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# Atopic Dermatitis and Attention-Deficit/Hyperactivity Disorder

## Is There an Association?

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### Commentary on: Is atopic disease a risk factor for attention-deficit/hyperactivity disorder? a systematic review

Schmitt J, Buske-Kirschbaum A, Roessner V  
*Allergy*. 2010;65(12):1506-24.

**Question:** Are people with atopic dermatitis (AD) more likely to have attention-deficit/hyperactivity disorder (ADHD)?

**Data Sources:** Data were obtained from PubMed (to February 2010) and PsychINFO (to February 2010) with languages limited to English and German. Reference lists of retrieved studies and review articles were checked for additional studies.

**Study Selection:** Observational studies were selected if all of the following 3 criteria were met: (1) the assessment of the presence, absence, or personal history of at least 1 atopic disease (ie, eczema, asthma, rhinitis); (2) dimensional assessment of ADHD symptoms (inattention, hyperactivity, impulsivity) and/or categorical assessment of the presence, absence, or personal history of ADHD; and (3) quantitative information on the association between atopic disease and ADHD.

**Data Extraction:** Two investigators independently assessed abstracts and reviewed relevant studies using a standardized data abstraction form. Data extraction procedures adhered to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) checklist for performing a systematic review of epidemiologic studies.

**Data Synthesis:** The authors analyzed 20 studies that met their inclusion criteria (1 cohort study, 2 case-control studies, and 17 cross-sectional or cross-sectional within cohort studies) amounting to a total of 170 175 individuals. Data were analyzed separately to define the relationship between ADHD (outcome) and each of the 3 atopic diseases (exposure). Where possible, the results were presented as odds ratios (ORs) of association with 95% confidence intervals (CIs). Four of the 6 studies that investigated eczema and ADHD found a statistically significant

positive association, 2 with an OR greater than 4 (**Table 1**). Two of the 3 studies that used multivariate logistic regression for confounding factors found a statistically significant positive relationship between AD and ADHD. With respect to asthma, all 12 studies that investigated asthma and ADHD reported a positive association (OR, 1.23-2.42). Most of the asthma studies (11 of 12) did not adjust for eczema, a potential cofounder. Finally, the 2 studies that investigated allergic rhinitis and ADHD found no association between the 2 diseases.

**Conclusions:** Overall, the data suggest that eczema and asthma but not allergic rhinitis or elevated serum IgE levels are positively associated with ADHD or ADHD symptoms. However, most studies did not adjust for cofounders. Because the studies were cross-sectional in design, a causal relationship between preexisting atopic disease and the development of ADHD could not be determined. Prospective controlled studies that use validated measures to define ADHD symptoms and that investigate sleeping disturbances within the affected populations are needed to better understand the biologic relationship between atopy and ADHD.

### Comment

The prevalence of psychiatric symptoms in the dermatology setting has been estimated to range from 21% to 43%.<sup>6</sup> Many psychiatric conditions are known to be exacerbated by skin disease, and, conversely, dermatologic symptoms can be worsened by psychological distress (the so-called psychosomatic effect).<sup>6,7</sup>

Patients with atopic disease often exhibit a lifelong, multisystem disease course that usually begins with the onset of AD in early childhood. The hallmark symptom of this condition is pruritus, which is often worse in the evening, can severely impair quality of life, and can prolong disease activity.<sup>8</sup> Both psychosocial stress and numerous psychiatric conditions (including affective disorders, somatoform disorders, and schizophrenia) have

**Table 1. Summary of Results of Studies Investigating the Association Between AD and ADHD<sup>a</sup>**

| Source                                    | Study Design                  | Data Source                                      | Participants/Study Population, No.                                        | Main Result                                                                                                                                                                                                           | Association Between AD and ADHD, OR (95% CI)             | Asthma or Allergic Rhinitis Also Investigated? |
|-------------------------------------------|-------------------------------|--------------------------------------------------|---------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------|------------------------------------------------|
| Schmitt et al, 2010                       | Prospective cohort study      | Clinical examinations and parent interviews      | 2916 Infants                                                              | Significant association between infant-onset AD and hyperactivity/inattention, $P=.04$ ; after adjustment of cofounders nonsignificant relationship, $P=.28$                                                          | Ever AD, 1.25 (0.97-1.61)<br>Infant, AD 1.19 (0.88-1.61) | Yes                                            |
| Romanos et al, <sup>1</sup> 2010          | Cross-sectional               | Parent interview                                 | 13 318 Children and adolescents                                           | AD and ADHD significantly associated; association independent of allergic comorbidity, age and sex, socioeconomic status, environmental and lifestyle factors<br>Significant effect modification by sleeping problems | 1.54 (1.24-1.93)                                         | Yes                                            |
| Schmitt et al, <sup>2</sup> 2009          | Case-control                  | Population-based outpatient health care database | 1436 Children and adolescents with AD; 1436 age- and sex-matched controls | AD and ADHD significantly associated; association independent of allergic comorbidity, health care utilization, age, and sex<br>Severity of AD related to probability of ADHD                                         | 1.47 (1.01-2.15)                                         | Yes                                            |
| O'Callaghan and Harvey, <sup>3</sup> 1997 | Cross-sectional within cohort | Parent and teacher questionnaire                 | 87 Infants with extremely low birth weight                                | AD and ADHD significantly associated, $P=.009$                                                                                                                                                                        | 7.75 (1.65-40.45) <sup>b</sup>                           | No                                             |
| Flannery and Leiderman, <sup>4</sup> 1995 | Cross-sectional within cohort | Not reported                                     | 11 578 Children, 394 with ADD or ADHD                                     | ADD positively associated with asthma, statistically significant; ADD not associated with AD                                                                                                                          | 1.09 (0.70-1.65) <sup>b,c</sup>                          | Yes                                            |
| Beyreiss et al, <sup>5</sup> 1988         | Cross-sectional               | Parent interview                                 | 81 Children with AD; 81 controls                                          | Significant association between AD and ADHD symptoms                                                                                                                                                                  | 4.16 (1.97-8.97) <sup>b</sup>                            | No                                             |

Abbreviations: AD, atopic dermatitis; ADD, attention-deficit disorder; ADHD, attention-deficit/hyperactivity disorder; CI, confidence interval; OR, odds ratio.

<sup>a</sup>Table adapted from article by Schmitt et al.

<sup>b</sup>The OR and 95% CI were calculated by Schmitt et al from data presented in the article.

<sup>c</sup>The OR reported in the original article was 1.03,  $\chi^2=.02$ .

been suspected to be associated with AD.<sup>2</sup> The association between ADHD and AD has not been established. Atopic dermatitis is of particular interest because of its early childhood onset, negative impact on quality of life, and connection to other psychiatric conditions. The systematic review by Schmitt et al investigated whether people with atopic disease (eczema, asthma, and allergic rhinitis) are more likely to have ADHD than people without atopic disease.

The authors reviewed 20 observational studies in accordance with the MOOSE criteria, which were first published by Stroup et al<sup>9</sup> in 2000. These studies explored the association between patients with atopic disease and coexisting ADHD or ADHD symptoms. Most studies (17 of 20) were cross-sectional in design and extracted data from 1 point in time. Where applicable, atopic disease (eczema, asthma, allergic rhinitis, or any combination thereof) was the exposure, lack of atopic disease history was the nonexposure, and the presence of ADHD (or ADHD symptoms) was the outcome.

The Centre for Evidence-Based Medicine has outlined guidelines for the appraisal of systematic reviews.<sup>10</sup> Although their recommendations are best applied to the critique of randomized controlled trials, their guidelines for analysis can be applied to systematic reviews of observational data. In this light, the review by Schmitt et al fulfills most of the criteria of a useful and

valid review. They addressed a useful clinical question. The criteria for article inclusion were appropriate, and observational studies are sufficient to answer their clinical question. Both authors (1 psychiatrist, 1 dermatologist) independently reviewed the body of literature and selected pertinent studies. The included studies were sufficiently valid for the question asked.

Relevant studies could have been missed in this review because the search was restricted to references in English or German. However, we replicated their search without language restriction and found no additional studies. In addition, authors of included studies were not contacted to inquire about unpublished studies.

The databases used for the search included MEDLINE and PsychINFO but did not include EMBASE or LILACS. A search encompassing these latter databases revealed 2 additional observational studies that showed a positive, statistically significant association between AD and ADHD symptoms (**Table 2**).<sup>11,12</sup> In contrast to the studies included in this systematic review, Cicek et al<sup>12</sup> used predetermined clinical criteria to define adults with AD (the Hanifin and Rajka classification) and used both *Diagnostic and Statistical Manual of Mental Health Disorders* (Fourth Edition, revised) (DSM IV-R) criteria and a validated survey to confirm ADHD diagnosis in adults (Turkay Adult ADD/ADHD DSM-IV-R-based screening and rating scale).

**Table 2. Summary of Study Results Investigating the Association Between AD and ADHD That Were Not Included in the Systematic Review by Schmitt et al**

| Source                          | Study Design | Data Source                                                                    | Participants/Study Population, No.             | Main Result                                                                                                                                                                                                                                                                                                                                                   | Association Between AD and ADHD, OR (95% CI) | Asthma or Allergic Rhinitis Also Investigated? |
|---------------------------------|--------------|--------------------------------------------------------------------------------|------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------|------------------------------------------------|
| Roth et al, <sup>11</sup> 1991  | Case-control | Parent questionnaire, performed in absence of AD symptoms; psychomotor testing | 81 Children with atopy, 79 had AD; 71 controls | Significant association between more ADHD symptoms, attention problems, disruptive behaviors, restlessness, and atopic patients; $P < .001$<br><br>Atopic children performed worse on psychomotor tests when compared with controls, delayed motor response; $P < .05$                                                                                        | Not reported                                 | Yes                                            |
| Cicek et al, <sup>12</sup> 2009 | Case-control | Patient questionnaire; clinical interviews                                     | 60 Adults with AD; 50 controls without AD      | 3 Subdimensions of ADD/ADHD scale, attention deficit, hyperactivity/impulsivity, and associated features of ADHD, in patients with AD were statistically significantly elevated when compared with controls; $P < .001$ , $P < .001$ , $P < .001$ , respectively<br><br>No significant difference in these parameters in the "active" vs "inactive" AD groups | Not reported                                 | No                                             |

Abbreviations: ADD, attention-deficit disorder; ADHD, attention-deficit/hyperactivity disorder; CI, confidence interval; OR, odds ratio.

In 5 of the 6 studies on AD and ADHD, Schmitt et al found a positive association between the 2 conditions. This association was statistically significant in 4 studies (Table 1). Three of the 6 studies included were authored by 1 of the authors of the systematic review (Schmitt).

Nineteen of 20 studies were restricted to the pediatric population, in which both AD and ADHD are both common conditions. The global prevalence of AD is rising and is currently estimated at 20%.<sup>13</sup> The estimated prevalence of ADHD in childhood as reported in the literature ranges from 3% to 7%.<sup>14,15</sup> There is some evidence to show that as children age, ADHD-like traits (impulsivity, hyperactivity, impulse control) can become more prevalent than ADHD itself, and that these core symptoms are also seen in children during normal development.<sup>14,15</sup> The inclusion of ADHD-like traits or ADHD symptoms as outcome measures could result in higher event rates in the AD group, and therefore increase the OR.

As the authors acknowledged, the measurement of both AD and ADHD across the studies was not consistent and was mainly accomplished by various patient or parent health questionnaires (for example, the measurement of ADHD symptoms using the Strength and Difficulties Questionnaire, or SDQ). Less often, *International Statistical Classification of Diseases* codes and various rating scales were used to define ADHD. The *DSM IV-R* remains the gold standard for a valid ADHD diagnosis, yet 1 of the 6 articles reviewed by Schmitt et al incorporated *DSM* criteria into the ADHD diagnosis.<sup>3,14</sup> In many of the studies reviewed, parental report of a child having an atopic disease was sufficient for study inclusion. Physician verification was rarely used to define ADHD or AD. Reporting bias of parent questionnaires to measure the outcome could have affected the results of the studies. For example, parents could perceive ADHD-like hyperactivity or hyperkinesis in a child who is frequently scratching his uncontrolled AD. A recent publication by the Centers for Disease Control (CDC) found

the prevalence of parent-reported ADHD among children aged 14 to 17 years increased from 7.8% to 9.5% from 2003 to 2007.<sup>16</sup> Follow-up research has yet to be conducted to explain this finding but could have implications in the reporting bias of these studies.

The diagnosis of ADHD can be complex, and it is often difficult for even experienced clinicians to distinguish children with ADHD from children having ADHD-like traits. The American Academy of Pediatrics has acknowledged this challenging spectrum. They propose that ADHD diagnosis guidelines be based on an individual's behavior in 2 or more settings in the context of *DSM-IV-R* criteria, information from parents or caregivers, information from another source such as classroom teacher, and a complete assessment of coexisting conditions.<sup>17</sup> Further contributing to the complexity of the diagnosis of ADHD is its overlap with other prevalent mental health conditions that share similar diagnostic features, including depression, learning disorders, adjustment disorder, oppositional defiant disorder, conduct disorder, and anxiety.<sup>14</sup> A 2003 survey by the CDC found that more children have ever received a diagnosis of ADD or ADHD than should have as predicted by published true prevalence rates, and that there exists significant variability in ADHD diagnosis by state or residence and socioeconomic class.<sup>18</sup>

Of all 6 studies that investigated AD as a risk factor for ADHD, the study by O'Callaghan and Harvey<sup>3</sup> demonstrated the greatest association, with an OR of 7.75 (95% CI, 1.65-40.45). The population they studied was children with extremely low birthweight. Furthermore, many of the patients had hypoxic perinatal brain injury, such as intraventricular hemorrhage. Research suggests that infants with low birthweight are at higher risk for inattentiveness, and perinatal complications (including intraventricular hemorrhage and hypoxia) augment this risk.<sup>19-21</sup> These authors did not adjust for correct confounders, which could account for the overrepresentation of ADHD in this population.

We found 1 additional cross-sectional study by Lien et al<sup>22</sup> published after February 2010 (the end date of the authors' literature search) that investigated atopic disease and the presence of "externalizing" mental health problems, which the authors define as hyperactivity, inattention, or conduct problems as measured by the SDQ. A subgroup analysis showed a positive association between patients with AD (boys and girls aged either 15-16 years or 18-19 years) and "externalizing" mental health problems (OR, 1.20-1.44). These data were not statistically significant. In fact, Lien et al<sup>22</sup> found that patients with AD were more likely to have "internalizing" mental health problems (ie, feeling panicky, anxious, dizzy, sleepless, sad, worthless, hopeless), an association that was statistically significant in all sex and age groups.

The development of ADHD is complex, and current etiologic theories include neurochemical, neuroanatomic, metabolic, psychosocial, and genetic factors, with recent research supporting that genetics are paramount.<sup>23</sup> Schmitt et al hypothesized that sleeping problems early in life caused by AD increase the risk for developing ADHD. Numerous studies, including a meta-analysis of 16 studies, have shown that sleep disturbances in patients with ADHD can impair neurobehavioral function and can worsen preexisting ADHD symptoms.<sup>24-26</sup> However, sleep disturbance has not yet been implicated as a risk factor for ADHD.

**Bottom Line:** This systematic review found a positive association between AD and ADHD symptoms. A causal relationship between AD and ADHD cannot be inferred from these data. The inclusion of ADHD-like traits as an outcome potentially inflates the association between AD and ADHD. Further epidemiologic studies that use consistent and validated measures to more accurately define atopic disease and ADHD and adjust for confounders and disease severity are needed to better elucidate this relationship.

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