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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 = 5193, 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 m from an agricultural area or a residential street and/or living fewer than 300 m 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.

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[1] http://www.udg.edu/grecs.htm.

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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 (Clinical Practice Guidelines on Attention Deficit Hyperactivity Disorder (ADHD), 2007). 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 (Grupo de trabajo de la, 2007; Peiró et al., 2017). Children with ADHD are, in fact, a heterogeneous population sharing common symptoms (Polańska et al., 2012).

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% (American Psychiatric Association, 2013). This figure, according to expert consensus, can be considered to be a very good approximation to the prevalence of ADHD in the total population (Schwartz, 2016). 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 (Polańska et al., 2012).

However, not only is the evidence of the association between environmental risk factors and developing ADHD (Polańska et al., 2012; Suades-González et al., 2015; Lam et al., 2017; ATSDR, 2017) 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. (2011), Perera et al. (2014). However, Abid et al., in a cross-sectional study of a nationally representative sample of U.S. children aged 6–15 years, did not find any association between postnatal exposure to PAHs (also measured by PAH metabolites in urine) and ADHD (Abid et al., 2014). Likewise, in a very recent cross-sectional study with children aged 8–12 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 (Mortamais et al., 2017). The evidence of an association between ADHD and exposure to other traffic-related air pollutants is simply insufficient (Siddique et al., 2011; Gong et al., 2014; Min and Min, 2017; Fluegge and Fluegge, 2017). Studies have, however, been somewhat more successful in associating air pollutants and some ADHD related symptoms (Newman et al., 2013; Chiu et al., 2013; Forns et al., 2016; Sentis et al., 2017).

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 (Mostafalou and Abdollahi, 2017). 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 (Braun et al., 2006; Bellinger et al., 1994; Swanson et al., 2007), selenium (Ode et al., 2015), and mercury (Sagiv et al., 2012a), 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 (1993–1998) residing in New Bedford, (Massachusetts, USA) (Vieira et al., 2017). 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 ρ,ρ'-dichlorodiphenyldichloroethylene (ρ,ρ'-DDE) (Korrick et al., 2000; Sagiv et al., 2010, 2012b) and metals such as mercury (Sagiv et al., 2012a). 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 (Vieira et al., 2017).

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 (Barceló et al., 2016)).

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