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## REVIEW ARTICLE

### Autism in 2016: the need for answers<sup>☆</sup>

Q1 Annio Posar<sup>a,b,\*</sup>, Paola Visconti<sup>a</sup>

<sup>a</sup> IRCCS Institute of Neurological Sciences of Bologna, Child Neurology and Psychiatry Unit, Bologna, Italy

<sup>b</sup> University of Bologna, Department of Biomedical and Neuromotor Sciences, Bologna, Italy

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#### KEYWORDS

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Neurobiology;  
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Environmental factors;  
Air pollutants;  
Epigenetics

#### Abstract

**Objective:** Autism spectrum disorders are lifelong and often devastating conditions that severely affect social functioning and self-sufficiency. The etiopathogenesis is presumably multifactorial, resulting from a very complex interaction between genetic and environmental factors. The dramatic increase in autism spectrum disorder prevalence observed during the last decades has led to placing more emphasis on the role of environmental factors in the etiopathogenesis. The objective of this narrative biomedical review was to summarize and discuss the results of the most recent and relevant studies about the environmental factors hypothetically involved in autism spectrum disorder etiopathogenesis.

**Sources:** A search was performed in PubMed (United States National Library of Medicine) about the environmental factors hypothetically involved in the non-syndromic autism spectrum disorder etiopathogenesis, including: air pollutants, pesticides and other endocrine-disrupting chemicals, electromagnetic pollution, vaccinations, and diet modifications.

**Summary of the findings:** While the association between air pollutants, pesticides and other endocrine-disrupting chemicals, and risk for autism spectrum disorder is receiving increasing confirmation, the hypothesis of a real causal relation between them needs further data. The possible pathogenic mechanisms by which environmental factors can lead to autism spectrum disorder in genetically predisposed individuals were summarized, giving particular emphasis to the increasingly important role of epigenetics.

**Conclusions:** Future research should investigate whether there is a significant difference in the prevalence of autism spectrum disorder among nations with high and low levels of the various types of pollution. A very important goal of the research concerning the interactions between genetic and environmental factors in autism spectrum disorder etiopathogenesis is the identification of vulnerable populations, also in view of proper prevention.

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\* Corresponding author.

E-mail: [annio.posar@unibo.it](mailto:annio.posar@unibo.it) (A. Posar).

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**PALAVRAS-CHAVE**

Transtorno do espectro autista;  
Neurobiologia;  
Epidemiologia;  
Fatores ambientais;  
Poluentes atmosféricos;  
Epigenética

**Autismo em 2016: necessidade de respostas****Resumo**

**Objetivo:** Os transtornos do espectro autista (TEAs) são vitalícios e normalmente são doenças devastadoras que afetam gravemente o funcionamento social e a autossuficiência. A etiopatogenia é presumivelmente multifatorial, resultante de uma interação muito complexa entre fatores genéticos e ambientais. O aumento drástico na prevalência de TEAs observado nas últimas décadas levou à maior ênfase no papel dos fatores ambientais na etiopatogenia. O objetivo desta análise da narrativa biomédica foi resumir e discutir os resultados dos estudos mais recentes e relevantes sobre os fatores ambientais hipoteticamente envolvidos na etiopatogenia dos TEAs.

**Fontes:** Foi realizada uma pesquisa na Biblioteca Nacional de Medicina dos Estados Unidos (PubMed) sobre os fatores ambientais hipoteticamente envolvidos na etiopatogenia dos TEAs não sindrômicos, incluindo: poluentes atmosféricos, pesticidas e outros desreguladores endócrinos, poluição eletromagnética, vacinas e alterações na dieta.

**Resumo dos achados:** Embora a associação entre poluentes atmosféricos, pesticidas e outros desreguladores endócrinos e o risco de TEA esteja recebendo cada vez mais confirmações, a hipótese de uma relação causal real entre eles ainda precisa de mais dados. Os possíveis mecanismos patogênicos por meio dos quais os fatores ambientais podem causar TEA em indivíduos geneticamente predispostos foram resumidos, com ênfase especial no papel cada vez mais importante da epigenética.

**Conclusões:** Futuras pesquisas devem investigar se há uma diferença significativa na prevalência de TEA entre nações com níveis altos e baixos de vários tipos de poluição. Um objetivo muito importante da pesquisa a respeito das interações entre fatores genéticos e ambientais na etiopatogenia do TEA é a identificação de populações vulneráveis, também em virtude da prevenção adequada.

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**Introduction**

Autism spectrum disorders (ASDs) are lifelong and often devastating conditions that severely affect social functioning and self-sufficiency, having a very negative impact on the lives of the entire family of the affected individuals. According to the criteria of the *Diagnostic and Statistical Manual of Mental Disorders*, 5th edition (DSM-5), ASDs are defined by persisting deficits in social communication and interaction, as well as by restricted and repetitive behaviors, interests, and activities.<sup>1</sup> ASDs presumably have a multifactorial etiopathogenesis, resulting from a very complex interaction between genetic and environmental factors.<sup>2,3</sup> Only in a minority of cases is the presence of a defined medical condition demonstrable.

Epidemiological studies during the last decades have shown a dramatic increase in ASD prevalence, which has reached as much as 1–2% of children in recent years.<sup>4</sup> The epidemiological study by Nevison suggests that this increase is mainly real,<sup>5</sup> and therefore only in small part attributable to better knowledge of the problem. This phenomenon needs further investigation and possible explanatory hypotheses in terms of public health. Of course this prevalence increase cannot be explained based only on genetic factors, and the role of possible environmental factors should be carefully considered. First, it is necessary to understand what has changed in the environment and habits during the last few decades. In literature, several

hypotheses have been considered. In this review, the authors carried out a synthesis of the most intriguing hypotheses as follows: all the recent (between January 1, 2013 and August 20, 2016) and relevant (preferably case-control studies involving humans) literature available on PubMed (United States National Library of Medicine) was selected, using the following keywords: ‘autism’, ‘air pollutants’, ‘pollution’, ‘pesticides’, ‘endocrine-disrupting chemicals’, ‘environmental factors’, ‘electromagnetic fields’, ‘vaccinations’, ‘omega-3’, and ‘epigenetics’.

**Air pollutants**

Over the last years, the etiopathogenic role of the exposure to air pollutants, mainly heavy metals and particulate matter (PM) during the pre-, peri-, and postnatal period, has been seriously considered in the literature, although definite conclusions are lacking. Here follows a brief description of some of the most important recent papers in this regard.

Becerra et al. investigated the possible effect of traffic-related air pollution exposure during pregnancy on the development of autism. The authors performed a population-based case-control study using data from air monitoring stations and a land-use regression (LUR) model to estimate exposure rates. They identified children born in Los Angeles, California, United States of America (USA), who were diagnosed with a primary autistic disorder (AD)

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