



Review article

Association of atopic diseases and attention-deficit/hyperactivity disorder: A systematic review and meta-analyses



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ABSTRACT

Over the last decades, the hypothesis has been raised that an atopic response could lead to the development of attention-deficit/hyperactivity disorder (ADHD). This study systematically reviews the observational cross-sectional and longitudinal studies that assessed the association between atopic disorders including asthma, atopic eczema, allergic rhinitis, and ADHD in children and adolescents. For longitudinal studies, a weighted Mantel-Haenszel odds ratio of these associations was estimated. The majority of cross-sectional and longitudinal studies reported a statistically significant positive association. The meta-analysis of longitudinal studies revealed an overall weighted odds ratio for asthma of 1.34 (95% confidence interval [CI] 1.24–1.44), 1.32 (95% CI 1.20–1.45) for atopic eczema, and 1.52 (95% CI 1.43–1.63) for allergic rhinitis. Heterogeneity of study data was low (I^2 : 0%, $p=0.46$ and $p=0.64$, respectively) for both studies examining asthma and eczema but substantial for rhinitis studies (I^2 : 82%, $p=0.004$). This current systematic review provides strong evidence that ADHD is associated with atopic diseases and that individuals have a 30% to 50% greater chance of developing ADHD compared to controls.

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1. Introduction

In 1975, the hypothesis was already being raised that different food components that could also act as allergens in an atopic response could lead to the development of hyperactivity (Feingold, 1975). Preliminary evidence suggested therapeutic benefits of a hypoallergenic diet for children with attention-deficit/hyperactivity disorder (ADHD), a childhood-onset neurodevelopmental disorder (Mullins et al., 2011; Pelsner et al., 2011; Poulton et al., 2011). Multiple hypotheses have been raised regarding the underlying mechanism of the association between atopy and ADHD. Besides shared risk factors for both diseases, an increase in the cytokines release caused by an allergic inflammation may affect specific regions in the prefrontal cortex and neurotransmitter systems that are known to play a role in the pathology of ADHD (Buske-Kirschbaum et al., 2013).

Over the last decade, multiple cross-sectional studies determined an association between the most common atopic diseases (i.e., asthma, atopic eczema, and allergic rhinitis) and ADHD (Chou et al., 2013b; Schmitt et al., 2010b; Yaghmaie et al., 2013a). Atopy often precedes ADHD which is the reason that current reasoning is focused on the onset of ADHD as a consequence of atopy. However, prospective longitudinal data is minimal, therefore, conclusions about temporality should be made with caution.

Until now, the majority of studies found a positive association between atopy in general and ADHD (Chen et al., 2014b). Studies focussing on specific atopic diseases remain inconclusive. The systematic review of Schmitt et al. (2010b), however, concluded that it is not atopy in general but only eczema that is related to ADHD independent of other atopic diseases. In this review, the authors conclude that this positive association between asthma and ADHD was at least partly confounded by eczema which precedes asthma and allergic rhinitis in the atopic procession. No association was found between allergic rhinitis and ADHD in the review of (Schmitt et al., 2010b), however, after that review, multiple studies determined a positive association between asthma and ADHD independent of eczema (Chen et al., 2013a; Hak et al., 2013; Mogensen et al., 2011b; Tsai and Lue, 2012). Also multiple recent studies found an association between allergic rhinitis and ADHD (Garg and Silverberg, 2014; Shyu et al., 2012; Tsai et al., 2011). Yet, there are still substantial differences in the quality between the recently published studies and, therefore, the associations of the three independent main atopic diseases with ADHD remains conflicting.

The objective of this study was to systematically review the available evidence of the association between the different atopic diseases such as asthma, eczema, and allergic rhinitis with the onset of ADHD in children and adolescents and to estimate the strength of the association in a meta-analysis.

2. Methods

The Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement was followed (Moher et al., 2009). A checklist of the PRISMA statement can be found in Appendix I in Supplementary material. In an attempt to first update the review of Schmitt et al. (2010b), a qualitative data synthesis was performed by systematically reviewing the newly available cross-sectional

studies examining the co-occurrence of atopy and ADHD. This was followed by a quantitative data synthesis with regard to the available longitudinal studies: through a meta-analysis, the strength of the association was estimated by pooling the studies with a longitudinal design investigating the presence of atopy and the onset of ADHD.

2.1. Selection criteria for eligible studies

Observational studies with the objective to assess the association between one of the three main atopic diseases (i.e., asthma, eczema, and/or allergic rhinitis) and ADHD in children and adolescents (under the age of 18 years old) were included. Any of the atopic diseases were defined as the exposure variable and ADHD as the outcome variable in accordance with the general order of development in children. Studies were included if they examined the prevalence and/or incidence of ADHD in relationship to one or more of the three atopic diseases in children/adolescents. Studies were only included when there was a comparative reference group available either matched or unmatched to the case or exposed group. Any exposure assessment method of asthma, eczema, and/or allergic rhinitis was included. Regarding the outcome measure, any method of assessment of ADHD and/or ADHD symptoms, all types, i.e., predominantly inattentive or predominantly hyperactive-impulsive and the combined type, were included in the narrative review as well as the quantitative meta-analysis. Studies were excluded if there was no quantitative information available on the association between any of the atopic diseases and ADHD. Either crude data on exposure and outcome or the odds ratio of the association between an atopic disease and ADHD needed to be reported. If there was an overlapping or similar dataset used in different published articles, the dataset with the shorter follow-up or substandard study quality was excluded. Studies published only as an abstract, not written in a peer reviewed journal, or not written in English were also excluded.

2.2. Search strategy and study selection

Medline, Embase, and PsychINFO were searched from the inception of each database until September 18, 2015. The following search terms were used in combination and modified according to the requirements of the database.

- Attention-Deficit/Hyperactivity Disorder, ADHD, Attention-Deficit Disorder, Hyperkinetic Disorder.
- Allergic asthma, Allergic rhinitis, Atopic dermatitis, Eczema, Asthma, Rhinitis, Dermatitis, Conjunctivitis, Urticaria, Immunoglobulin E, Allergy, Allerg*, Atopy, Atopic.

The complete search terms are located in Appendix II in Supplementary material. Two authors (JVDS and RC) independently scanned the outcomes of the search based on the abstracts and titles. Those studies according with the eligibility criteria were retrieved as full text and reviewed for inclusion. Disagreement between authors concerning eligibility and inclusion was resolved with a discussion followed by mutual consensus. All references of the included articles were reviewed in order to identify other studies.

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