The association between exposure to environmental factors and the occurrence of attention-deficit/hyperactivity disorder (ADHD). A population-based retrospective cohort study

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Abstract

Background: A number of factors contribute to attention deficit hyperactivity disorder (ADHD) and although they are not fully known, the occurrence of ADHD seems to be a consequence of an interaction between multiple genetic and environmental factors. However, apart from pesticides, the evidence is inadequate and inconsistent as it differs not only in the population and time period analysed, but also in the type of study, the control of the confounding variables and the statistical methods used. In the latter case, the studies also differ in the adjustment of spatial and temporal variability. Our objective here, is to provide evidence on an association between environmental factors and ADHD.

Methods: In our study, we used a population-based retrospective cohort in which we matched cases and controls (children free of the disease) by sex and year of birth (n=5,193, 78.9% boys). The cases were children born between 1998 and 2012 and diagnosed with ADHD (n=116).

To evaluate whether there was a geographical pattern in the incidence of ADHD, we first represented the smoothed standardized incidence rates on a map of the region being studied. We then estimated the probability of being a case by using a generalized liner mixed model with a binomial link. As explanatory variables of interest, we included the following environmental variables: distance to agricultural areas, distance to roads (stratified into three categories according to traffic density and intensity), distance to petrol stations, distance to industrial estates, and land use. We control for both observed (individual and family specific variables and deprivation index) and unobserved confounders (in particular, individual and familial heterogeneity). In addition, we adjusted for spatial extra variability.

Results: We found a north-south pattern containing two clusters (one in the centre of the study region and another in the south) in relation to the risk of developing ADHD. The results from the multivariate model suggest that these clusters could be related to some of the environmental variables. Specifically, living within 100 metres from an agricultural area or a residential street and/or living fewer than 300 metres from a motorway, dual carriageway or one of the industrial estates analysed was associated (statistically significant) with an increased risk of ADHD.

Conclusion: Our results indicate that some environmental factors could be associated with ADHD occurring, particularly those associated with exposure to pesticides, organochlorine compounds and air pollutants because of traffic.

Key words: attention deficit hyperactivity disorder (ADHD); environmental variables; pesticides; air pollutants; spatial dependence.

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Ethical considerations of the study

The data for this study came from an anonymised clinical administrative database and only the lead researcher, where necessary, had access to the identity of each individual. This study has also been reviewed and approved by the Ethics and Clinical Research Committee of the Institute of Health Care (IAS).

1.- Introduction

Attention deficit hyperactivity disorder (ADHD) is one of the most frequent neurobehavioral disorders found in children and adolescents in the general population. ADHD is a childhood onset disorder comprising a persistent pattern of inattention, impulsivity, and hyperactivity^[1]. ADHD occurs when these behavioural patterns are more frequent and intense than would be expected in children of the same age and cause significant cognitive impairment in schoolwork performance and daily activities^[1,2]. Children with ADHD are, in fact, a heterogeneous population sharing common symptoms^[3].

In 2013 (using the Diagnostic and Statistical Manual of Mental Disorders (DSM-5) diagnostic criteria), the American Psychiatric Association estimated the prevalence of ADHD in the school-age population as being equal to 5%^[4]. This figure, according to expert consensus, can be considered to be a very good approximation to the prevalence of ADHD in the total population^[5]. That said, the prevalence of ADHD presents a great variability depending on factors such as the geographic origin of the studies, the sex and age of the children, the diagnostic criteria and the level of care. In fact, a large part, if not all, of this heterogeneity could be because of an interrelation between the multiple genetic and environmental factors that can be involved in the occurrence of ADHD. These include traffic-related air pollutants, exposure to chemicals and heavy metals, nutritional factors and variables associated with lifestyle^[3].

However, not only is the evidence of the association between environmental risk factors and developing ADHD^[3,6-8] very limited, it is also inadequate or even insufficient. Evidence, although not from systematic reviews, can be found in a few studies. A possible association between ADHD and its symptoms and prenatal exposure to polycyclic aromatic hydrocarbons (PAHs) has been proposed by Perera *et al.*^[9,10]. However, Abid *et al.*, in a cross-sectional study of a nationally representative sample of U.S. children aged 6 to 15 years, did not find any association between postnatal exposure to PAHs (also measured by PAH metabolites in urine) and ADHD^[11]. Likewise, in a very recent cross-sectional study with children aged 8 to 12 years in Barcelona (Catalonia, Spain) during 2012-2013, Mortamais *et al.*, found that although ADHD symptoms were higher in children with higher exposure to PAHs and, above all, benzo[a]pyrene, associations were not statistically significant^[12]. The evidence of an association between ADHD and exposure to other traffic-related air pollutants is simply insufficient^[13-16]. Studies have, however, been somewhat more successful in associating air pollutants and some ADHD related symptoms^[17-20].

Comparatively, the association of ADHD with exposure to pesticides has much more evidence. For example, Mostafalou and Abdollahi performed a systematic review into the association between pesticides and human diseases^[21]. In the case of ADHD and behavioural problems, they reviewed eleven epidemiological studies, which included six cohort, four cross-sectional and one case-control study published between 2004 and 2016. Associations were found for both prenatal (in cohort studies assessing exposure to organophosphorus and organochlorine pesticides) and postnatal (in cross-sectional studies assessing exposure to organophosphorus and pyrethroid pesticides) exposure, as well as

in a case-control study evaluating exposure to organophosphorus pesticides. Postnatal exposure to some metals, in particular lead^[22-24], selenium^[25], and mercury^[26], has been found to be associated with ADHD and its symptoms.

Evidence has also been provided on a local level. ADHD related symptoms have been associated with prenatal environmental exposures in a birth cohort (1993 to 1998) residing in New Bedford, (Massachusetts, USA)^[27]. New Bedford Harbor was listed as a Superfund Site by the Environmental Protection Agency in 1982 because of the contamination caused by polychlorinated biphenyl (PCB)-laden waste released between 1940 and 1977. The cohort had been exposed to, among others, organochlorines, PCB and p,p'-dichlorodiphenyldichloroethylene (p,p'-DDE)^[28-30] and metals such as mercury^[26]. In a very recent paper, Vieira *et al.*, initially found increased ADHD related symptoms in children whose mothers had lived in the west of New Bedford Harbor during pregnancy, although after adjusting for socioeconomic conditions this association was no longer statistically significant^[27].

In summary, apart from pesticides, there is very limited evidence from the systematic reviews for the association between environmental factors and ADHD. Furthermore, evidence from other types of studies is inconsistent and differs not only in the populations and the time periods analysed, but also in the type of study, the control of the confounding variables and the statistical methods used. In the case of the latter, these also differ in the adjustment of spatial and temporal variability. Our objective is to provide evidence on the association between environmental factors and the spatial variability of the occurrence of ADHD. To do this we used a population-based retrospective cohort and controlled for both observed confounders (associated with the individual, family and other contextual variables) as well as unobserved confounders (particularly individual and familial heterogeneity). In addition, we adjusted for spatial extra variability.

2.- Methods

2.1.- Design

We used a retrospective population-based cohort composed of individuals who had made use of the primary healthcare services offered by any one of the three Basic Areas of Health (ABS, '*Àreas Bàsiques de Salut*', acronym in Catalan) between January 1, 2005 and December 31, 2012. ABSs are primary healthcare centres managed by the Institute of Health Care (IAS, '*Institut d'Assistència Sanitària*' in Catalan). The IAS manages all the ABSs providing healthcare to the region known as '*La Selva Interior*', (Girona, Spain).

Catalonia is divided into seven health regions of which an ABS is a territorial division. All residents in an area covered by an ABS are 'assigned' to the provider responsible for that particular ABS. The IAS, a primary healthcare service provider manages all the ABSs that provide healthcare to the region of '*La Selva Interior*', Girona (ABS Anglès, ABS Breda-Hostalric and ABS Cassà de la Selva). *La Selva Interior* and *La Selva Marítima* form the *La Selva* 'comarca' (equivalent to a county) (further details can be found elsewhere^[31]).

In our study, we included children from the cohort who had been born in 1998 or later. In other words, they were eight years old or younger in 2005 (the first year of the follow-up of the cohort). Meanwhile, we excluded children who were not of school age (i.e. born from 2009 onwards) and those who, for one reason or another, had been removed from the ABS lists.

Cases were children who, according to the WHO criteria (ICD-10: F90.0, F98.8), had been diagnosed with ADHD by an IAS primary care physician between 2005 and 2012 (n=116). To increase the statistical power of our study, instead of randomly choosing a control for each case, we chose, all those who had the same sex and year of birth as the cases did. That is, we used all children free of ADHD who had had contact with the IAS primary healthcare services from 2005 to 2012 as controls and who, like the cases, would have been born in 1998 or later. As a result, multiple controls corresponded to each case. Cases were matched with controls by sex and year of birth. The final sample size was 5,193 children (79.8% boys).

The clinical and sociodemographic data concerning both the cases and the controls were collected from the IAS database. This database meets all the quality controls required for primary care providers in Catalonia. (These quality control and assurance standards are commissioned by the Catalan Health Service and the Catalan Health System Observatory assesses their compliance).

2.2.- Variables

- *Environmental explanatory variables*

As explanatory variables of interest we included several environmental variables. In fact, we were interested in evaluating the effect that long-term exposure to these environmental variables might have. We assumed that each child has been subjected to an (average) level of exposure throughout the follow-up period (2005-2012) and that the geographical variation of that exposure was what contributed to the risk of ADHD throughout the period.

- Air pollutants and exposure to pesticides

For both cases and controls we included the distance between the child's home (i.e. their last recorded address) to the nearest traffic route as a proxy for exposure to air pollutants associated with traffic. Traffic routes were classified as: i) streets, ii) local and county roads and iii) dual-carriageways and motorways.

As a proxy for exposure to pesticides, we considered the distance from the child's home to the nearest agricultural area.

In each case, the distances were constructed by considering a geographical layer. The road layer was obtained using the 2012 Catalonia Road Map available from the Cartographic and Geologic Institute of Catalonia (ICGC)^[32]

while the agricultural area layer was obtained from the ICGC 2012 Soil Map of Catalonia (further details can be found elsewhere^[33]).

- Other environmental variables

The distances considered (to traffic routes and to agricultural areas) were only proxies of environmental exposure and so there may well be other environmental variables that influence the risk of developing ADHD.

To this end we considered variable land use. We constructed a land-use map for 2010 by applying classification techniques based on LANDSAT MSS images^[34,35] to land cover orthophoto maps of Catalonia (1:5,000) from 2005-2007. Next, we constructed a 50 metre in diameter buffer around each child's address. As land use for each child's address, we assigned only the percentage value corresponding to the principal land use within the 50m buffer. We also converted the twenty-two categories we had obtained from the ICGC into four: i) forests (dense, coniferous and mixed), ii) fruit trees and berries, iii) transitional woodland scrub and natural grassland, and iv) urban (further details can be found elsewhere^[41]).

In addition, we included two further distance variables: the distance from the child's home to i) the nearest petrol station and ii) to each of the (twenty-five) industrial estates found in the study area (*La Selva Interior*). In this case, the layers required to compute the distances were obtained from OpenStreetMap^[36] (2012 data).

All distance variables were categorized and we performed previous sensitivity analyses to determine all the cut-off points. In particular, we estimated auxiliary logistic regressions in which we included only the distance variables (one to one) categorized in multiples of 50m (25m for the distance to residential streets) as an explanatory variable. After calculating the deviance of the regression, we grouped the categories and re-estimated the logistic regression. We were left with a categorization that corresponded to a logistic regression with the least deviance.

Distances to local and county roads and to the nearest agricultural area were categorized as follows: fewer than 50 metres, 50-100 metres, 101-200 metres, and more than 200 metres. We took this last category as the reference. In distance to dual carriageways, carriageways and motorways we introduced an additional category: within 50 metres, 50-100 metres, 101-200 metres, 201-300 metres, and more than 300 metres (NB: this final marker was taken as the reference). Here we also considered an additional categorization: up to 300 metres and more than 300 metres (reference category). Distance to streets was categorized as fewer than 25 metres, 25-100 metres and more than 100 metres (this last category was the reference). Distance to the nearest petrol station was categorized as within 150 metres (more than 150 metres was the reference category) and the distance to the industrial estate: fewer than 300 metres (more than 300 metres was the reference category).

- Control variables

We included variables associated with the child's family as control variables. Once we had identified the child's family in the original cohort, we determined whether or not a member of that family had been diagnosed with i) ADHD or conduct disorders, ii) anxiety, iii) depression, or iv) psychosis (in all cases regardless of the child in question).

Finally we included, at a census tract level, a deprivation index based on the one used in the IneqCities project^[37]. The index was created by combining seven socioeconomic indicators for where the child was domiciled: i) percentage of unemployed, ii) percentage of manual workers, iii) population percentage of illiterate, without studies or incomplete primary schooling, iv) percentage of population with primary education, v) percentage of population with a university degree (NB: the indicators iii, iv and v were stratified by age groups: from 16-64 years and 65 years or more), vi) percentage of foreigners from low income countries and, vii) percentage of dwellings with an area of less than 45m². These indicators were obtained from the 2011 Spanish Population and Housing Census^[38]. The distance indicator DP₂ was used to combine the above-mentioned indicators into a single deprivation index^[39] (further details can be found elsewhere^[37]). The index was categorized into quartiles, taking the last quartile (i.e. that corresponding to the most depressed census tracts) as the reference.

It is feasible that some of the ADHD risk factors associated with the children were time-dependent and the effect of some of these time-dependent factors had been modified by other variables specific to each child. As we did not have any information about these, we included age (in fact, year of birth) and sex (girl is the reference category) as the proxies for time-dependent risk factors and for possible modifications of the effect. To allow a non-linear relationship, year of birth was included as a categorical variable and 1998 was taken as the reference.

Since the original cohort consisted of a non-random sample (i.e. individuals who had made use of the primary healthcare services offered by the ABS in the IAS during 2005-2012), as an offset the expected numbers of ADHD cases in each census tract from each municipality in the study area (*La Selva Interior*) were introduced into the model. In fact, the offset can be used to perform an indirect standardization which allows hypothetical populations from non-random samples to be reconstructed^[40]. These numbers were calculated annually from 2005 to 2012 using the population from each year and the incidence rates of ADHD observed in each census tract by sex and age were taken as the references. Population data by census tract, age and sex were obtained from the Catalan Institute of Statistics^[41] and from the Spanish Population and Housing Census^[38].

2.3.- Statistical analysis

The baseline characteristics of all the children were summarized by means, medians, standard deviations, by the first and the third quartiles (quantitative

variables) and by proportions (qualitative variables). The bivariate associations between the explanatory variables and ADHD were assessed with nonparametric tests: Mann-Whitney U (for quantitative variables) and chi-squared tests (for qualitative variables).

During the follow-up of the cohort (2005-2012), 86.55% of the children assigned to the ABS made use of its primary healthcare services. The sample, however, was non-random, meaning there may have been a selection bias. Consequently, the method proposed by Saez *et al.*,^[42] based on reweighting the estimates according to the probability of being included in the sample, was used to calculate the prevalence of ADHD. More specifically, these probabilities were estimated using a treatment effects model with discrete outcome (the Hurdle model)^[43].

In the multivariate analysis, we specified a generalized linear mixed model with binomial response (case or control) and a logistic link,

$$\log\left(\frac{\text{Pr ob}(Y_i = 1)}{1 - \text{Pr ob}(Y_i = 1)}\right) = \eta_i \quad \{1\}$$

where Y denoted the response variable, the subscript *i* denoted the study subject (0 for a control, 1 for a case) and η_i a linear predictor for subject *i*.

- Estimating and representing the smoothed standardized incidence rates

First, to evaluate whether there was a geographical pattern in the incidence of ADHD, we represented the smoothed standardized incidence rates on a map of the region (*La Selva Interior*, Girona) being studied.

The reasons for not directly using the standardized incidence rates (i.e. the ratio between the observed count and the expected count of ADHD in a particular area) are well known (see, for instance, Pascutto *et al.*,^[44] and Lawson *et al.*^[45], among many others). Although the standardized incidence rates are an estimator of the underlying relative risk in a small area (a census tract in our case), the problem is that these rates are very imprecise for diseases with a low prevalence and/or small populations^[44] (both relevant cases in our study). This problem can be addressed by the spatial smoothing of the rates over space. That is, using a model that controls the extra variability inherent in the spatial design^[45,46].

In our case, we used the model {1}, and at this stage we included three random effects in the linear predictor but no observable explanatory variables (although we did include the expected cases in each census tract as an offset).

The most important source of extra variability in a spatial design (as in our case) is 'spatial dependence' or clustering. That is to say, areas close in space show more similar disease incidence than areas that are not close. In fact, this dependence could be the consequence of unobserved confounders that were spatially distributed (in our case, probably other environmental variables that

have been omitted in the model). To capture spatial dependence we included in the regression model and structured random effect with a Matérn structure explicitly constructed through the Stochastic Partial Differential Equation (SPDE) approach^[47].

Furthermore, we controlled for the presence of heterogeneity. Heterogeneity can be defined as those variables which, although relevant in explaining the probability of being a case (child with ADHD), are not observable^[48]. We considered transversal heterogeneity, namely unobserved variables invariant over time, that were specific to each individual child as well as their family. From the various methods employed for random validity inferences in the presence of unobserved heterogeneity, we chose random effects^[48] and we specifically included two additional unstructured random effects: one associated with each child and the other with the family.

Once we had estimated the model {1}, we calculated the probability of being an ADHD case. Using these probabilities, we then estimated the cases of ADHD in each census tract (by sex and year of birth) and, finally, the smoothed standardized incidence rates. Lastly, we represented these relative risks on a map of *La Selva Interior*. The census track maps used were obtained from the Spanish Population and Housing Census^[38].

To help evaluate the existence of agglomerations (clusters) of excess cases we calculated the exceedance probabilities, i.e. the probability that the relative risks were above 1. By classifying an area as having an elevated risk if the probability was higher than 80%, both higher sensitivity (probability of detection above 80%) and specificity (false detection below 10%) were achieved^[49]. The exceedance probabilities were also represented on a map of the study area.

- Estimating the probability of being a case

Our hypothesis was that if there was a geographical pattern for ADHD, most of it could be explained by environmental variables, which is why at this stage we included the environmental variables that might explain the probability of being a case in the linear predictor of each subject in the model {1}.

Furthermore, we controlled for observed confounders, (including all the covariates indicated above), and for unobserved confounders (individual and familial heterogeneity and spatial dependence) as well. These unobserved confounders were captured by the three random effects explained earlier.

We also included the expected cases in each census tract as an offset.

Given the complexity of our model, we preferred to perform inferences using a Bayesian framework. In particular, we followed the Integrated Nested Laplace Approximation (INLA) approach^[50], within a (pure) Bayesian framework.

ADHD is a disease with a reduced number of cases in relation to the controls. This implies a reduced statistical power of the tests used. To increase this, and since we obviously could not increase the sample size, we chose to allow the

level of significance (α) to increase (up to 10%), which would reduce the probability of making Type II errors and increase the statistical power at the expense of having a greater risk of making false positive (Type I) errors.

All analyses were made with the free software R (version 3.4.0)^[51], available through the INLA package^[52,50]. The maps were represented in QGIS (version 2.18)^[53].

3.- Results

The prevalence of ADHD in children was 3.35% and was 3.53 times greater among boys (5.43%, $n=91$) than girls (1.54%, $n=25$). The highest prevalence was found in the group of children born between 1998 and 2000 (those aged 5-8 years in the first year of the cohort follow-up). In this group prevalence was 4.12% (6.71% for boys and 1.2% for girls). In our sample, 56.89% of the children had been born before 2002 and 30.6% between (and including) 2002 and 2005.

The maps of the smoothed relative risks and, above all, of the exceedance probabilities (i.e. the probability that the relative risk was greater than 1) in the study area are shown in Figures 1a and 1b, respectively. These risks were calculated from a model that contains neither explicative variables of interest nor covariables, but does include random effects and the expected cases in each census tract as an offset. As can be observed in Figure 1b, there is a north-south pattern with two clusters, one in the centre and the other in the south of the study region, in relation to the risk of developing ADHD.

Table 1 shows the baseline characteristics of the individuals who participated in the study. The distances to the environmental variables of interest (from the residence of the case or control) were smaller for the cases than for the controls. As can be seen, however, there were no statistical differences. Nonetheless, it must be pointed out that in the cases of distances to agricultural areas, dual-carriageways and motorways, the p-value was less than 20%.

Although there were no significant statistical differences between cases and controls, among the controls there was a much higher frequency of forests and transitional woodland scrub and natural grassland and mixed land use.

There were no significant differences between cases and controls in the control variables such as deprivation index (slightly less for the cases, with a p-value of 20%) and family members (apart from the child) diagnosed with a pathology related to ADHD.

Table 2 shows the results from the multivariate analysis. In addition to the odds ratios (OR) and their 95% credibility intervals (95% CI), the probability of the parameter estimator ($\log [OR]$) in absolute value being greater than 1 (Prob) is also shown (note that this is unilateral and so does not necessarily have to coincide with the CI in all cases). Unlike the p-value in a frequentist environment, this probability allows inferences to be carried out on the possible association. As can be observed, there was an association between the

occurrence of ADHD and the distance from the child's residence to the nearest agricultural area. Children who lived within 50 metres from an agricultural area had a greater risk of suffering from ADHD than those who lived further away (OR 2.20; 95% CI 1.11-4.25; Prob 98.9%). To a lesser degree, the same happened with the children living 50-100 metres from an agricultural area (OR 1.68; 95% CI 0.87-3.35; Prob 94.1%). Furthermore, living fewer than 25 metres from the nearest road increased the risk of suffering from ADHD with respect to living more than 100 metres away (OR 3.85; 95% CI 0.96-17.11; Prob 97.0%), as did, albeit to a lesser degree, living between 25 and 100 metres from the nearest road, (OR 2.11; 95% CI 0.69-7.53; Prob 92.0%). An association was also found between suffering from ADHD and living within 300 metres from a dual-carriageway or a motorway (as opposed to living more than 300m away) (OR 2.03; 95% CI 0.94-4.08; Prob 96.4%) Moreover, living within 300m from industrial estate A increased the risk of having ADHD (OR 1.51; 95% CI 0.93-37.25 Prob 96.9%).

Inverse associations for the occurrence of ADHD were also found: forests as the principal land use (OR 0.21; 95% CI 0.07-1.10; probability of the odds ratio being less than 1 97.1%) or transitional woodland scrub and natural grassland (OR 0.37; 95% CI 0.28-1.26; probability of the odds ratio being less than 1 93.9%) (always in relation to predominantly urban land use).

Figures 2, 3 and 4 show the graphical representation of the OR of suffering from ADHD in relation to the distance (in metres) from agricultural areas, residential streets, dual-carriageways and motorways, respectively. Figure 2 reveals that children living within 195-200 metres from an agricultural area are at greater risk of suffering from ADHD. The same is true for children living within 125-130 metres from a road (Figure 3) and/or within 150 metres from a dual-carriageway or motorway (Figure 4).

Note that there is a local maximum at about 150 metres (Figure 2). This peak is because of the interaction of distances to agricultural areas and dual-carriageways/motorways, but is not statistically significant. In fact, the odds of being a case were 3.69 times higher in children living within 100-150 metres from an agricultural area or from a dual-carriageway/motorway than for those living within 100-150 metres from an agricultural area (irrespective of the distance from a dual-carriageway/motorway) and were 2.03 times higher in relation to those living within 100-150 metres from a dual-carriageway/motorway. However, for the rest of the distances, the odds were no different from 1.

4.- Discussion

In relation to the risk of developing ADHD, we found a north-south pattern that had two clusters; one in the centre of the study region and another in the south. In general, these clusters are shown to coincide with proximity to agricultural areas, dual-carriageways and motorways. The results from the multivariate model suggest that these clusters could be related to some of the environmental variables. Specifically, living within 100 metres from an agricultural area or a residential street, or living fewer than 300 metres away

from a motorway or dual carriageway or industrial estate A was associated (statistically significant) with an increased risk of ADHD.

We were able to find some studies, albeit with differences in population, time period, type of study, control of confounding variables, and statistical methods used, in line with our own findings.

We considered the distance (from the child's home) to the agricultural area as a proxy for pesticide exposure. In this sense, our results are in line with those where associations between exposure to pesticides and the occurrence of ADHD and ADHD related symptoms have been found^[27-30,54-57]. We specifically note those which find a relationship between postnatal exposure to pesticides and ADHD^[55,57]. Yu *et al.*, in a case-control study with 4-15 year old children recruited in outpatient waiting rooms at the Taipei City Hospital, Taiwan, found that children with higher urinary dialkyl phosphate metabolite (biomarkers of organophosphate pesticide exposure) concentrations may have a two to threefold increased risk of being diagnosed with ADHD^[57]. Using a cross-sectional design from the National Health and Nutrition Examination Survey (2000-2004), which included 1,139 children representative of the general US population, Bouchard *et al.*, found that children with higher urinary dialkyl phosphate concentrations (organophosphate pesticide), especially dimethyl alkyl phosphate, were more likely to be diagnosed with ADHD^[55]. Associations between exposure to organochlorines (another type of pesticide) and ADHD and ADHD related symptoms were found only^[58] for prenatal exposure^[30,54,58].

Exposure to organochlorine compounds could be related to the excess risk found for children living within 300m from industrial estate A. While industrial estate A cannot be identified for reasons of confidentiality, we can reveal that factories producing cardboard tubes and packaging are located there and although the wood pulp used in this process is not manufactured on site (potentially a greater pollutant), these factories do bleach it. The wood pulp bleaching process requires the use of chemical agents derived from chlorine and generates organochloride compounds that are partly released into the atmosphere. This industrial estate (albeit on a much smaller scale) resembles the New Bedford Harbor (USA) Superfund site, where ADHD related symptoms have been associated with prenatal exposure to organochlorines, among others^[27,29,30]. It should be noted, however, that Vieira *et al.*, show that this possible association disappears after adjusting for socioeconomic conditions^[27]. In fact, areas with greater localised pollution are usually where less wealthy families live and parents of children with ADHD and who also have ADHD themselves suffer from the well-described downward social drift of so many psychiatric disorders^[1, 2].

The distances (from the children's home) to residential streets (63.8% of the cases and 66.4% of the controls resided in the 50m urban buffers) and to motorways and dual-carriageways (11% of the cases and 9% of the controls resided within 300m of them) could be proxies for exposure to air pollutants as a result of traffic. In this context, Min and Min, using a population-based cohort of 8,936 children born in 2002 (followed over a 10-year period) and after adjusting for relevant confounders, found that cumulative exposure to PM₁₀ and

NO₂ (from birth to diagnosis) was associated with the incidence of ADHD in childhood^[15]. On the other hand, several studies of different populations, age ranges, temporal periods, designs, confounding adjustment and exposure assessment (prenatal and postnatal), have found associations between exposure to air pollutants, (e.g. black carbon^[17,18] and NO₂^[20]), and noise exposure (as a consequence of traffic^[19]) and some of the ADHD related symptoms. In addition, Perera *et al.*, reported a possible association between prenatal exposure to polycyclic aromatic hydrocarbons (PAHs) (motor vehicle exhaust fumes are one of its sources) and ADHD and ADHD related-symptoms, although their results must be treated with caution as there is a possible selection bias^[9,10]. Nevertheless, Mortamais *et al.*, in a very recent cross-sectional study with children aged 8 to 12 years in Barcelona (Catalonia, Spain) during 2012-2013, found that the associations between ADHD symptoms and (postnatal) exposure to benzo[a]pyrene (a PAH) associations were not statistically significant^[12].

Our study may have some limitations. First, the address of the child's house that we used was the last one registered for them in the IAS database. Although, in theory, children's parents must communicate any changes of address, they almost never do so. Therefore, it's highly likely that the address of the child is the very first address they were ever registered at (i.e. when they were born). The child could have changed their address, but in no case had they left the study area, because if they had, they would no longer be assigned to the ABS managed by the IAS and would have been excluded.

Second, we used proxies to approximate exposure to environmental variables (especially distances). We were not able to determine to which particular variable or the amount of the environmental variable the child was exposed to. We believe, however, that we controlled for part of this information bias (on the other hand, non-differential) by including a structured random effect that captured spatial dependence. In fact, this dependence is the consequence of unobserved confounders that were spatially distributed.

As a third limitation, the exposure to the environmental variables could have been a combination of prenatal and postnatal exposure. In fact, only 12.5% of the children were born after 2005 (the first year of the follow-up of the original cohort), and so most of the children (87.5%) had had postnatal exposure.

Our fourth limitation lies in the low prevalence we found for ADHD (3.35%). However, while a diagnosis of ADHD could also have been made by doctors in the private sector, only public-sector doctors can write prescriptions for ADHD drugs. In our case, this means only the doctors who were working for the primary care service provider (IAS) in the study region. Furthermore, during the follow-up of the cohort, 86.55% of the children assigned to the ABS managed by the IAS made use of the primary healthcare services, and so almost all the children with ADHD were identified in the IAS database. Also, in our study the cases were diagnosed according to the WHO criteria (ICD-10), whereas when the American Psychiatric Association (DSM-IV) criteria rather than the WHO criteria (ICD-10)^[59] is applied, the diagnosis of ADHD is five times more likely. We also found that the prevalence of ADHD was 3.53 times higher among boys

than girls, which is a ratio consistent with the literature^[8-10]. Finally, the prevalence for boys (5.43%), and for children born between 1998 and 2000 (i.e. aged 6 to 8 years in the first year of the follow-up of the cohort: 4.12% for both boys and girls and 6.71% for boys) is closer to the prevalence which, according to expert consensus, can be considered a very good approximation of the population prevalence (5.0%)^[5,60-62].

A fifth limitation is related to residual confounding. The introduction of random effects may not have collected all the unobserved confounders. There are other potential risk factors for ADHD (for instance maternal smoking) however, as there was no information for these they were not included as covariates.

Our sixth limitation is that, as in any Bayesian analysis, the choice of the prior distributions of the model's parameters (i.e. priors) may have had a considerable impact on the results. However, we used priors that penalize the complexity (PC priors)^[63] and which have been found to be very robust. Furthermore, we performed sensitivity analyses to assess how the prior hyperparameters influenced the estimation results. We did this by increasing the precision (lowering the variance) and by testing other priors (namely, those used by default in R INLA (log gamma)) with different shape and inverse-scales: uniform and centred half-normal. In all cases the PC priors provided better results.

We believe that these limitations are offset by the strengths of our study; three of which we would like to highlight. First, we used a case-control constructed from a population-based retrospective cohort. The fact that it is population-based allows it to be generalised. Only two of the studies analysed (Min and Min^[15] and Sentis *et al.*^[20]) also used data from a population-based cohort. Our second strength is that, in addition to controlling for the observed confounding, we used random effects to control for unobserved confounding. Mortamais *et al.*,^[12] and Forns *et al.*,^[19] also used random effects to control for heterogeneity, while Fortenberry *et al.*,^[64] included random effects to control for temporal heterogeneity. Our third strength is that we adjusted for the spatial extra variability inherent in all spatial designs. Only Sentis *et al.*,^[20] (by means of Land Use Regression (LUR) models) and Vieira *et al.*,^[27] (including a smoother of the location of each child) to some extent controlled for that extra variability.

While it is true that exposures to environmental factors have always been approximate and that there could be other explanations for the geographical differences that are not related to environmental factors, we would suggest to public health authorities to adopt some preventive measures. For instance, the use of organophosphate (and most probably organochlorine pesticides) should be reduced. Substituting chemical pesticides with biological ones, such as those already used in ecological farming, should be subsidized. Furthermore, the use of chlorine when bleaching cellulose should be strictly limited to a minimum or, better still, be replaced with processes using oxygen or oxygen compounds (such as the Elemental Chlorine Free (ECF) method, partially free of chlorine or, better yet, the Totally Chlorine Free (TFC) method). Lastly, measures should be taken to reduce air polluting vehicle emissions.

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Conflict of interest: None

The manuscript is an original contribution that has not been published before, whole or in part, in any format, included electronically. All authors will disclose any actual or potential conflict of interest including any financial, personal or other relationships with other people or organizations, that could inappropriately influence or be perceived to influence their work, within three years of beginning the submitted work.

Data availability

Due to the restrictions on the transfer of data to third parties, both ethical (in accordance with the protocol approved by the Ethics and Clinical Research Committee of the Institute of Health Care (IAS), Girona, Spain) and legal (in accordance with the provisions of the Spanish Law on Data Protection, Fundamental Law 15/1999 of 13 December on the Protection of Personal Data, article 7.3); data (appropriately anonymized) will be available to all interested researchers upon request to Marc Saez (marc.saez@udg.edu).

Authors' Contributions

MS had the original idea for the paper. MS and MAB designed the study. The bibliographic search and the writing of the introduction were by MS and MAB. The choice of methods and statistical analysis was performed by MS, and MF and MS built the tables and figures. All authors wrote the results and the discussion. The writing and final editing was done by MS. MAB, MF and GLC. All authors reviewed and approved the manuscript.

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Table 1.- Baseline data of patients included in the analyses.

Variables	n	Cases	n	Controls	p-value
Dist. agricultural area; metres, mean (SD)	116	97.90 (92.55)	5077	109.70 (95.94)	0.141
Median (Q1-Q3)		70.71 (25.00-156.60)		79.06 (35.36-167.71)	
Dist. streets; metres ,mean (SD)	116	45.63 (294.89)	5077	59.33 (358.29)	0.315
Median (85th-95th percentiles)		0.00 (25.00-70.71)		0.00 (25.00-77.27)	
Dist_ local and county; metres, mean (SD)	116	271.83 (408.54)	5077	265.12 (424.14)	0.892
Median (Q1-Q3)		125.00 (39.02-300.00)		134.63 (50.00-270.42)	
Dist. dual-carriageways /motorways; metres mean (SD)	116	2489.74 (2564.68)	5077	3100.08 (3273.86)	0.157
Median (Q1-Q3)		1558.96 (774.48-3284.33)		1550.00 (915.49-3824.27)	
Dist. petrol stations; metres, mean (SD)	116	1399.90 (1235.30)	5077	1610.30 (1525.40)	0.513
Median (Q1-Q3)		925.17 (556.07-1824.91)		980.12 (538.52-2150.15)	
Dist. industrial estates, metres, mean (SD)	116	16496.32 (7908.45)	5077	17403.60 (7901.40)	0.252
Median (Q1-Q3)		14979.90 (11064.75-18330.50)		15033.30 (11221.20-21372.40)	
Land use, n (%)	116		4950		
Forest		15 (12.9%)		764 (15.4%)	0.221
Fruit trees and berries		22 (19.0%)		798 (16.1%)	
Transitional woodland scrub and natural grassland		5 (4.3%)		316 (6.4%)	
Urban		74 (63.8%)		3287 (66.4%)	
Sex; n (%)	116		5077		0.321
Boys		91 (78.4%)		4006 (78.9%)	
Girls		25 (21.6%)		1071 (21.1%)	
Deprivation index, mean (SD)	116	17.05 (1.93)	5077	17.28 (2.09)	0.157
Median (Q1-Q3)		16.91 (16.07-17.78)		17.11 (16.506-18.65)	
Members of the child's family with					
ADHD, n (%)	45	8 (17.8%)	1641	266 (16.2%)	0.795
Anxiety, n(%)	45	38 (83.5%)	1641	1349 (82.2%)	0.628
Depression, n(%)	45	5 (11.1%)	1641	169 (10.3%)	0.938
Psychosis, n(%)	45	1 (2.2%)	1641	39 (2.4%)	0.946

p-values of the chi-square (categorical variables) and Mann-Whitney's U (median, quantitative variables)

The number of cases and controls did not coincide in all variables due to the presence of missing data.

Table 2.- Association between environmental variables and occurrence of ADHD (5079)

Cases	Controls	Variables	OR (95% credibility interval)	Prob(log(OR))>0
Distance to agricultural areas				
15	886	> 200m	1	
39	1490	<50m	2.20 (1.11-4.25)	0.9894 ^[1]
32	1398	50m –100m	1.68 (0.87-3.35)	0.9412 ^[2]
30	1342	101m-200m	1.32 (0.78-2.55)	0.7869
Distance to streets				
10	203	>100m	1	
83	4077	<25m	3.85 (0.96-17.11)	0.9707 ^[1]
23	797	25m-100m	2.11 (0.69-7.53)	0.9203 ^[2]
Distance to local and county				
45	1725	>200m	1	
29	1177	<50m	0.80 (0.47-1.40)	0.7600
14	842	50m –100m	0.62 (0.33-1.17)	0.7240
28	1333	101m-200m	0.71 (0.41-1.18)	0.6997
Distance to dual-carriageways and motorways				
88	4625	>300m	1	
6	20	<50m	1.83 (0.15-14.26)	0.7243
4	69	50m-100m	1.15 (0.18-5.23)	0.5960
10	188	101m-200m	1.08 (0.27-3.65)	0.5453
8	145	200m-300m	1.22 (0.31-4.07)	0.6211
28	452	<300m	2.03 (0.94-4.08)	0.9635 ^[1]
Distance to petrol stations				
100	4957	>150m	1	
16	120	≤ 150m	0.43 (0.09-1.67)	0.8674
Distance to industrial estate A				
98	4798	>300m	1	
18	279	≤300m	1.51 (0.93-37.25)	0.9687 ^[1]
Land use				
74	3287	Urban	1	
15	764	Forests	0.21 (0.07-1.10)	0.971 ^[1]
22	798	Fruit trees and berries	0.42 (0.08-4.89)	0.7836
5	316	Transitional woodland scrub and natural grassland	0.37 (0.28-1.26)	0.9389 ^[2]

Adjusted by sex, year of birth, and a diagnosis of a member of the child's family: i) ADHD or conduct disorders, ii) anxiety, iii) depression, or iv) psychosis (in all cases regardless of the child); contextual deprivation index.

[1] Prob(abs(log(OR))>0) higher than 0.95.

[2] Prob(abs(log(OR))>0) higher than 0.90.

Figure 1a.- Map of the smoothed relative risks for the region studied^[1]

[1] Model with heterogeneity and spatial adjustment only (besides the expected cases in the census tract as an offset), without explanatory variables

Figure 1b.- Map of the posterior probability that the smoothed relative risks were greater than unity for the study region ^[1]

[1] Model with heterogeneity and spatial adjustment only (besides the expected cases in the census tract as an offset), without explanatory variables

Figure 2.- Distance to agriculture areas**Figure 3.- Distance to residential streets****Figure 4.- Distance to dual-carriageways and motorways**