

INVITED COMMENT

Attention: this is one itchy problem!

Jon Genuneit

Institute of Epidemiology and Medical Biometry, Ulm University, Ulm, Germany

E-mail: jon.genuneit@uni-ulm.de

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Comorbidity between allergic disease and attention-deficit/hyperactivity disorder (ADHD) has been observed, documented and investigated for almost 100 years (1). Evidence has evolved from case series (2), a survey among allergists (3) and a survey among members of a patient organization (4) to epidemiological studies which were summarized in a systematic review (5) and have been replicated and extended several times thereafter.

In this issue of PAI, Johansson et al (6), now provide evidence for the lack of an association. This piece is well worth reading and includes a thoughtful and balanced discussion of issues related to the suspected association. But why are the results inconsistent with previous evidence?

In the present study (6), ADHD is ascertained using secondary data on dispensed drugs most often used for ADHD treatment. The authors make the case that about 20% of diagnosed ADHD cases may not have been prescribed drugs and may thus have been included in the non-diseased comparison group. Since $n = 162$ subjects had been prescribed ADHD medication, this would add up to about $n = 33$ untreated ADHD cases. If treatment was non-differential with regard to preschool eczema, the crude odds ratio if every ADHD case was treated would have been 1.16 (95% confidence interval: 0.86; 1.57) – very similar to what is published in Table 2 in the present study (6). If, however, subjects with preschool eczema and ADHD were less likely to be treated than their non-eczema counterparts (say, 28% instead of 20% were untreated, an absolute difference of just 10 subjects), the crude odds ratio would reach 1.47 (1.09; 1.97). Conversely, if subjects with preschool eczema and ADHD were more likely to be treated, the crude odds ratio would change in the opposite direction.

So, could non-differential treatment of ADHD with lower treatment rates among those with preschool eczema have occurred in the present study to this extent? Potentially. Of three other studies using routinely recorded data on dispensed ADHD medication, two found statistically significant associations with atopic dermatitis (7, 8) whereas another one did not (odds ratio 1.3 (0.9; 1.7), $p = 0.10$, restricted to boys) (9). The two positive reports were substantially larger than the present study whereas the other negative report had a similar number of ADHD cases with atopic dermatitis history.

Certainly, the use of administrative healthcare data offers the advantage of larger sample size over observational studies

with primary data. However, it often comes at the expense of detailed information and – despite wide coverage of the source population – it may be prone to selection of disease information severe enough to result in seeking healthcare advice. The authors of the present study rightfully claim they have identified potential cases of atopic dermatitis which may not be documented in the healthcare system. This is an important step to avoid the discussed ascertainment bias. Still, atopic dermatitis is an episodic disease which often starts in early childhood. The timing of the parental questionnaires on atopic dermatitis at 1, 2, 4 and 8 years of age as well as later ages leaves some room for misclassification of atopic dermatitis due to lack of recalling symptoms or diagnosis. This is likely non-differential with regard to later ADHD medication and will thus bias the association towards the null.

Timing of the onset or of identification of the diseases may be another important issue. A particular case is the study using cross-sectional data from Taiwan's National Health Insurance Research Database from the year 2005 which found no association between atopic dermatitis and ADHD (10). A further, longitudinal evaluation of this database from 2002 to 2009 documented a positive association between atopic dermatitis and subsequent ADHD, even after accounting for comorbid asthma and allergic rhinitis (11). This suggests that ADHD is developing subsequently to atopic dermatitis. A time window of opportunity for existing atopic dermatitis to affect risk for ADHD has been suggested by data from a smaller birth cohort study (12) but was not confirmed by a larger study based on secondary data (7). Still, the attempt to characterize eczema phenotypes based on the natural history of symptoms in the present article seems promising and should be repeated, preferably along with data offering the opportunity to investigate the onset and course of ADHD.

Potentially linked to the investigation of eczema phenotypes is the observation of comorbid asthma and allergic rhinitis. Various studies have tried to disentangle which of the allergic diseases or which comorbidity pattern is most strongly associated with ADHD. Approaches include mutual adjustment (11), restriction to subjects without other allergic disease (12), stratification into comorbidity patterns (13), additive scores of numbers of present diseases (11) and structural equation modelling of direct and indirect effects (14) which hinders comparison

across studies. If numbers are sufficient, full stratification of comorbidity patterns and structural equation modelling may show the most detailed information for comparison. Of note, the study using the latter approach also investigated impaired sleep as a potential mediator and documented that all allergic diseases exerted their effects via sleep impairment (14).

It is hard to glean whether there is more evidence for or against the association of atopic dermatitis with ADHD. Previous reports, on both sides, are difficult to compare due to varying operationalization of atopic dermatitis and ADHD. They have been conducted in diverse settings, with differing methodology, and with differing analytical strategies. The studies known to the author which documented no statistically significant association beyond the aforementioned were (i) likely too small (15, 16), (ii) prone to misclassification of atopic dermatitis due to ascertainment at a single point in time (17, 18) and (iii) assessed ADHD symptoms via parent-reported psychometric instruments at one point in time (18–20). Similar objections apply to some of the articles that document the association with statistical significance.

How should we move forward? First, investigators (and editors) should not hesitate to publish thoroughly discussed negative findings from well-designed studies. They have at least the same potential to stimulate discussion and new ideas as mere replications of previously documented associations. Second, future studies on this topic should be suited to provide data on both atopic dermatitis and ADHD that have a low likelihood of being misclassified or biased. This may be particularly difficult for these two traits due to potential 'under-documentation' in the healthcare system and in the case of atopic dermatitis due to the episodic nature and high remission rates. Third, comorbid allergic diseases including atopic dermatitis, asthma, allergic rhinitis, and food allergy and/or subphenotypes of these diseases should be concurrently investigated with appropriate methodology to identify the subphenotype, disease or comorbidity pattern with the strongest association. Fourth, previously suggested mediators of the association require attention. Itchy or not, we are likely to scratch our heads a few more times and may even lose some sleep over this one. . .

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