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THE ASSOCIATION BETWEEN EXPOSURE TO ENVIRONMENTAL FACTORS AND THE OCCURRENCE OF ATTENTION-DEFICIT/HYPERACTIVITY DISORDER (ADHD). A POPULATION-BASED CASE CONTROL STUDY.

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

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Abstract

Background: A number of factors contribute to attention deficit hyperactivity disorder (ADHD) and while not all are known, when ADHD occurs, it is considered to be an interrelationship between multiple genetic and environmental factors. However, (apart from pesticides), the systematic evidence is extremely inadequate. In addition, non-systematic evidence is inconsistent and 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, they also differ in the adjustment of spatial and temporal variability. Here, our objective is to provide evidence on an association between environmental factors and the occurrence of ADHD.
Methods: In our study, we use a case control study constructed from a population-based retrospective cohort (n=5,193, 49.0% girls). The cases were children born between 1998 and 2012 and diagnosed with ADHD (n=116). They were matched with controls by sex and year of birth.
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: For the risk ADHD occurring, we found a certain north-south pattern containing two clusters, one in the centre of the study region and another in the south. The results from the multivariate model suggest that these clusters could be related to some of the environmental variables. Specifically, living less than 100 metres from an agricultural area or a residential street and/or living less than 300 metres from a motorway, dual carriageway or one of the industrial estates analysed in this study, 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 as a result of traffic, could be associated with the occurrence of ADHD.

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

1.- Introduction

Attention deficit hyperactivity disorder (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].

ADHD is one of the most frequent neurobehavioral disorders found in children and adolescents in the general population. In 2011, the US Centers for Disease Control and Prevention (CDC), using both survey data on diagnosis and medication treatment (answered by parents) and healthcare claim data on medication and psychological services, estimated an 11% prevalence of ADHD in children 4-17 years of age[4]. 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%[5]. This figure, according to expert consensus, can be considered to be a very good approximation to the population prevalence of ADHD[6]. Polanczyk *et al.,* conducted a systematic review and a meta-analysis of 102 articles from around the world, which included 171,756 children (from 1978 to 2005), and estimated a prevalence of around 5.29% (95% CI: 5.0%-5.6%) for subjects aged 18 years or younger[7]. In 2011, Wittcchen *et al.*, also using a systematic review and meta-analysis, pointed out that in the European Union 5% of children and adolescents between 6 and 17 years old had ADHD[8]. In 2012, Willcutt conducted a meta-analysis[9] which included 86 studies and 163,688 children and adolescents, and found a prevalence of between 5.9% and 7.1%. For Spain, Peiró *et al.,* also carried out a systematic review and meta-analysis of 14 studies, including a total of 13,026 children and adolescents aged between 5 and 16 years (from 1980 to 2011), and found a 6.8% prevalence of ADHD (95% CI: 4.9%-8.8%)[2].

That said, the prevalence of ADHD presents a great variability depending on the following factors: 1) Origin. The geographic origin of the studies in question shows that prevalence is significantly lower in Asia and Africa[7], and somewhat smaller (although statistically significant) in Europe compared to North America[10]. 2) Sex. With a ratio of 3 to 1, respectively[13], ADHD is much more present in boys than girls[11,12]. 3) Age. The range of prevalence of ADHD is higher in children and adolescents together, than in adolescents separately. Polanczyk et *al.*, point out that the range of prevalence was 2.4%-4% for adolescents, i.e., half that of the prevalence in children and adolescents together[7]. 4) Diagnostic criteria. When the American Psychiatric Association (DSM-IV) criteria rather than the WHO criteria (ICD-10)[14] is applied, the diagnosis of ADHD is five times more likely since they capture different groups (hyperkinetics). 5) Level of care[15]. A CDC study pointed out that, according to their estimates, half of the children who had ADHD had actually been diagnosed[6,16]. In contrast, a study in Spain found that ADHD was confirmed in only 24% of children referred from primary care services to mental health services for consultation or suspected diagnosis[17].

Although not all the factors involved in the occurrence of ADHD are known, an interrelationship between the multiple genetic and environmental factors in a broad sense is considered to exist. These include traffic-related air pollutants, exposure to chemicals and heavy metals, nutritional factors and variables associated with lifestyle[3].

However, the evidence of the association between environmental risk factors and ADHD occurring is not only very limited, it is also inadequate or even insufficient. Polańska *et al.*, in their systematic review of 40 studies published between 2000 and 2012, did not find a consistent association[3]. Suades-González *et al.*, in their systematic revision of 31 studies published between 2012 and 2015 on the association between outdoor air pollution and neuropsychological development in children, found inadequate or insufficient evidence for both pre- and postnatal exposure[18]. Lam *et al.*, who conducted a systematic review and a meta-analysis on developmental exposure to polybrominated diphenyl ethers (PBDEs) and intelligence or ADHD and ADHD related symptoms between 2009 and 2015 found, (as a consequence of the moderate quality of the body of evidence) limited evidence for the association of ADHD and attention-related-behaviours with PBDEs[19]. PBDEs are a group of synthetic chemicals used as chemical flame retardants found in a variety of every day products such as, among others, furniture, cars, building materials, textiles or computers and other electronic equipment[20].

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.*[21,22]. PAHs are widespread environmental pollutants generated primarily during the incomplete combustion of organic materials. The main, although not unique, sources of PAHs are anthropogenic activities which involve not only the incomplete combustion of carbon-containing fuels such as wood, coal, diesel oil, and tobacco[21,3] but, above all, activities that employ fossil fuels such as residential heating, coal gasification and liquefying plants, power plants, activities in petroleum refineries and motor vehicles [23]. Using a birth cohort of New York City children born to non-smoking women who were followed from the womb to childhood, Perera *et al.* found that higher umbilical cord PAH-DNA and other bulky aromatic adducts were associated with higher ADHD symptom scores at 4.8 and 7 years old, although this result has to be viewed with caution since selection bias is possible as a consequence of the distribution of sex and ethnicity of the children[21]. In a more recent article, they found that exposure to PAHs during the prenatal period (PAH-DNA adducts were measured in maternal blood at delivery) was associated with fivefold higher odds of behavioural problems associated with ADHD at age 9[22]. Perera *et al.,* considered that postnatal exposure to PAHs (measured by PAH metabolites in urine at ages 3 and 5) could be a confounder[21,22], thus giving it some kind of role in the association between prenatal exposure and ADHD. 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[24]. Likewise, 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 although ADHD symptoms were higher in children with higher exposure to PAHs and, above all, benzo[a]pyrene, associations were not statistically significant[25].

The evidence of an association with ADHD and exposure to other traffic-related air pollutants is simply insufficient. Siddique *et al.*, using a cross-sectional study with a random sample of school children in India, found that the prevalence of ADHD was much higher in children in Delhi when compared with the control group (OR=4.17, 95% CI 2.77-7.29) which had levels (annual averages) of air pollution (PM_{10}, SO_x and NO_x) practically half that in Delhi[26]. Nevertheless, the results of this study must be viewed cautiously because the study does not adjust for confounding variables such as health programs, access to child and adolescent mental health services, etc. Gong *et al.*, in a birth cohort study from Sweden between 1992 and 2012, found no association between either prenatal and postnatal exposure to NO_x and PM_{10} and ADHD[27]. Much more recently, Min and Min concluded that cumulative exposure to PM_{10} and NO_2 (from birth to diagnosis) was associated with the incidence of ADHD in childhood[28]. Using a population-based cohort of 8,936 children born in 2002 (followed over a 10-year period) and after adjusting for relevant confounders, they estimated a hazard ratio equal to 1.18 (95% CI: 1.15-1.21) for an increase in 1 $\mu g/m^3$ in PM_{10} and 1.03 (95% CI: 1.02-1.04) in NO_2. However, Fluegge and Fluegge, in response to Min and Min, found that exposure to PM_{10} and NO_2 was not associated with an increased risk of hospitalization for ADHD or conduct disorders[29]. It should be noted, however, that while in Min and Min the response variable was a diagnosis of ADHD (according to the DSM-IV criteria), Fluegge and Fluegge used a severe phenotype (i.e. hospitalization for ADHD and conduct disorders).

Studies have been somewhat more successful in associating air pollutants and some of the ADHD related symptoms. Newman *et al.*, using a prospective birth cohort from 2001 to 2003 in the Cincinnati (Ohio) metropolitan area, estimated a statistically significant association between exposure during infancy to elemental black carbon and increasing hyperactivity scores[30]. Chiu *et al.*, through a longitudinal pregnancy cohort study in Boston (Massachusetts) between November 1996 and December 1998, found an association between attention and children's lifetime exposure to black carbon[31]. Forns *et al.*, in a cross-sectional study of children aged 7 to 11 years in Barcelona (Catalonia, Spain) during 2012-2013, found that noise exposure at school (in an urban environment the main source of which is traffic, as is the case of air pollutants) was associated with more ADHD symptoms[32]. Notice, however, that noise as an obstacle for concentration is not a surrogate for air pollution. Very recently, Sentis *et al.*, using data from 2003 to 2008 from four regions in a population-based birth cohort (the Spanish INMA Environment and Childhood Project) including 1,298 children with complete data, found that higher exposure to ambient NO_2, both prenatal and postnatal, was associated with impaired intentional function in children 4-5 years of age, although the postnatal associations were only borderline statistically significant[33].

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[34]. In the

case of ADHD and behavioural problems, they reviewed 11 epidemiological studies, which included 6 cohort, 4 cross-sectional and 1 case-control study, published between 2004 and 2016. Associations were found for both prenatal (in cohort studies assessing exposure to organophosphorus[35-37] and organochlorine pesticides[38-41]) and postnatal exposures (in cross-sectional studies assessing exposure to organophosphorus[42,43] and pyrethroid pesticides[44]), and in a case-control study evaluating exposure to organophosphorus pesticides. Fluegge and Fluegge found that for every one-log unit increase in (state-level sum totals) the farm use of nitrogen fertilizers, the risk of hospitalization for ADHD, and also for conduct disorders was, after controlling for PM_{10} and NO_x[29], equal to 1.16 (95% CI: 1.06-1.28 for ADHD, 95% CI: 1.03-1.31 for conduct disorders). Associations were found for both ADHD[35-37,42-45] and ADHD-related symptoms such as irritability and behavioural problems[38-41]. Very recently, Dadvand *et al.*, using 2003-2013 INMA data from the population-based cohorts of Sabadell (Catalonia, Spain) and Valencia (Spain), found that exposure to residential surrounding greenness is associated with better scores on attention tests at 4-5 and 7 years of age[46]. Shortly after, Rosenquist *et al.* found that prenatal and postnatal exposures to two organochlorine compounds, polychlorinated biphenyls (PCBs) and dichlorodiphenyldichloroetylene (DDE), a breakdown product of dichlorodiphenyltrichloroethane, (DDT - used primarily as pesticide and for vector control), are associated with a higher prevalence of abnormal scores for conduct and hyperactivity at 5-9 years in Greenland and the Ukraine[47].

Postnatal exposure to some metals, in particular lead[45,48,49], selenium[50], and mercury[51], has been found to be associated with ADHD and its symptoms. It has even been proposed that the harmful effects of lead exposure could be confounded or modified by the neuroprotective role of iron deficiency[52-54]. However, the evidence is very limited and, in some cases, subject to caution due to a lack of control of confounding variables[55,56].

Only 3 of the 9 studies in the systematic review by Lam *et al.*, reported statistically significant associations[19]. However, of those 3 only 2 were rated as having a 'low' or 'probably low' risk of bias. In particular, Eskenazi *et al.,* reported a significant association between exposure to PBDEs (both, prenatal and postnatal) and ADHD[57] and Chen *et al.,* between prenatal exposure to PBDEs and ADHD related symptoms[58].

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)[59]. New Bedford Harbor was listed as a Superfund Site by the Environmental Protection Agency in 1982 because of contamination caused by polychlorinated biphenyl (PCB)-laden waste released between 1940 and 1977. These exposures include, among others, organochlorines, PCB and ρ,ρ'-dichlorodiphenyldichloroethylene (ρ,ρ'-DDE)[60,39,40] and metals such as mercury[51]. 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[59].

In summary, with the exception of pesticides, the systematic evidence for the association between environmental factors and ADHD is very limited. In addition, non-systematic evidence is inconsistent and differs not only for 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, and using a case-control constructed from a population-based retrospective cohort, we controlled 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 case-control study constructed from a retrospective population-based cohort. This cohort is composed of individuals who, between January 1, 2005 and December 31, 2012, 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), primary healthcare centres which are 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 (further details can be found elsewhere[61]).

In our case-control study, we included children from the cohort who had been born after 1998, that is, at most eight years of age in the first year of the follow-up of the cohort (n=5,193; 49.0% girls).

2.2.- Variables

- Response variable

Cases were children who, according to the WHO criteria (ICD-10: F90.0, F98.8), were diagnosed with ADHD by some of the IAS primary care physicians between 2005 and 2012 (n=116). The controls were all the children free of ADHD who had had contact with the IAS primary healthcare services from 2005 to 2012 (n=5077). Cases were matched with controls by sex and year of birth.

- Environmental explanatory variables

As explanatory variables of interest we included several environmental variables.

First, as a proxy of exposure to air pollutants associated with traffic, we included the distance between the child's home (either case or control) to the nearest traffic route. Traffic routes were classified as: i) streets, ii) local and county roads and iii) dual-carriageways and motorways.

Secondly, as a proxy to the exposure of pesticides, we considered the distance from the child's home to the nearest agricultural area.

In each case these distances were constructed by considering a geographical layer. Road and agricultural area layers were obtained from the Department of Territory and Sustainability of the Catalan Government, through the Cartographic and Geologic Institute of Catalonia (ICGC)[62] (further details can be found elsewhere[63]).

The distances considered were only proxies of environmental exposure and there might be other environmental variables that could influence the risk of having ADHD.

First, we considered the variable land use. We applied classification techniques based on LANDSAT MSS images[64,65] to land cover orthophoto maps of Catalonia (1:5,000) for the period 2005-2007, and constructed a land use map for 2010. Next, we constructed a 50 metre in diameter buffer around each child's address. We assigned only the percentage value corresponding to the principal land use within the 50m-buffer as the land use for each child's address. In this paper, we converted the twenty-two categories, obtained from the ICGC, into seven categories: i) dense forests, ii) fruit trees and berries, iii) transitional woodland scrub, iv) natural grassland, v) mixed forests, vi) coniferous forests, and vii) urban (further details can be found elsewhere[63]).

Second, we included two additional 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 in the study area (i.e. *La Selva Interior*). In these last two cases, the layers to compute the distances were obtained from OpenStreetMap (OMS) data[66].

All distance variables were categorized. To determine all the cut-off points, we performed previous sensitivity analyses. The distances to local and county roads and to the nearest agricultural area were categorized as follows: less than 50 metres, 50-100 metres, 101-200 metres, and more than 200 metres. We took this last category as the reference. In the distance to dual-carriageways, carriageways and motorways we introduced an additional category: less than 50 metres, 50-100 metres, 101-200 metres, 201-300 metres, and more than 300 metres (NB: this last category was taken as the reference). Here we also considered an additional categorization: at most 300 metres and more than 300 metres (reference category). The distance to streets was categorized as: less than 25 metres, 25-100 metres and more than 100 metres (taking this last category as the reference). The distance to the nearest petrol station was categorized as: less than 150 metres (more than 150 metres was the reference category) and the distance to the industrial estate: less than 300 metres (more than 300 metres was the reference category).

- Control variables

As control variables, we included variables associated with the child such as sex (girl was the reference category) and year of birth. In order to allow a non-linear relationship, year of birth was included as a categorical variable, taking 1998 as the reference.

We also considered variables associated with the child's family. After identifying 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 a deprivation index based on that used in the IneqCities project[67]. The index was created by combining seven socioeconomic indicators at the level of the census track in which the child was domiciled: i) percentage of unemployed persons, 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 45m^2. These indicators were obtained from the Spanish Population and Housing Census 2011[68]. The distance indicator DP_2 was used to combine the above-mentioned indicators into a single deprivation index[69] (further details can be found elsewhere[67]). The index was categorized into quartiles, taking the last quartile (i.e., that corresponding to the most depressed census tracts) 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 of the IAS during the study period, 2005-2012), as an offset we introduced into the model the expected numbers of ADHD cases in each census tract from each municipality of the study area (i.e., *La Selva Interior*). These numbers were calculated annually from 2005 to 2012 with the population of each year and the incidence rates observed in each census tract of ADHD by sex and age were taken as the reference. Population data by census tract, age and sex were obtained from the Catalan Institute of Statistics[70] and from the Spanish Population and Housing Census[68].

2.3.- *Statistical analysis*

The baseline characteristics of all the children were summarized by means, medians, standard deviations and by the first and the third quartile (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).

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

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

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 under study (i.e., *La Selva Interior*, Girona).

The reasons for not directly using the standardized incidence rates (i.e., the ratio between the observed count of ADHD in a particular area and the expected count in such an area) are well known (see, for instance Pascutto *et al.*[71] and Lawson *et al.*[72], 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[71] (both cases in our study). This problem can be addressed by spatial smoothing of the rates over space. That is, using a model that controls the extra variability inherent in the spatial design[72,73].

In our case, we used the model {1}, including in the linear predictor in this stage three random effects but no observable explanatory variables (although it 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 the '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 the spatial dependency we included in the regression and structured random effect with a Matérn structure explicitly constructed through the Stochastic Partial Differential Equation (SPDE) approach[74].

Further, we also controlled for the presence of heterogeneity, that is to say, unobserved variables, invariant over time, that are specific to the unit of analysis (children in our case), by introducing two additional unstructured random effects into the model. In particular, we considered individual heterogeneity, associated with each child, and familial heterogeneity, associated with the family to which the child belonged.

Once we had estimated the model {1}, we calculated the probability of being a case of ADHD. Using these probabilities, we 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 in a map of *La Selva Interior*. Maps at the census track level were obtained from the Spanish Population and Housing Census[68].

To help evaluate the existence of agglomerations of excess cases (i.e., clusters), we calculated the probability that the relative risks were above 1. 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[75]. The probabilities were also represented on a map of the study area.

- Estimating the probability of being a case

Our hypothesis was that most of the geographical pattern, if any, for ADHD could be explained by environmental variables. For this reason, at this stage we included in the linear predictor of each subject in the model {1} those variables that might explain the probability of being case, i.e., the environmental variables.

Furthermore, we controlled for both, observed confounders, including all the covariates indicated above, and unobserved confounders, i.e., individual and familial heterogeneity, and spatial dependence. 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[76], 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. In order to increase it, and since we obviously could not increase the sample size, we chose to allow the level of significance (i.e. alpha) to increase, which would reduce the probability of making a Type II error and, therefore, increase the statistical power.

All analyses were made with the free software R (version 3.4.0)[77], through the INLA package[78,76]. The maps were represented in QGIS (version 2.18)[79].

3.- Results

During the follow-up of the cohort (2005-2012), 86.55% of the children assigned to the ABS managed by the IAS made use of the 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.*[80] 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)[80]. The prevalence of ADHD was 3.35%, 3.53 times greater in boys (5.43%, n=91) than in girls (1.54%, n=25). Maximum prevalence was found in the group of children born between 1998 and 2000 (those aged 6-8 years in the first year of the cohort follow-up) with a prevalence of 4.12% (6.71% for boys and 1.2% for girls).

The maps of the smoothed relative risks of both the study area and the probability of these later increasing to more than 1 are shown in Figures 1a and 1b, respectively. These risks are 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. A certain north-south pattern for the risk of the occurrence of ADHD (Figure 1a) can be observed, with two clusters, one in the centre and the other in the south, of the study region. In general, these clusters are shown to coincide with proximity to agricultural areas, dual-carriageways and motorways.

Table 1 shows the baseline characteristics of the individuals participating in the study. The distances to the environmental variables of interest (from the residence of the case or control) were smaller in the cases than in 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, note that there was a much higher frequency of forest and natural grassland mixed-land use among the controls than among the cases, while land used for coniferous forests and, to a lesser degree, fruit trees and berries was more frequent among cases than among controls (always in relative terms).

Except for sex (with a much higher proportion of boys in the cases than in the controls), neither were there any significant differences between cases and controls in the control variables such as deprivation index (slightly less in the cases than in the controls, 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 of 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 less than 50 metres from an agricultural area had a greater risk of suffering from ADHD than those who lived further away (OR 2.208; 95% CI 1.121-4.523, Prob 98.9%). The same occurred, but to a lesser degree, in the children living 50-100 metres from an agricultural area (OR 1.688; 95% CI 0.854-3.449; Prob 93.2%). Furthermore, living less than 25 metres from the nearest road increased the risk of suffering ADHD with respect to living more than 100 metres away (OR 3.836; 95% CI 0.948-18.19; Prob

97.0%), as did living between 25 and 100 metres from the nearest road, albeit to a lesser degree (OR 2.109; 95% CI 0.673-8.378; Prob 91.6%). An association was also found between suffering from ADHD and living less than 300 metres from a dual-carriageway or a motorway (as opposed to living more than 300m away) (OR 2.052; 95% CI 0.922-4.100; Prob 96.4%) Moreover, living less than 300m from industrial estate A increased the risk of suffering from ADHD (OR 1.507; 95% CI 0.912-38.25 Prob 96.4%). While industrial estate A cannot be identified for reasons of confidentiality, we can reveal that factories producing cardboard tubes and packaging are located there. While 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.

Protective factors for the occurrence of ADHD were also found: mixed forest as the principal land use (OR 0.004; 95% CI 0.001-1.877; probability of the odds ratio being less than 1 95.5%) or natural grassland (OR 0.147; 95% CI 0.008-2.625; probability of the odds ratio being less than 1 90.5%) (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 less than 195-200 metres from an agricultural area are at greater risk of suffering from ADHD than the unit. The same is true for children living less than 125-130 metres from a road (Figure 3) and/or less than 150 metres from a dual-carriageway or motorway (Figure 4).

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

4.- Discussion

We found a certain north-south pattern for the risk of occurrence of ADHD, with two clusters; one in the centre of the study region and another in the south. The results of the multivariate model suggest that these clusters could be related to some of the environmental variables. Specifically, living less than 100 metres from an agricultural area or a residential street, or living less 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 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 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 would be in line with those where associations between exposure to pesticides and the occurrence of ADHD and ADHD related symptoms have been found[35-44]. We note in particular, those which find a relationship between postnatal exposure to pesticides and ADHD[42,44]. 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[44]. Using a cross-sectional design from the National Health and Nutrition Examination Survey (2000-2004), including 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 as having ADHD[42]. Associations between exposure to organochlorines (another type of pesticide) and ADHD and ADHD related symptoms were found only[34] for prenatal exposure[38-41].

Exposure to organochlorine compounds could be related to the excess risk found for children living less than 300 m from industrial estate A. 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[59,39,40]. It should be noted, however, that Vieira *et al.,* show that this possible association disappears after adjusting for socioeconomic conditions[59]. Indeed, local areas with greater pollution are usually where less wealthy families live and parents of children with ADHD 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 sense, 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 PM_{10} and NO_2 (from birth to diagnosis) was associated with the incidence of ADHD in childhood[28]. 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, such as black carbon[30,31], NO_2[33], and noise exposure as a consequence of the traffic[32], and some of the ADHD related symptoms. In addition, Perera *et al.,* reported a possible association between prenatal exposure to polycyclic aromatic hydrocarbons (PAHs) (one of whose sources are motor vehicle exhaust fumes) and ADHD and ADHD related-

symptoms, although results have to be treated with caution since there is a possible selection bias[21,22]. However, 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[25].

Our study might have some limitations. First, 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 environmental variable the child was exposed to. We believe, however, that we controlled 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 second limitation, the exposure to environmental variables could be a mix between prenatal and postnatal exposure. In fact, 12.5% of the children were born after 2005 (the first year of follow-up of the original cohort).

Our third limitation lies in the low prevalence we found for ADHD (3.35%). However, first and foremost, in our study the cases were diagnosed according to the WHO criteria (ICD-10), which provides a much lower prevalence than had the DSM-IV criteria been applied[14]. Second, we found that the prevalence of ADHD was 3.53 times higher in boys than in girls, a ratio that is in line with the literature[11-13]. 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, 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%)[6-9].

A fourth limitation is related to the fact that ICD-10 does not give an ADHD diagnosis, rather it gives an hyperkinetic diagnosis and, as discussed, this produces a different ADHD population. Even with 'residing in the same area' it is important to identify the effective functioning of the primary healthcare facilities and the role played by paediatricians, general practitioners, psychiatrists, and child and adolescent psychiatrists, since these factors are fundamental in obtaining an idea of the accuracy of the diagnoses. As we found, the expected numbers of hyperkinetic disorder are lower (2-2,5%) if ICD-10 is used, and expected cases of ADHD, are higher 5-6% if DSM is applied. Some other limitations when a longer period is used, can arise from the fact that some of the cases may have not been fully diagnosed.

Our fifth limitation is that, as in any Bayesian analysis, the choice of the prior distributions of model parameters (i.e., priors) may have had a considerable impact on the results. However, we used priors that penalize the complexity (PC priors)[81] and which have been found to be very robust. Furthermore, we performed sensitivity analyses to assess how the prior on the hyperparameters influenced the estimation results. First, by increasing the precision (lowering the variance) and second, by testing other priors i.e., 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.

Finally, further research on the relationship between genetics and environment and ADHD may be needed.

We believe that these limitations are offset by the strengths of our study. In particular, we point to three. First, we used a case-control constructed from a population-based retrospective cohort. The fact that it is population-based would allow its generalization. Only two of the studies analysed (Min and Min[28] and Sentis *et al.* [33]) also used data from a population-based cohort. Our second strength lies in the fact that, in addition to controlling for the observed confounding, we used random effects to control for unobserved confounding. Mortamais *et al.,*[25] and Forns *et al.,*[32] also used random effects to control for heterogeneity. Fortenberry *et al.,*[36] included random effect to control for temporal heterogeneity. Our third strength is that we adjusted for the spatial extra variability inherent in all spatial design. Only Sentis *et al.,*[33] (by means of Land Use Regression (LUR) models) and Vieira *et al.,* [59] (including a smoother of the location of each child) to some extent controlled that extra variability.

We believe that the results of our study suggest to public health authorities that they could 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 compounds of oxygen (such as the ECF method, partially free of chlorine or, better still, the TCF method which is completely chlorine free). Lastly, measures should be taken to reduce air polluting vehicle emissions.

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Competing interest

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).

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).

Authors' Contributions

MS had the original idea for the paper. MAB and MS 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 and MAB. 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; mean (SD)	116	97.902 (92.550)	5077	109.703 (95.939)	0.141
Median (Q1-Q3)		70.711 (25.000-156.603)		79.057 (35.355-167.705)	
Dist. streets; mean (SD)	116	45.634 (294.886)	5077	59.326 (358.289)	0.315
Median (85th-95th percentiles)		0.000 (25.000-70.711)		0.000 (25.000-77.271)	
Dist_local and county; mean (SD)	116	271.829 (408.535)	5077	265.124 (424.144)	0.892
Median (Q1-Q3)		125.000 (39.017-300.000)		134.629 (50.000-270.416)	
Dist. dual-carriageways /motorways; mean (SD)	116	2489.743 (2564.679)	5077	3100.075 (3273.862)	0.157
Median (Q1-Q3)		1558.959 (774.482-3284.327)		1550.000 (915.492-3824.265)	
Dist. petrol stations; mean (SD)	116	1399.901 (1235.304)	5077	1610.297 (1525.396)	0.513
Median (Q1-Q3)		925.169 (556.072-1824.912)		980.115 (538.516-2150.145)	
Dist. industrial estates, mean (SD)	116	16496.32 (7908.45)	5077	17403.6 (7901.4)	0.252
Median (Q1-Q3)		14979.90 (11064.75-18330.5)		15033.3 (11221.2-21372.4)	
Land use, n (%)	116		4950		
Coniferous forest		1 (0.9%)		15 (0.3%)	0.221
Dense forest		14 (12.1%)		536 (10.8%)	
Fruit trees and berries		22 (19.0%)		798 (16.1%)	
Transitional woodland scrub		4 (3.4%)		103 (2.0%)	
Natural grassland		1 (0.9%)		213 (4,3%)	
Mixed forest		0 (0.0%)		213 (4.3%)	
Urban		74 (63.8%)		3287 (66.4%)	
Sex; n (%)	116		5077		<0.001
Boys		91 (78.4%)		2635 (51.9%)	
Girls		25 (21.6%)		2442 (48.1%)	
Deprivation index, mean (SD)	116	17.045 (1.932)	5077	17.275 (2.085)	0.157
Median (Q1-Q3)		16.906 (16.066-17.779)		17.113 (16.506-18.649)	
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.

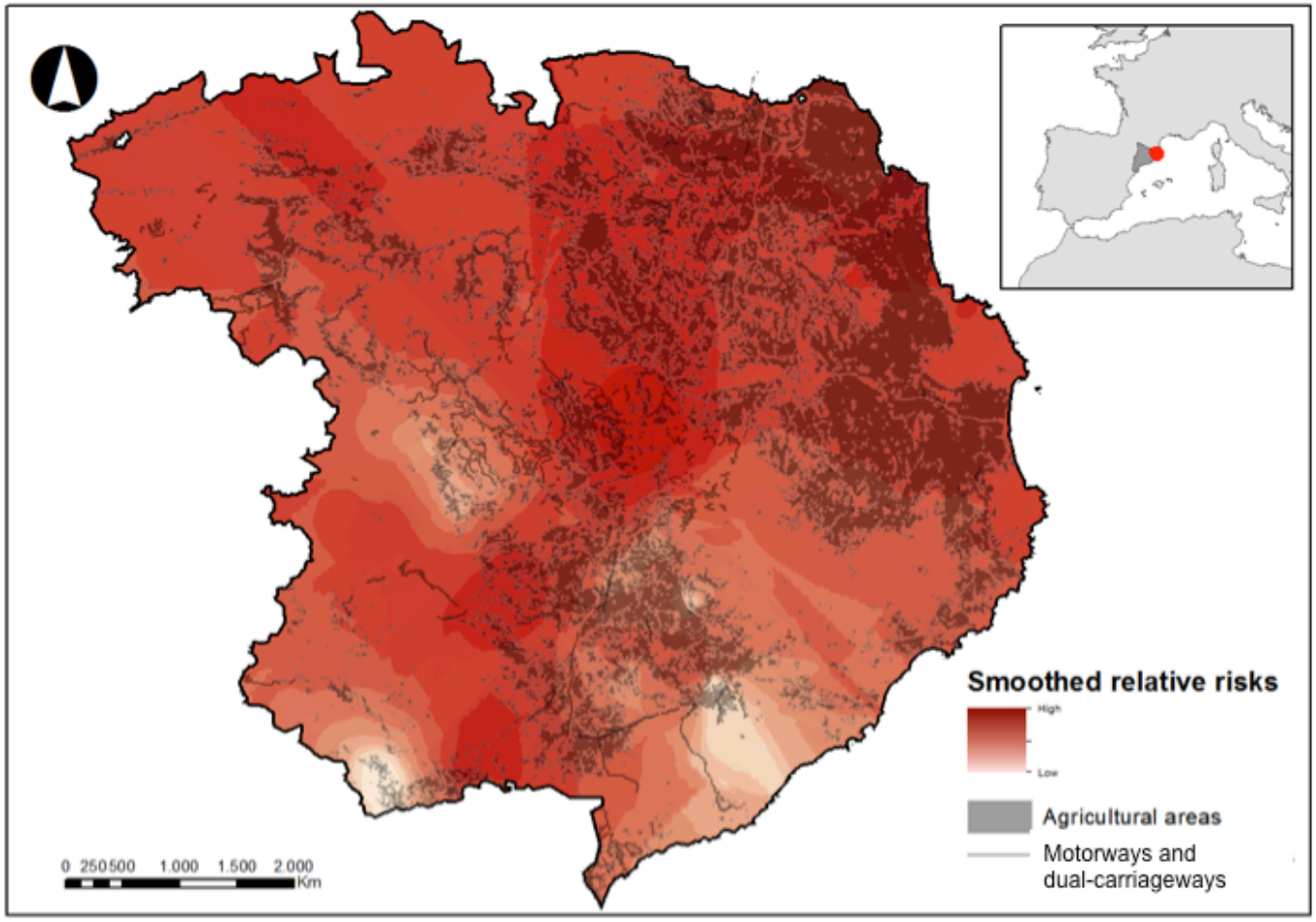
Table 2.- Association between environmental variables and occurrence of ADHD

Variables	OR (95% credibility interval)	Prob(|log(OR)|)>0
Dist. agricultural areas [>200m]		
<50m	2.208 (1.121-4.523)	0.9893
50m –100m	1.688 (0.854-3.449)	0.9322
101m-200m	1.321 (0.680-2.647)	0.7875
Dist. streets [>100m]		
<25m	3.836 (0.948-18.19)	0.9700
25m-100m	2.109 (0.673-8.378)	0.9158
Dist. local and county [>200m]		
<50m	0.816 (0.466-1.411)	0.7666
50m –100m	0.620 (0.309-1.183)	0.7247
101m-200m	0.696 (0.404-1.184)	0.7097
Dist. dual-carriageways and motorways [>300m]		
<50m	1.875 (0.144-14.30)	0.7244
50m-100m	1.162 (0.186-5.250)	0.5959
101m-200m	1.078 (0.254-3.666)	0.5653
200m-300m	1.215 (0.294-4.095)	0.6311
<300m	2.052 (0.922-4.100)	0.9635
Dist. petrol stations [>150m]	0.438 (0.082-1.678)	0.8674
Dist. industrial estate A [>300m]	1.507 (0.912-38.25)	0.9693
Land use [Urban]		
Dense forest	0.408 (0.057-4.846)	0.7970
Fruit trees and berries	0.417 (0.060-4.911)	0.7936
Transitional woodland scrub	0.660 (0.076-9.262)	0.6591
Natural grassland	0.147 (0.008-2.625)	0.9045
Mixed forest	0.004 (0.001-1.877)	0.9550
Coniferous forest	0.346 (0.052-3.950)	0.8350

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.

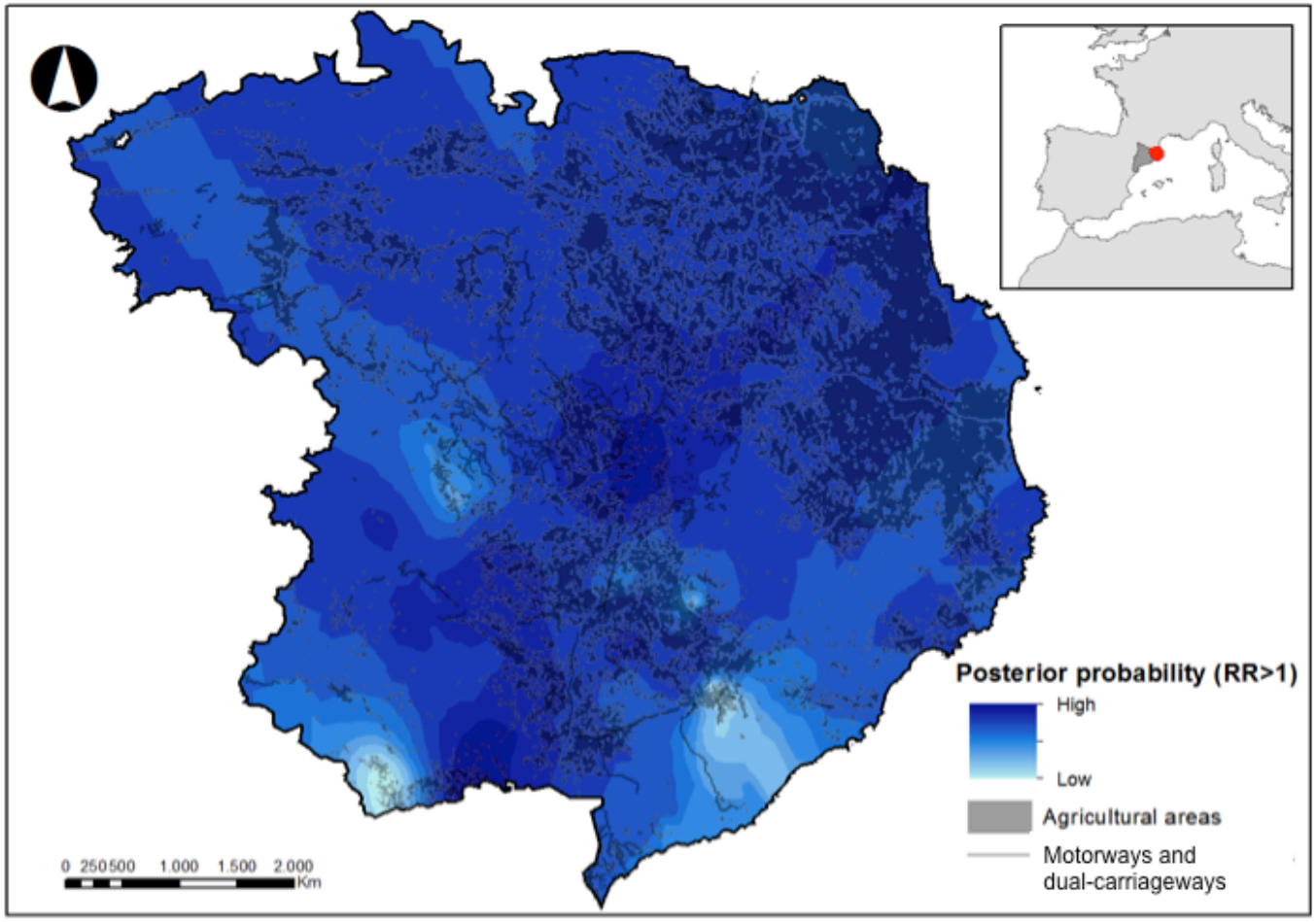
Prob(abs(log(OR))>0) higher than 0.95.
Prob(abs(log(OR))>0) higher than 0.90.

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



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

Figure 2.- Distance to agriculture areas

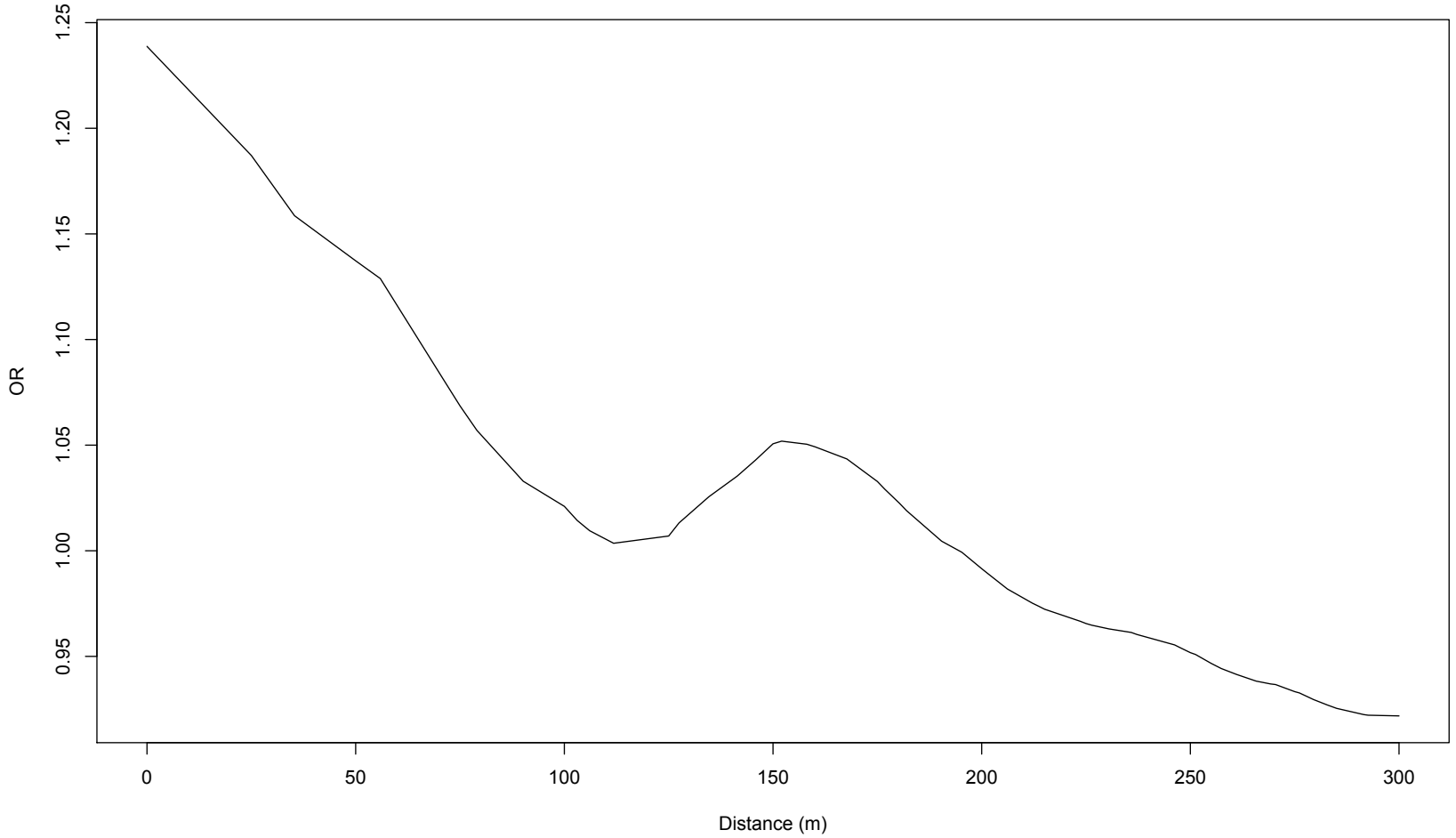


Figure 3.- Distance to residential streets

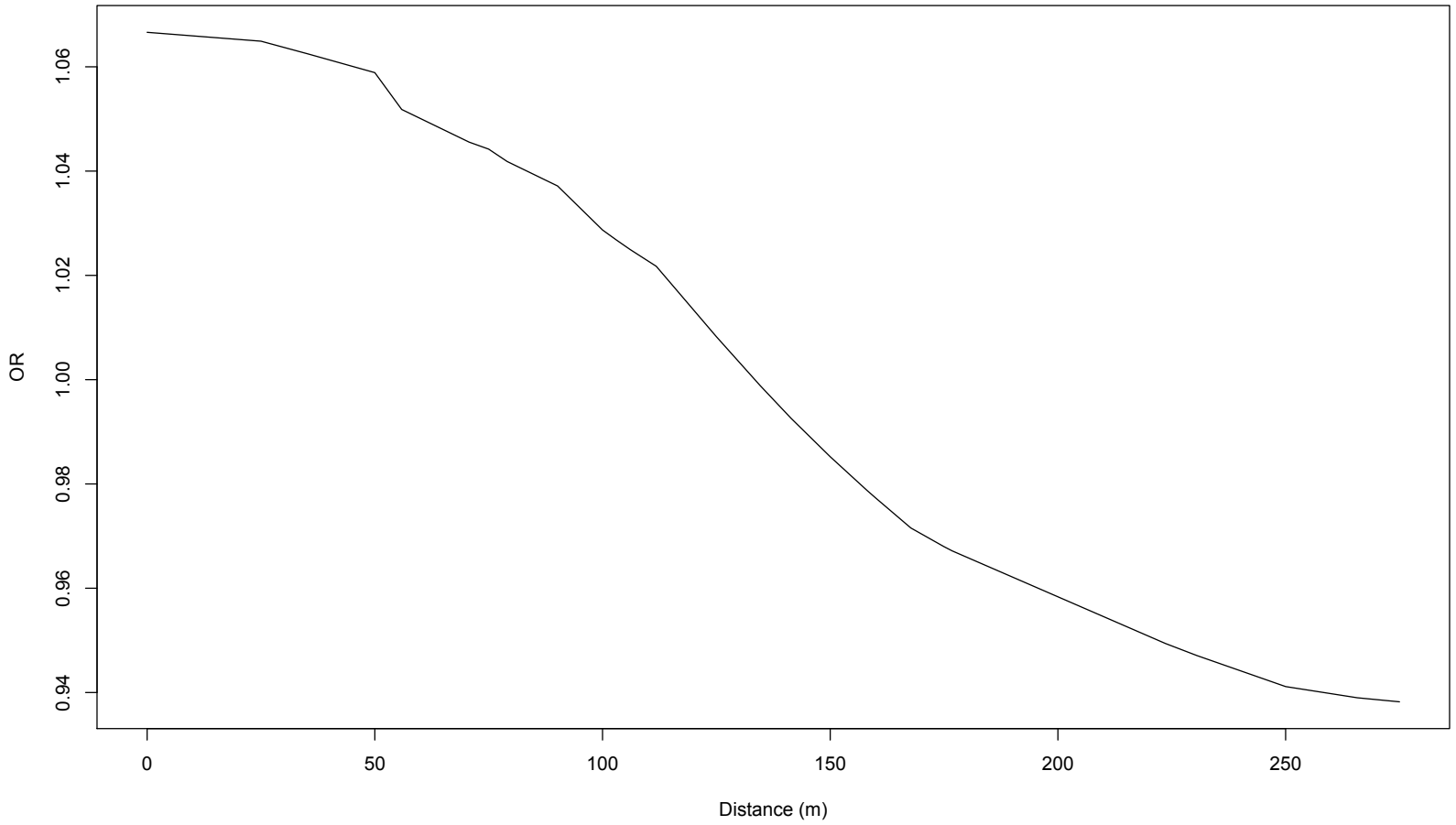
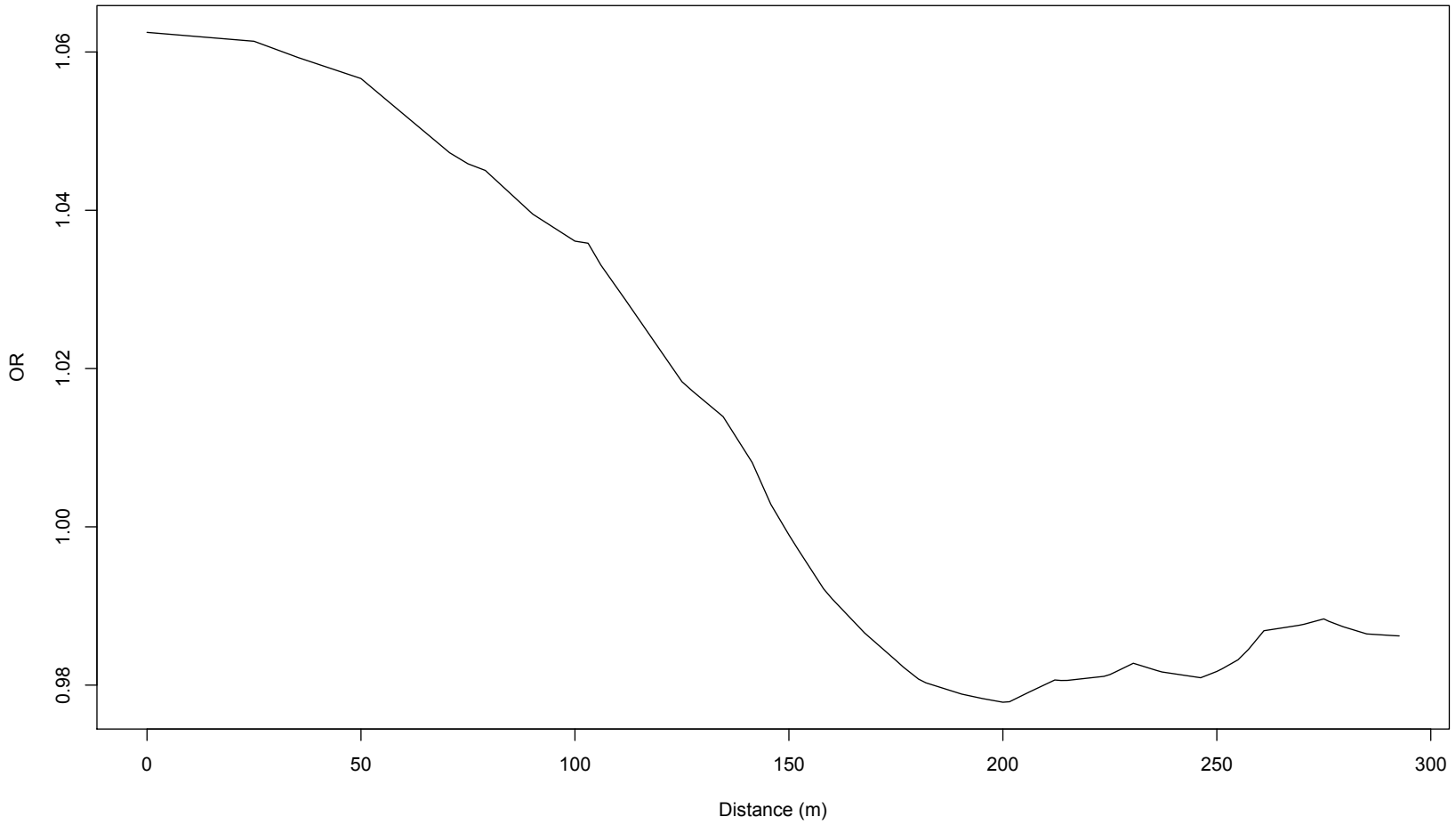


Figure 4.- Distance to dual-carriageways and motorways



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