosis as at birth, and for the group with the total of cases; however, the power of these analyses is low, due to the small number of cases in the exposure categories, and we cannot rule out that postnatal exposure could have a stronger effect. In the same year 2014, Carlos-Wallace et al. published a meta-analysis on benzene exposure (Carlos-Wallace et al., 2016). Part of this analysis included fifteen studies on traffic density or traffic-related air pollution and its summary relative risk was 1.48 for all leukaemia, 1.49 for ALL and 2.07 for AML. A year later Filippini et al. published another meta-analysis which analyzed twenty-six studies (Filippini et al., 2015). The summary OR for the eleven case-control studies which used traffic density was 1.09. When the analysis was limited to those studies focusing only on ALL, the OR was 1.26. In our study we also found higher ORs when we analyzed ALL cases than when analyzing all subtypes together.

The key point in these studies is the proxies of traffic exposure used. The most common proxy used is traffic density; this has been expressed as number of vehicles per day and/or distance from major roads (Filippini et al., 2015). Another indicator used is the density and proximity to repair garages and petrol stations (Brosselin et al., 2009; Weng et al., 2009). Other proxies are levels of traffic-related pollutants that come from real measurements or models, and in these studies they have assessed pollutants such as NO<sub>2</sub> and benzene (Badaloni et al., 2013; Houot et al., 2015; Janitz et al., 2016; Weng et al., 2008). In the present study we used traffic density expressed as number of vehicles per day and distance from roads – considering as dangerous the busiest motorways, > 20,000 vehicles per day (Table 1), at < 50 m distance. Furthermore, in order to obtain a better approximation, we computed the quantiles and defined a shared reference group for all the traffic variables. Our results show that at any distance the most exposed groups, Q4 and Q3, have increased risk, though our estimated ORs are higher than the summary OR reported in the meta-analyses; but, on the other hand, they are similar to those estimated in some other individual studies. A study from the USA reported an OR of 2.70 (Savitz and Feingold, 1989); a British study reported an OR of 1.61 (Harrison et al., 1999); an Italian study reported an OR of 2.09 (Crosignani et al., 2004); and a French study reported an OR of 2.20 (Amigou et al., 2011).

In contrast, the use of traffic density as a proxy could be seen as a limitation since it does not allow us to study the effects of particular

toxins. However, in reality people are exposed to a mixture of toxins from traffic, not to isolated individual substances; in that respect, we think that this proxy is well-chosen. Traffic is a major source of ambient air pollution and the IARC classifies outdoor air pollution as carcinogenic to humans (International Agency for Research on Cancer, 2013). As mentioned at the beginning of this paper, traffic emissions include a number of harmful substances such as carbon monoxide, ozone, particulate matter, nitrogen dioxide aldehydes, benzene, 1, 3 – butadiene, polycyclic aromatic hydrocarbons, and metals.

With reference to benzene, its concentrations from motor-vehicle exhaust could be elevated along heavily-trafficked roads and streets. Children exposed to benzene experienced significantly altered blood profiles, liver enzymes, and somatic symptoms – indicating that children exposed to benzene are at a higher risk of developing hepatic or blood-related disorders (D'Andrea and Reddy, 2014). Furthermore, benzene has been listed by the IARC as a Group 1 carcinogen for leukaemia in adults due to its hematotoxicity and leukemogenicity (McHale et al., 2012; Whysner et al., 2004). Even though there are studies reporting positive association and mechanisms have been proposed, the literature is inconclusive and does not conclude that benzene exposure is linked to increased leukaemia risk in children (Pyatt and Hays, 2010). Other pollutants like carbon monoxide (Strasser et al., 2015) or particulate matters (Malagoli et al., 2015) also have been associated with leukaemia and other studies have also analyzed traffic density to measure cancer risk (Heck et al., 2013). In general, however, the literature remains inconclusive.

Another hypothesis to identify why major roads could be associated with higher risk is the speed of the cars on those roads. In 2000 Heeb et al. indicated that when the speed of the vehicles is high the catalytic converters are less effective, and consequently the cars produce more pollution such as benzene, toluene and C2-benzenes (Heeb et al., 2000).

With regard to the final model, we used AIC for selection and the best model was the one that included only exposure to crops. ORs for crop exposure were very similar to those reported in Gómez-Barroso et al. suggesting association with crop exposure reported (Gómez-Barroso et al., 2016). On the contrary, the covariates socio-economic status or industrial pollution exposure did not showed effect, however in a previous study García-Pérez et al. found relationship with industrial pollution (García-Pérez et al., 2016).

One of this study's limitations is the non-inclusion of individual data relating to possible confounding factors that might be associated with the distance, such as socio-economic variables or life-style-related factors, because of their unavailability at an individual level. Moreover,

this study uses distance to the pollution source as a proxy of exposure, assuming an isotropic model, something that could introduce a misclassification problem; this is because actual exposure is critically dependent on prevailing winds, geographic landforms and releases into aquifers. Despite this limitation, the use of many cut points for both distances and roads could be considered as ameliorating this limitation. Nevertheless, this problem would limit the capacity to find positive results but would in no way invalidate the associations found.

We did not have information about address changes between birth and diagnosis hence we could not rule out potential bias due to using the address at diagnosis for cases and address at birth for controls. According to official data in Spain, only around 1% of the children change their residence to a different province (“*Instituto Nacional de Estadística. (National Statistics Institute), n.d.*”), but we should assume that the residential mobility within provinces is higher than 1%. To overcome this limitation we tried to identify cases with the same address in the two instants. We compared the two registries and we were able to identify 473 cases with the exact same address at birth and at diagnosis, the 45% of the cases. However we could not know if the remaining 55% of the cases moved between birth and diagnosis or not due to differences in the recording between the RETI and the Birth Registry. Nevertheless, the results from the sensitivity analysis (Table 4) showed not much different to those from the total number of cases (Table 3). Furthermore, we performed a descriptive analysis of the characteristics of the two groups (Table 2) and we did not find differences in the variables that could make us think that the groups were different. We could conclude that there is not significant misclassification or bias due to residence mobility.

A principal strength of our study is the large control group (6 controls per case), which provides a much more realistic image of the spatial distribution of the at-risk population. The controls were randomly selected from birth certificates without the exclusion of the cases from the pool, what opened up the possibility of having the same child case and as control; nevertheless (Janitz et al., 2016). Moreover we could not know if children from the control group were diagnosed with cancer after the studied period; but then again, the exclusion of the forthcoming cases from the control group could have biased the results (Grimes and Schulz, 2005). The control group should give a clear view of the spatial distribution of the population at risk and should have the same risk of exposure as the cases. We matched the controls by sex, year of birth and region of residence to account for the temporal and regional variations in the child population.

## 5. Conclusion

In conclusion, despite having imprecise estimates, our study agrees with previous literature and suggests that living in the proximity of motorways could be a risk factor for childhood leukaemia. Yet, further studies should be carried out to support this conclusion. In any case the authors agree with Whitehead et al. (2016) when they assert that to protect children's health, it is prudent to initiate programs designed to reduce exposure to quite probable leukaemia risk-factors rather than to suspend judgment until no uncertainty remains. Primary prevention programs for childhood leukaemia would also result in the significant co-benefits of reductions in other adverse health outcomes that are common in children, such as detrimental effects on neurocognitive development (Clifford et al., 2016).

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The views expressed are those of the authors and not necessarily those of the Carlos III Institute of Health.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envint.2018.08.056>.

## References

- Amigou, A., Sermage-Faure, C., Orsi, L., Leverger, G., Baruchel, A., Bertrand, Y., Nelken, B., Robert, A., Michel, G., Margueritte, G., Perel, Y., Mechinaud, F., Bordigoni, P., Hémond, D., Clavel, J., 2011. Road traffic and childhood leukemia: the ESCALE study (SFCE). *Environ. Health Perspect.* 119, 566–572. <https://doi.org/10.1289/ehp.1002429>.
- Badaloni, C., Ranucci, A., Cesaroni, G., Zanini, G., Vienneau, D., Al-Aidroun, F., De Hoogh, K., Magnani, C., Forastiere, F., 2013. Air pollution and childhood leukaemia: a nationwide case-control study in Italy. *Occup. Environ. Med.* 70, 876–883. <https://doi.org/10.1136/oemed-2013-101604>.
- Bates, D., Mächler, M., Bolker, B., Walker, S., 2015. Fitting linear mixed-effects models using lme4. *J. Stat. Softw.* 67, 1–48. <https://doi.org/10.18637/jss.v067.i01>.
- Beelen, R., Hoek, G., Vienneau, D., Eeftens, M., Dimakopoulou, K., Pedeli, X., Tsai, M.Y., Künzli, N., Schikowski, T., Marcon, A., Eriksen, K.T., Raaschou-Nielsen, O., Stephanou, E., Patelarou, E., Lanki, T., Yli-Tuomi, T., Declercq, C., Falq, G., Stempfelet, M., Birk, M., Cyrys, J., von Klot, S., Nádor, G., Varró, M.J., Dedele, A., Gražulevičiene, R., Molter, A., Lindley, S., Madsen, C., Cesaroni, G., Ranzi, A., Badaloni, C., Hoffmann, B., Nonnemacher, M., Krämer, U., Kuhlbusch, T., Cirach, M., de Nazelle, A., Nieuwenhuijsen, M., Bellander, T., Korek, M., Olsson, D., Strömberg, M., Dons, E., Jerrett, M., Fischer, P., Wang, M., Brunekreef, B., de Hoogh, K., 2013. Development of NO<sub>2</sub> and NO<sub>x</sub> land use regression models for estimating air pollution exposure in 36 study areas in Europe - the ESCAPE project. *Atmos. Environ.* 72, 10–23. <https://doi.org/10.1016/j.atmosenv.2013.02.037>.
- Booth, V.L., Boehmer, T.K., Wendel, A.M., Yip, F.Y., 2014. Residential traffic exposure and childhood leukemia: a systematic review and meta-analysis. *Am. J. Prev. Med.* 46, 413–422. <https://doi.org/10.1016/j.amepre.2013.11.004>.
- Brosselin, P., Rudant, J., Orsi, L., Leverger, G., Baruchel, A., Bertrand, Y., Nelken, B., Robert, A., Michel, G., Margueritte, G., Perel, Y., Mechinaud, F., Bordigoni, P., Hémond, D., Clavel, J., 2009. Acute childhood leukaemia and residence next to petrol stations and automotive repair garages: the ESCALE study (SFCE). *Occup. Environ. Med.* 66, 598–606. <https://doi.org/10.1136/oem.2008.042432>.
- Carlos-Wallace, F.M., Zhang, L., Smith, M.T., Rader, G., Steinmaus, C., 2016. Parental, in utero, and early-life exposure to benzene and the risk of childhood leukemia: a meta-analysis. *Am. J. Epidemiol.* 183, 1–14. <https://doi.org/10.1093/aje/kwv120>.
- Clifford, A., Lang, L., Chen, R., Anstey, K.J., Seaton, A., 2016. Exposure to air pollution and cognitive functioning across the life course—a systematic literature review. *Environ. Res.* 147, 383–398. <https://doi.org/10.1016/j.envres.2016.01.018>.
- Crosignani, P., Tittarelli, A., Borgini, A., Codazzi, T., Rovelli, A., Porro, E., Contiero, P., Bianchi, N., Tagliabue, G., Fissi, R., Rossitto, F., Berrino, F., 2004. Childhood leukemia and road traffic: a population-based case-control study. *Int. J. Cancer* 108, 596–599. <https://doi.org/10.1002/ijc.11597>.
- D'Andrea, M.A., Reddy, G.K., 2014. Health effects of benzene exposure among children following a flaring incident at the British petroleum refinery in Texas City. *Pediatr. Hematol. Oncol.* 31, 1–10. <https://doi.org/10.3109/08880018.2013.831511>.
- European Environmental Agency EEA CORINE land cover 2006 [WWW document], 15Adb. URL: <http://www.eea.europa.eu/publications/COR0-landco>.
- Filippini, T., Heck, J.E., Malagoli, C., Del Giovane, C., Vinceti, M., 2015. A Review and Meta-Analysis of Outdoor Air Pollution and Risk of Childhood Leukemia. *J. Environ. Sci. Health C Environ. Carcinog. Ecotoxicol. Rev.* 33, 36–66. <https://doi.org/10.1080/10590501.2015.1002999>.
- García-Pérez, J., López-Abente, G., Gómez-Barroso, D., Morales-Piga, A., Romaguera, E.P., Tamayo, I., Fernández-Navarro, P., Ramis, R., 2015. Childhood leukemia and residential proximity to industrial and urban sites. *Environ. Res.* 140, 542–553. <https://doi.org/10.1016/j.envres.2015.05.014>.
- García-Pérez, J., Morales-Piga, A., Gómez-Barroso, D., Tamayo-Uria, I., Pardo Romaguera, E., López-Abente, G., Ramis, R., 2016. Residential proximity to environmental pollution sources and risk of rare tumors in children. *Environ. Res.* 151. <https://doi.org/10.1016/j.envres.2016.08.001>.
- Gómez-Barroso, D., García-Pérez, J., López-Abente, G., Tamayo-Uria, I., Morales-Piga, A., Pardo Romaguera, E., Ramis, R., 2016. Agricultural crop exposure and risk of childhood cancer: new findings from a case-control study in Spain. *Int. J. Health Geogr.* 15. <https://doi.org/10.1186/s12942-016-0047-7>.
- Greaves, M., 2006. Infection, immune responses and the aetiology of childhood leukaemia. *Nat. Rev. Cancer* 6, 193–203. <https://doi.org/10.1038/nrc1816>.
- Grimes, D.A., Schulz, K.F., 2005. Compared to what? Finding controls for case-control studies. *Lancet* 365, 1429–1433. [https://doi.org/10.1016/S0140-6736\(05\)66379-9](https://doi.org/10.1016/S0140-6736(05)66379-9).
- Harrison, R.M., Leung, P.L., Somerville, 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, 774–780.
- Heck, J.E., Wu, J., Lombardi, C., Qiu, J., Meyers, T.J., Wilhelm, M., Cockburn, M., Ritz, B., 2013. Childhood cancer and traffic-related air pollution exposure in pregnancy and early life. *Environ. Health Perspect.* 121, 1385–1391. <https://doi.org/10.1289/ehp.1306761>.
- Heeb, N.V., Forss, A.-M., Bach, C., Mattrel, P., 2000. Velocity-dependent emission factors

- of benzene, toluene and C2-benzenes of a passenger car equipped with and without a regulated 3-way catalyst. *Atmos. Environ.* 34, 1123–1137. [https://doi.org/10.1016/S1352-2310\(99\)00356-8](https://doi.org/10.1016/S1352-2310(99)00356-8).
- Houot, J., Marquant, F., Goujon, S., Faure, L., Honoré, C., Roth, M.-H., Hémon, D., Clavel, J., 2015. Residential proximity to heavy-traffic roads, benzene exposure, and childhood leukemia—the GEOCAP study, 2002–2007. *Am. J. Epidemiol.* <https://doi.org/10.1093/aje/kwv111>. (kwv111).
- Inaba, H., Greaves, M., Mullighan, C.G., 2013. Acute lymphoblastic leukaemia. *Lancet* 381, 1943–1955. [https://doi.org/10.1016/S0140-6736\(12\)62187-4](https://doi.org/10.1016/S0140-6736(12)62187-4).
- Instituto Nacional de Estadística (National Statistics Institute) [WWW document]. n.d. URL: <http://www.ine.es/jaxi/tabla.do?path=/t15/p417/a2012/10/&file=01001.px&type=pcaxis&I=0>, Accessed date: 29 September 2014.
- International Agency for Research on Cancer, 1982. IARC monographs on the evaluation of the carcinogenic risks to humans: chemicals, industrial processes and industries associated with cancer in humans. In: IARC Monographs, Volumes 1 to 29. Vol. Supplement 4, Lyon, France.
- International Agency for Research on Cancer, 2013. Air pollution and cancer. In: Straif, K. (Ed.), IARC Scientific Publication No. 161, Lyon, France.
- Jacobson, M.Z., 2002. Atmospheric Pollution: History, Science, and Regulation. Cambridge University Press.
- Janitz, A.E., Campbell, J.E., Magzamen, S., Pate, A., Stoner, J.A., Peck, J.D., 2016. Traffic-related air pollution and childhood acute leukemia in Oklahoma. *Environ. Res.* 148, 102–111. <https://doi.org/10.1016/j.envres.2016.03.036>.
- Kehm, R.D., Spector, L.G., Poynter, J.N., Vock, D.M., Osypuk, T.L., 2017. Socioeconomic status and childhood cancer incidence: a population-based multilevel analysis. *Am. J. Epidemiol.* <https://doi.org/10.1093/aje/kwx322>.
- Magnani, C., Ranucci, A., Badaloni, C., Cesaroni, G., Ferrante, D., Miligi, L., Mattioli, S., Rondelli, R., Bisanti, L., Zamboni, P., Cannizzaro, S., Michelozzi, P., Cocco, P., Celentano, E., Assennato, G., Merlo, D.F., Mosciatti, P., Minelli, L., Cuttini, M., Torregrossa, M.V., Lagorio, S., Haupt, R., Forastiere, F., SETIL Working Group, 2016. Road traffic pollution and childhood leukemia: a Nationwide case-control study in Italy. *Arch. Med. Res.* 47, 694–705. <https://doi.org/10.1016/j.arcmed.2017.02.001>.
- Malagoli, C., Malavolti, M., Costanzini, S., Fabbri, S., Tezzi, S., Palazzi, G., Arcolin, E., Vinceti, M., 2015. Increased incidence of childhood leukemia in urban areas: a population-based case-control study. *Epidemiol. Prev.* 39, 102–107.
- Marcos-Gragera, R., Galceran, J., Martos, C., de Munain, A.L., Vicente-Raneda, M., Navarro, C., Quirós-García, J.R., Sánchez, M.-J., Ardanaz, E., Ramos, M., Mateos, A., Salmerón, D., Felipe, S., Peris-Bonet, R., 2017. Incidence and survival time trends for Spanish children and adolescents with leukaemia from 1983 to 2007. *Clin. Transl. Oncol.* 19, 301–316. <https://doi.org/10.1007/s12094-016-1531-z>.
- Martins, H., Miranda, A., Borrego, C., 2012. Urban structure and air quality. In: Air Pollution - A Comprehensive Perspective. InTech. <https://doi.org/10.5772/50144>.
- McHale, C.M., Zhang, L., Smith, M.T., 2012. Current understanding of the mechanism of benzene-induced leukemia in humans: implications for risk assessment. *Carcinogenesis* 33, 240–252. <https://doi.org/10.1093/carcin/bgr297>.
- Ministerio de Fomento, 2016. Carreteras. [http://www.fomento.gob.es/MFOM/LANG\\_CASTELLANO/DIRECCIONES\\_GENERALES/CARRETERAS/](http://www.fomento.gob.es/MFOM/LANG_CASTELLANO/DIRECCIONES_GENERALES/CARRETERAS/).
- Pearce, N., 2016. Analysis of matched case-control studies. *BMJ* 352, 1969. <https://doi.org/10.1136/bmj.i969>.
- Peris-Bonet, R., Salmerón, D., Martínez-Beneito, M.A., Galceran, J., Marcos-Gragera, R., Felipe, S., González, V., Sánchez de Toledo Codina, J., Spanish Childhood Cancer Epidemiology Working Group, 2010. Childhood cancer incidence and survival in Spain. *Ann. Oncol.* 21 (Suppl. 3), iii103–110. <https://doi.org/10.1093/annonc/mdq092>.
- Peris-Bonet, R., Pardo Romaguera, E., Muñoz López, A., Sayas Sánchez, S., Valero Poveda, S., 2017. Cáncer infantil en España. Estadísticas 1980–2016. Registro Español de Tumores Infantiles (RETI-SEHOP). Universitat de València, Valencia.
- Pyyat, D., Hays, S., 2010. A review of the potential association between childhood leukemia and benzene. *Chem. Biol. Interact.* 184, 151–164. <https://doi.org/10.1016/j.cbi.2010.01.002>.
- Raaschou-Nielsen, O., Reynolds, P., 2006. Air pollution and childhood cancer: a review of the epidemiological literature. *Int. J. Cancer* 118, 2920–2929. <https://doi.org/10.1002/ijc.21787>.
- Ramis, R., Gómez-Barroso, D., Tamayo, I., García-Pérez, J., Morales, A., Pardo Romaguera, E., López-Abente, G., 2015. Spatial analysis of childhood cancer: a case-control study. *PLoS One* 10, e0127273. <https://doi.org/10.1371/journal.pone.0127273>.
- Ramis, R., Tamayo-Uria, I., Gómez-Barroso, D., López-Abente, G., Morales-Piga, A., Pardo Romaguera, E., Aragonés, N., García-Pérez, J., 2017. Risk factors for central nervous system tumors in children: new findings from a case-control study. *PLoS One* 12. <https://doi.org/10.1371/journal.pone.0171881>.
- Richardson, David B., Wing, Steve, Schroeder, Jane, Schmitz-Feuerhake, Inge, Hoffmann, Wolfgang, 2005. Ionizing Radiation and Chronic Lymphocytic Leukemia. *Environ. Health Perspect.* 113 (1), 1–5.
- Rothman, K.J., Professor, T.L.L.A., Greenland, S., 2012. Modern Epidemiology, Third, Mid-cycle Revision Edition. LWW, Philadelphia.
- Savitz, D.A., Feingold, L., 1989. Association of childhood cancer with residential traffic density. *Scand. J. Work Environ. Health* 15, 360–363.
- Spycher, B.D., Feller, M., Röösl, M., Ammann, R.A., Diezi, M., Egger, M., Kuehni, C.E., 2015. Childhood cancer and residential exposure to highways: a nationwide cohort study. *Eur. J. Epidemiol.* 30, 1263–1275. <https://doi.org/10.1007/s10654-015-0091-9>.
- Steliarova-Foucher, E., Colombet, M., Ries, L.A.G., Moreno, F., Dolya, A., Bray, F., Hesselting, P., Shin, H.Y., Stiller, C.A., IICC-3 contributors, 2017. International incidence of childhood cancer, 2001–10: a population-based registry study. *Lancet Oncol.* [https://doi.org/10.1016/S1470-2045\(17\)30186-9](https://doi.org/10.1016/S1470-2045(17)30186-9).
- Stieglitz, E., Loh, M.L., 2013. Genetic predispositions to childhood leukemia. *Ther. Adv. Hemat.* 4, 270–290. <https://doi.org/10.1177/2040620713498161>.
- Strasser, B., Gostner, J.M., Fuchs, D., 2015. Carbon monoxide exposure may underlie the increased leukaemia risk in children living next to motor highways. *Eur. J. Epidemiol.* 30, 1329–1330. <https://doi.org/10.1007/s10654-015-0108-4>.
- Weng, H.-H., Tsai, S.-S., Chen, C.-C., Chiu, H.-F., Wu, T.-N., Yang, C.-Y., 2008. Childhood leukemia development and correlation with traffic air pollution in Taiwan using nitrogen dioxide as an air pollutant marker. *J. Toxicol. Environ. Health A* 71, 434–438. <https://doi.org/10.1080/15287390701839042>.
- Weng, H.-H., Tsai, S.-S., Chiu, H.-F., Wu, T.-N., Yang, C.-Y., 2009. Childhood leukemia and traffic air pollution in Taiwan: petrol station density as an indicator. *J. Toxicol. Environ. Health A* 72, 83–87. <https://doi.org/10.1080/15287390802477338>.
- Whitehead, T.P., Metayer, C., Wiemels, J.L., Singer, A.W., Miller, M.D., 2016. Childhood leukemia and primary prevention. *Curr. Probl. Pediatr. Adolesc. Health Care* 46, 317–352. <https://doi.org/10.1016/j.cppeds.2016.08.004>.
- Whysner, J., Reddy, M.V., Ross, P.M., Mohan, M., Lax, E.A., 2004. Genotoxicity of benzene and its metabolites. *Mutat. Res.* 566, 99–130.