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Review article

Systematic review of the association between particulate matter exposure and autism spectrum disorders

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ABSTRACT

Particulate matter (PM) as an environmental pollutant is suspected to be associated with autism spectrum disorders. The aim of the present study was to review the epidemiological literature currently available on the relation between PM exposure and diagnosis of ASD. The PubMed database was searched from November 2015 up to January 2016 by one of the authors. We included observational studies (cohort and case–control studies) published in English carried out in children within the last 10 years, measuring PM exposure and health outcomes related to ASD. 13 studies met the inclusion criteria. Four of the studies found no association between PM exposure and ASD. The other 8 studies show positive associations restricted to specific exposure windows which however do not reach statistical significance at times. To conclude, the evidence from the studies allows us to conclude that there is an association between PM exposure and ASD whose strength varies according to the particle size studied with the association with $PM_{2.5}$ and diesel PM being stronger. Given the potential importance for public health, cohort studies with proper adjustment for confounding variables and identification of critical windows of exposure are urgently needed to further improve knowledge about potential causal links between PM exposure and the development of ASD.

1. Introduction

Autism spectrum disorders (ASD) is a group of heterogeneous neurodevelopmental disorders characterized by impairment in communication and social interaction accompanied with repetitive and restrictive behaviors (Lai et al., 2014). These symptoms present themselves in the early developmental period and can cause significant social and occupational impairment. ASD now encompasses the previous autistic disorder (autism), Asperger's disorder, childhood disintegrative disorder, and pervasive developmental disorder not otherwise specified (PDD-NOS).

Globally speaking, the prevalence today of ASD is estimated to be between 6.2 and 7.6/1000 persons and rising (Elsabbagh et al., 2012; Baxter et al., 2015) which leads to a higher interest in the possible causes and risk factors associated with it. Up until recently, the study of the etiology of ASD was centered around its genetic component (Sandin et al., 2014; Lai et al., 2014; Geschwind et al., 2007; Newschaffer et al., 2007) and the potential environmental contributions were less investigated [Lawler, 2008].

Recent studies present evidence that suggest that environmental factors such as air pollution play a greater role as risk factors than previously thought (Hallmayer et al., 2011; Lyall et al., 2014; Grandjean et al., 2014; Sandin et al., 2014; Kalkbrenner et al., 2014).

Environmental or air pollution can be defined as the mixture of gases and particles that contaminate the atmosphere and modify its natural characteristics (WHO, 2006). The emission of air pollution can be commonly traced back to the burning of fossil fuels as well as industrial and agricultural processes It has become a global public health concern and among the pollutants of most concern we find particulate matter (PM) ($PM_{2.5}$, PM_{10} and diesel PM), carbon monoxide (CO), ozone (O_3), nitrogen dioxide (NO_2) and sulfur dioxide (SO_2) (WHO 2005; WHO, 2013). A large number of studies support an association between air pollution and ASD; however specific evidence for individual constituents is conflicting or limited. The different components of air pollution could act synergistically and further studies on this phenomenon are needed. However, PM is a component of particular interest in relation to neurodevelopment and specifically ASD. PM components are suspected to be one of the major culprits of

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the neurological effects of air pollution (Block et al., 2012) given that they may penetrate cellular membranes (Geiser et al., 2005; Rothen-Rutishauser et al., 2008) and translocate from the systemic circulation or via the nasal mucosa and the olfactory bulb to the lungs and into the brain (Campbell et al., 2009; Oberdorster et al., 2009). Therefore a review of its stand-alone association with ASD is warranted. The data included here from the selected publications is that from the one-pollutant models when data from both one and multi-pollutant models was available. PM is a very broad category, containing not only particles of different sizes, but also different sources and constituents. In this review PM will be divided into the following three categories; $PM_{2.5}$, PM_{10} and diesel PM. Below this review will explore the possible relation between PM and ASD through a systematic review of the literature published on the possible relation among air pollution and ASD.

2. Methods

2.1. Study identification and eligibility criteria

A preliminary search performed to assess the prevalence of other systematic reviews covering the possible association between $PM_{2.5}$, PM_{10} and/or diesel PM and ASD yielded 4 relevant articles (Kalkbrenner et al., 2014; Rossignol et al., 2014; Suades-González et al., 2015 and Weisskopf et al., 2015) whose findings have been taken into account when discussing our own conclusions. The database we based our search on to identify publications eligible for inclusion in our review was PubMed, which was accessed between November 1, 2015 and January 1, 2016 for relevant studies, using the keywords: "environmental," "pollution," and "particulate" combined with "autism". Fig. 1 shows the search strategy followed for this review. A total of 1063 articles were identified. Due to the large number of studies found the first item on the eligibility criteria (human study subjects) was used at this point to reduce the number of articles to be examined, which left n=717 articles. Initial screening identified 51 candidate studies. The initial screening of the studies was performed using the information available in the title and abstract. These potentially relevant studies were retrieved in full text and assessed for eligibility. The eligibility criteria used were that the study had to:

1. Include humans as study subjects without restriction on the demographic characteristics of the population.
2. Conduct exposure assessment to $PM_{2.5}$, PM_{10} and/or diesel PM during pregnancy or early childhood.
3. Include measures of autism symptoms or diagnosis.
4. Be a primary research article published after 2005.

The publications were only included in the analysis if they met all the eligibility criteria. After a full assessment of the potentially relevant studies, initially 13 were proposed to be included in this systematic review. Of these, 12 included data relating specifically to PM exposure. 5 studies included data on $PM_{2.5}$ (Guxens et al., 2015; Becerra et al., 2013; Talbott et al., 2015a; Raz et al., 2015 and Volk et al., 2013), 7 on PM_{10} (Jung et al., 2013; Gong et al., 2014; Guxens et al., 2015; Becerra et al., 2013, Kalkbrenner et al., 2015; Raz et al., 2015, and Volk et al., 2013) and 5 on diesel PM (Kalkbrenner et al., 2010; Talbott et al., 2015b; Windham et al., 2006; Roberts et al., 2013 and Volk et al., 2011). The remaining publication included indirect information based on the distance of the exposure area to freeways but after consideration was deemed apt to be included in this study. All of the 13 research articles included in this review have been included in at least one of the three previously mentioned reviews. However, the different approach with which this review has been conducted justifies the inclusion of these studies.

This paper was written taking into account the methodological norms established for the publication of systematic reviews and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) recommendations (Friedenreich, 1993; Liberati et al., 2009).

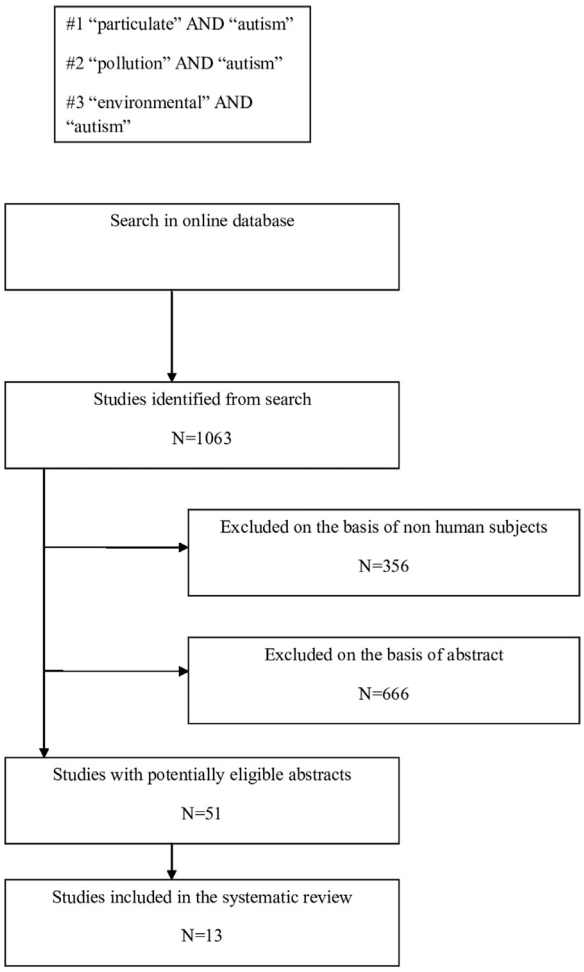

Fig. 1. Search strategy.

2.2. Internal validity

To further assess the chosen articles and guide the evaluation of the data included in them, we classified the publications using the scale proposed by the Scottish Intercollegiate Guidelines Network [SIGN, 2008] for establishing levels of evidence (Table 1) and recommendations (Table 2). Evidence is classified by its epistemologic strength and only the strongest gives way to strong recommendations while the weaker evidence can only yield weak recommendations. The scale proposes that the study design and the risk of bias be used to assess the quality of the scientific evidence provided (level of evidence). To rate the study design numbers (1–4) are used, while signs (++, + and -) are used to represent the assessed risk of bias. Based on this assessment of the quality of the evidence in the articles, grades (A–D) are then used to classify the strength of associated recommendations.

This scale was chosen following the principles of evidence based medicine (EBM) which emphasizes the use of evidence from well designed and conducted research. EBM is about making sure that when a decision is made it is based on the most up to date, reliable and scientifically solid evidence available on the particular situation being studied (Sackett, 1997). Depending on the defined area of study, the quality or rating of the current best evidence available may be constrained due to ethical or other limitations. These restrictions on the rating of the evidence are at times insurmountable and must not be seen as detrimental to the study just as another characteristic of it. The