

Reply to Fluegge: Association Between Atopic Dermatitis and Autism Spectrum Disorders: A Systematic Review

Lucia Billeci^{1,2} · Alessandro Tonacci² · Gennaro Tartarisco³ · Liliana Ruta^{4,2} · Giovanni Pioggia³ · Sebastiano Gangemi⁵

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We would like to thank Dr Fluegge [1] for his interest and comments on our recently published systematic review [2], which investigates the association between autism spectrum disorders (ASD) and atopic dermatitis (AD).

Dr Fluegge suggests that a possible explanation for the relationship between ASD and AD could be the complex interaction between an enhanced opioidergic activity and reduced baseline vitamin D levels, both determined by a gestational exposure to nitrous oxide (N₂O) [1].

ASD is a complex heterogeneous disorder, the etiology of which seems to be determined by genetic susceptibility, immunological alterations, and likely environmental factors [3]. Indeed, the role of environmental exposure in ASD etiology has been repeatedly suggested [4]. Nitrogen oxides (NO_x), consisting of nitric oxide (NO), nitrogen dioxide (NO₂) and N₂O, are among the compounds that are

emitted in the environment. Their presence in the atmosphere occurs both naturally (i.e., bacterial processes, biological growth and decay) and due to man's activities (i.e., fossil fuels).

NO is one of the biomarkers of oxidative stress, which has in turn been investigated as a possible mechanism explaining ASD pathogenesis [5]. Oxidative stress may act as a result of the cumulative influence of toxic environmental factors, which could lead to neuronal damage in genetically predisposed individuals [5]. NO is involved in many neuropsychiatric disorders and is known to affect neurodevelopmental processes in the central nervous system [6]. Indeed, elevated NO plasma levels have been found in subjects with ASD compared with control groups [7]. In addition, a positive correlation between ASD and perinatal exposure to air pollution, in particular NO and NO₂, has been found [8].

Since both high plasma ammonia and high plasma NO have been observed in subjects with ASD [6, 7], elevated levels of N₂O might also be hypothesized. It has been suggested that high amounts of N₂O could explain the observation of uncontrollable laughter and high pain tolerances seen in some subjects with ASD [9]. However, to the best of our knowledge, until now there has been no study evaluating the N₂O level in subjects with ASD and correlating it with ASD symptoms.

It could be hypothesized, as Dr Fluegge suggested, that N₂O could mediate vitamin D reduction in ASD. It has been suggested, for example, that N₂O could reduce solar radiation, therefore having an adverse effect by reducing vitamin D synthesis by the mother and thereby vitamin D insufficiency in the neonate, leading to susceptibility to respiratory infection and other conditions [10]. Our review on the association between ASD and vitamin D [11] has

✉ Giovanni Pioggia
giovanni.pioggia@cnr.it

¹ Department of Clinical and Experimental Medicine, University of Pisa, via Savi 10, 56126 Pisa, Italy

² Institute of Clinical Physiology, National Research Council of Italy (CNR), via Moruzzi 1, 56124 Pisa, Italy

³ Institute of Applied Sciences and Intelligent Systems “Eduardo Caianiello” (ISASI), National Research Council of Italy (CNR), via Torre Bianca, Mortelle, 98164 Messina, Italy

⁴ Department of Developmental Neuroscience, Stella Maris Scientific Institute, viale del Tirreno 331, 56018 Pisa, Calambrone, Italy

⁵ School and Division of Allergy and Clinical Immunology, Department of Clinical and Experimental Medicine, University Hospital “G. Martino”, via C. Valeria 1, 98125 Messina, Italy

suggested a putative role of vitamin D in the etiology of ASD, at least in a subgroup of subjects.

However, it is worth mentioning that none of the studies that we have analyzed in our systematic reviews on AD [2] and vitamin D [11] have evaluated N₂O in the association among AD, vitamin D, and ASD. Therefore, further studies need to be performed to elucidate the possible role of N₂O in the interaction between vitamin D and AD, and in the etiology of ASD.

Moreover, the toxicity of N₂O has been assessed in healthy individuals and is still controversial [12], although it seems that it could cause adverse effects in certain vulnerable populations. Finally, further studies are needed to elucidate the possible use of opioid antagonists for ASD treatment since they could improve hyperactivity and restlessness without having an impact on core features of ASD in the majority of the participants [13].

In conclusion, in our opinion it is important to bear in mind that ASD is an heterogeneous disorder and that its etiology is multifactorial, so N₂O exposure might be one of the putative factors contributing to the pathogenesis of ASD, particularly in a subset of genetically susceptible individuals. Furthermore, the use of opioid antagonists and similar medications for ASD treatment should be considered with caution in a subgroup of individuals with specific characteristics.

Compliance with Ethical Standards

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Conflict of interest Lucia Billeci, Alessandro Tonacci, Gennaro Tartarisco, Liliana Ruta, Giovanni Pioggia, and Sebastiano Gangemi declare that they have no conflicts of interest.

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