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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 $PM_{2,5}$, 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; $PM_{2.5}$, 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 child-years 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 Words 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 aslo 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: