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Infant atopic eczema and subsequent attention-deficit/hyperactivity disorder – A prospective birth cohort study

Jon Genuneit[1], Stefanie Braig[1], Stephanie Brandt[2], Martin Wabitsch[2], Ines Florath[3], Hermann Brenner[3] & Dietrich Rothenbacher[1]

[1]Institute of Epidemiology and Medical Biometry, Ulm University, Ulm, Germany; [2]Division of Pediatric Endocrinology and Diabetes, Department of Pediatrics and Adolescent Medicine, University Medical Center Ulm, Ulm, Germany; [3]Division of Clinical Epidemiology and Aging Research, German Cancer Research Center, Heidelberg, Germany

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Correspondence
Jon Genuneit, Institute of Epidemiology and Medical Biometry, Ulm University, Helmholtzstr. 22, D-89081 Ulm, Germany
Tel.: +0049 731 500 31067
Fax: +0049 731 5012 31067
E-mail: jon.genuneit@uni-ulm.de

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Abstract

Background: Comorbidity between childhood atopic eczema (AE) and attention-deficit/hyperactivity disorder (ADHD) has been observed, but temporal relationships remain unclear.

Methods: We analyzed data of a population-based, prospective birth cohort study among 770 children included at baseline in 2000/2001 with follow-up up to age 11. Information on age at diagnosis of AE, rhinoconjunctivitis, and ADHD was obtained by questionnaires administered to parents and for AE also to caring physicians. Adjusted relative risks (aRR) with 95% confidence intervals (95% CI) were modeled with a modified Poisson regression.

Results: Early AE up to age 4 yr was reported for 14.8% of the children by the parents and for 26.0% by the physicians with only fair agreement between these reports (kappa = 0.36). Based on parental reports, the association of early AE with early ADHD was strong (aRR: 5.17, 95% CI: 2.18; 12.28), but absent for late ADHD [aRR: 0.50 (0.13; 2.02)]. The association of late AE with late ADHD [aRR: 3.03 (0.75; 12.29)] was not statistically significant. This pattern was independent of the presence of rhinoconjunctivitis.

Conclusions: The observed comorbidity between AE and ADHD may indicate vulnerability to develop ADHD symptoms in response to AE symptoms or through a common underlying mechanism. This vulnerability seems to decrease with time since AE onset and may be greater in early life. These temporal relationships should be considered in future research investigating mechanisms linking both diseases and in clinical efforts to screen for and prevent ADHD symptoms in children with AE.

Comorbidity between childhood atopic diseases and attention-deficit/hyperactivity disorder (ADHD) has been previously documented and investigated in a systematic review (1). Since then, one cross-sectional study did not observe the comorbidity (2). Conversely, two cross-sectional, three case–control, and a prospective birth cohort study reported an association between atopic disease, specifically atopic eczema (AE), and ADHD (3–8).

Underlying pathomechanisms and temporal relationships remain unclear (9). The authors of the systematic review conclude that AE appears to be independently related to ADHD, whereas no association was found for rhinitis or total IgE levels (1). Conversely, a recent case–control study showed significant associations of AE as well as allergic rhinitis and allergic conjunctivitis and to a lesser extent of asthma with subsequent ADHD in mutually adjusted models (6). Furthermore, a recent cross-sectional study found allergic rhinitis to be the atopic disease with the strongest association with ADHD, while AE alone showed no association (3).

The lack of longitudinal data has been clearly identified in the systematic review and recently published studies on the association (1, 4, 6, 8). Only two prospective birth cohort studies and one case–control study provide stronger evidence for a temporal relationship between AE and ADHD (6, 8, 10). However, in both birth cohort studies (8, 10), ADHD symptoms were measured only once at age 10 yr using a symptom-oriented rating scale, which identifies a large number of potentially false-positive ADHD cases (11, 12). In the case–control study that made use of historical health insurance

claims data, the association between AE and ADHD seemed strongest among children who received their ADHD diagnosis below 7 yr of age but was also detected among older children (6). Data on the time between diagnosis of any of the investigated atopic diseases and diagnosis of ADHD were presented, but the effects of age at diagnosis specifically of AE remain unclear in this study (6).

We aimed at investigating the association between AE and ADHD diagnosis in a prospective birth cohort with 11 yr of follow-up accounting for atopic comorbidities. The objective was to further determine the temporal sequence, especially with respect to the ages at diagnosis of AE and ADHD.

Methods

Study population

We conducted a population-based, prospective birth cohort study at Ulm University, Germany, with baseline assessment between 11/2000 and 11/2001 and follow-ups at ages 1, 2, 3, 4, 6, 8, and 11. Further details are described elsewhere (13). In total, 1066 (67%) mothers and their offspring (n = 1090) were recruited during their hospital stay after delivery. We excluded women who left the hospital immediately after birth, gave birth at <32 gestational weeks, had a child of <2500 g, or whose infant was transferred to pediatric care after delivery. We also excluded women who were not speaking German, Turkish, or Russian, the languages in which study material and questionnaires were available.

The study was approved by the ethics boards of Ulm University, of the University of Heidelberg, and of the Physicians' Boards of the states Baden-Wuerttemberg and Bavaria.

Assessment of atopic eczema

Doctor-diagnosed AE was assessed in parental questionnaires throughout the study and, in addition, directly from the child's caring physician at ages 1 through 4. Symptoms of AE were assessed by parental reports at each follow-up: Itchy rash was an affirmative response to 'Has your child had an itchy rash which was coming and going for at least 6 months in the last 12 months?' Flexural eczema was itchy rash together with an affirmative response to 'Has this itchy rash at any time affected any of the following places: folds of the elbows, behind the knees, in front of the ankles, in the face, or around the neck?' Early AE was defined as reports of doctor-diagnosed AE up to age 4 yr separately for parental and physicians' reports; late AE were parental reports of doctor-diagnosed AE at ages 5–8 yr. The same age ranges were used for the definition of early and late itchy rash as well as flexural eczema.

Assessment of rhinoconjunctivitis

Physician-reported rhinoconjunctivitis was defined as reports of diagnoses of allergic rhinitis or allergic conjunctivitis assessed in questionnaires answered by the child's caring physician. At each follow-up, symptoms of allergic rhinitis and allergic rhinoconjunctivitis were assessed by parental reports using the following questions of the International Study of Asthma and Allergies in Childhood (ISAAC) (14): 'In the past 12 months, has your child had a problem with sneezing or a runny or blocked nose, when he/she did not have a cold or the flu?' and 'If yes, has this nose problem been accompanied by itchy-watery eyes?' Parent-reported rhinoconjunctivitis was defined as affirmative responses to both questions in at least one follow-up from age 1 yr through age 4 yr. Sensitivity analyses were performed basing this definition on all available follow-up years.

Assessment of attention-deficit/hyperactivity disorder

Doctor-diagnosed ADHD and ADHD medication (methylphenidate, amphetamines, atomoxetine, omega-3/omega-6 fatty acids) were assessed in parental questionnaires at ages 6, 8, and 11. Two subjects reported ADHD medication without a diagnosis and were assumed to have doctor-diagnosed ADHD for further analyses. Early ADHD was defined as report of doctor-diagnosed ADHD up to age 8 yr; late ADHD reports at age 11 yr (retrospectively for the period 9–11 yr).

Statistical methods

Apart from simple descriptive statistics, agreement between physicians' and parental reports was described using the kappa coefficient. We estimated adjusted relative risks (aRR) with 95% confidence intervals (95% CI) using a modified Poisson regression approach to obtain robust standard errors (15). Interaction was assessed by fitting a multiplicative interaction term in these regression models. The following putative confounders were based on previous literature, assessed at baseline, and adjusted for in the models: child's sex; maternal age, nationality (German; other), and school education (in years: ≤9; 10–11; ≥11); any parental atopic disease (reported diagnosis of hay fever, asthma, or eczema). In addition, a potential role of physician- and parent-reported rhinoconjunctivitis was assessed by stratification and adjustment. All statistical analyses were performed with SAS® 9.3 (The SAS Institute, Cary, NC, USA).

Results

The study population comprised 770 children (71%), for whom follow-up information on early AE (reported from physicians and parents) as well as early or late ADHD was available. Characteristics of this study population are shown in Table 1. Due to the loss of follow-up, maternal age and prevalence of maternal German nationality, of high maternal education, and of parental atopic disease were higher in the study population compared to the baseline population.

The cumulative incidence of ADHD was 6.2% up to age 11 yr, and 73% of the ADHD cases were boys. One-third of the ADHD cases reported the use of ADHD medication, regardless of the age of onset.

Doctor-diagnosed AE up to age 4 yr was reported for 14.8% of the children by the parents and for 26.0% by the physicians (Table 1). The overlap between both together with

Table 1 Characteristics of the study population (n = 770) and the population at baseline (n = 1090)

	Study population n (%)	Population at baseline n (%)
Child's sex (female)	386 (50.1)	537 (49.4)
Maternal age [years, mean (SD)]	32.2 (4.6)	31.0 (5.2)
Maternal nationality		
German	700 (90.9)	930 (85.3)
Other	70 (9.1)	160 (14.7)
Maternal school education [years]		
≤9	115 (15.2)	252 (23.8)
10–11	303 (39.9)	410 (38.7)
≥12	341 (44.9)	398 (37.5)
Parental atopic disease	351 (45.6)	471 (43.3)
Doctor-diagnosed atopic eczema		
Early (0–4 yr)		
Physician-reported	200 (26.0)	
Parent-reported	114 (14.8)	
Without parent-reported Rhinoconjunctivitis	92 (11.9)	
Late (5–8 yr, only parent-reported)	26 (3.4)	
Atopic eczema symptoms		
Early itchy rash	131 (17.0)	
Early flexural eczema	112 (14.5)	
Rhinoconjunctivitis		
Physician-reported	48 (6.2)	
Parent-reported	109 (14.2)	
Without parent-reported early atopic Eczema	87 (11.3)	

parent-reported early symptoms of AE is shown in Fig. 1. There was only fair agreement between parental and physicians' reports of early AE (kappa = 0.36). Among those with physician-reported early AE, only about 35% reported typical symptoms. For those with parental reports, this figure was about 65%.

The crude associations between AE and ADHD are displayed in Table 2. Fig. 2 depicts the adjusted associations between AE and ADHD, which followed the same pattern but were weaker for physician- compared to parent-reported early AE. When early AE cases were restricted to children who had physician- and parent-reported AE and parent-reported flexural eczema, the point estimates for all and early ADHD were similar to those derived from parent-reported early AE. Furthermore, the association of early AE with early ADHD was strong but absent for late ADHD. The association of late AE with late ADHD (aRR: 3.03, 95% CI: 0.75; 12.29) was not statistically significant. While the confidence limit was wide, the point estimate did not reach the magnitude of the association of early AE with early ADHD (aRR: 5.17 (2.18; 12.28), both based on parental reports).

Exclusion of children with physician- or parent-reported rhinoconjunctivitis led to the same pattern of associations (Table 3). Further adjustment for parent-reported rhinoconjunctivitis also had no marked effect on the associations of AE with ADHD (Table 3 vs. Fig. 2). Moreover, among children without parent-reported AE, no association of parent-reported rhinoconjunctivitis was detected with all, early, and late ADHD [aRR: 1.65 (0.77; 3.55), 2.63 (0.72; 9.65), and 1.24 (0.45; 3.42), respectively]. Basing the definition of parent-reported rhinoconjunctivitis on all available follow-up years did not lead to substantially different results (data not shown).

Discussion

In our study, AE was associated with an increased risk of subsequent ADHD only within the first few years after AE diagnosis and possibly to a greater extent in early compared to later childhood. However, the sample size was too small to determine the effects of new-onset AE in later childhood on subsequent ADHD.

In contrast to the previously published two birth cohorts, we ascertained doctor-diagnosed ADHD rather than employing the symptom-focused Strengths and Difficulties Questionnaire (SDQ) (16). Clearly, a single assessment of the SDQ does not meet the diagnostic criteria for ADHD according to DSM-IV or ICD-10; neither the onset of symptoms before 7 yr of age nor presence of the symptoms in at least two settings is assessed (17, 18). Moreover, the SDQ captures the specific symptoms of ADHD listed in the DSM-IV only broadly. In general, a review of clinical validation studies of ADHD behavior rating scales has shown that use of these rating scales alone will lead to substantial numbers of false positives and false negatives (11). In Germany, the ADHD prevalence based on a reported diagnosis is 5.3% among 7- to 10-yr-old children, whereas an additional 6.4% are probable ADHD cases based on a single assessment of SDQ (12).

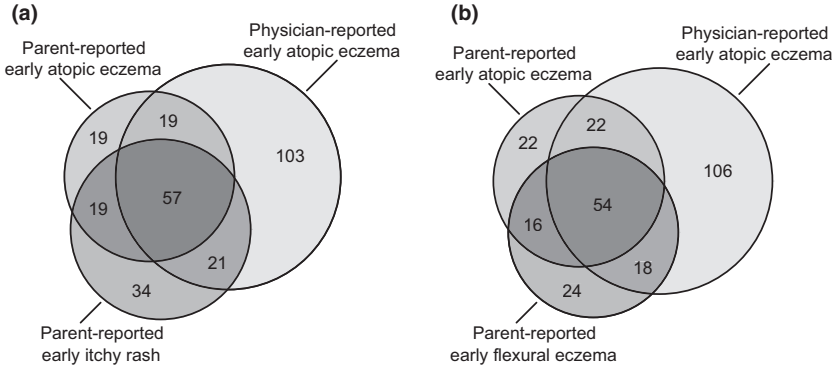

Figure 1 Overlap between physician- and parent-reported early atopic eczema and parent-reported early itchy rash (a) as well as early flexural eczema (b). Proportional Venn diagram: The outer box represents the study population (n = 770); sample sizes are given in each section of the circles; the areas of the circles are proportional to the sample size.

Table 2 Crude association of atopic eczema with ADHD

	Doctor-diagnosed ADHD					
	All n = 48 (6.2%)		Early n = 21 (2.8%)		Late n = 27 (3.5%)	
Doctor-diagnosed atopic eczema	n (%)	RR (95% CI)	n (%)	RR (95% CI)	n (%)	RR (95% CI)
Early (0–4 yr)						
Physician-reported						
No	33 (5.8)	1.00	11 (2.0)	1.00	22 (3.9)	1.00
Yes	15 (7.5)	1.30 (0.72; 2.33)	10 (5.1)	**2.58 (1.11; 5.99)**	5 (2.5)	0.65 (0.25; 1.69)
Parent-reported						
No	36 (5.5)	1.00	11 (1.7)	1.00	25 (3.8)	1.00
Yes	12 (10.5)	**1.92 (1.03; 3.57)**	10 (8.8)	**5.21 (2.27; 11.99)**	2 (1.8)	0.46 (0.11; 1.92)
Late (5–8 yr, only parent-reported)						
No	46 (6.2)	1.00	21 (2.9)	1.00	25 (3.4)	1.00
Yes	2 (7.7)	1.24 (0.32; 4.85)	0 (0.0)	n.e.	2 (7.7)	2.29 (0.57; 9.16)

Text in boldface indicates statistically significant associations.
ADHD, attention-deficit/hyperactivity disorder; n.e., not estimable due to insufficient numbers.

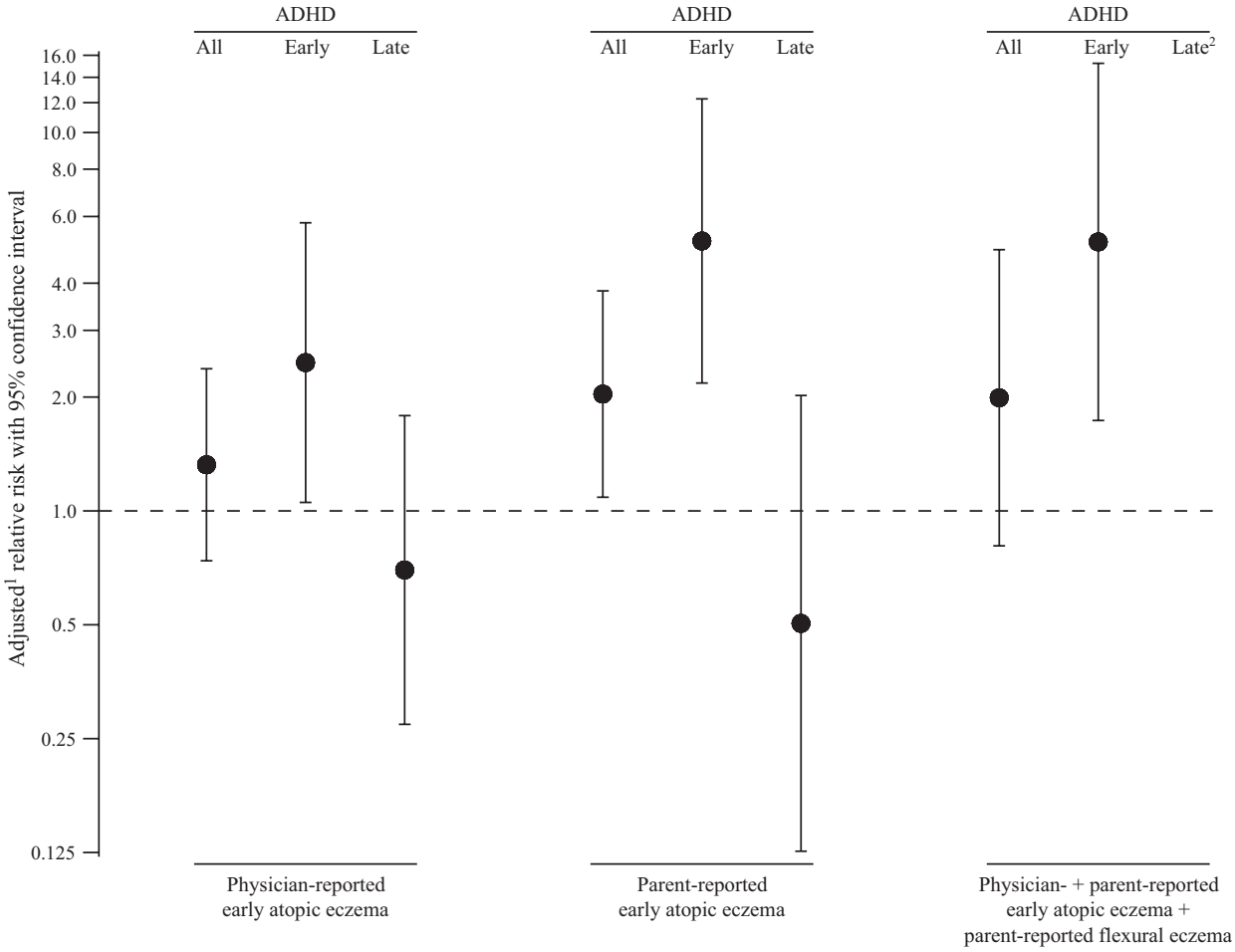

Figure 2 Adjusted[1] association of atopic eczema with attention-deficit/hyperactivity disorder. [1]adjusted for child's sex, maternal age, maternal nationality, maternal school education, and parental atopic disease. [2]not estimable due to insufficient numbers.

Table 3 Adjusted association of atopic eczema with ADHD accounting for rhinoconjunctivitis

Association of	Restricted to children Without physician-reported Rhinoconjunctivitis* RR (95% CI)	Restricted to children Without parent-reported Rhinoconjunctivitis* RR (95% CI)	Additionally adjusted For parent-reported Rhinoconjunctivitis† RR (95% CI)
Physician-reported early atopic eczema			
With all ADHD	1.38 (0.77; 2.48)	1.32 (0.66; 2.61)	1.27 (0.71; 2.28)
With early ADHD	**2.43 (1.04; 5.65)**	2.59 (0.95; 7.03)	2.29 (0.96; 5.46)
With late ADHD	0.74 (0.29; 1.90)	0.72 (0.25; 2.07)	0.69 (0.27; 1.75)
Parent-reported early atopic eczema			
With all ADHD	**1.98 (1.02; 3.82)**	1.76 (0.84; 3.67)	**1.99 (1.07; 3.73)**
With early ADHD	**5.28 (2.23; 12.49)**	**5.36 (2.00; 14.39)**	**4.88 (2.03; 11.70)**
With late ADHD	0.27 (0.04; 1.98)	0.30 (0.04; 2.08)	0.50 (0.13; 2.02)
Physician- + parent-reported early atopic eczema + Parent-reported flexural eczema			
With all ADHD	2.09 (0.85; 5.15)	1.33 (0.40; 4.41)	1.91 (0.79; 4.63)
With early ADHD	**5.14 (1.76; 14.96)**	3.72 (0.98; 14.20)	**4.67 (1.59; 13.72)**
With late ADHD	n.e.	n.e.	n.e.
Parent-reported late atopic eczema			
With late ADHD	3.33 (0.84; 13.24)	n.e.	2.94 (0.70; 12.32)

Text in boldface indicates statistically significant associations.

ADHD, attention-deficit/hyperactivity disorder; n.e., not estimable due to insufficient numbers.

*Adjusted for child's sex, maternal age, maternal nationality, maternal school education, and parental atopic disease.

†Adjusted for child's sex, maternal age, maternal nationality, maternal school education, parental atopic disease, and in addition for parent-reported rhinoconjunctivitis.

The reported diagnosis of ADHD is probably a more integrative and accurate measure of ADHD than assessing only ADHD symptoms once. On the one hand, there may be misclassification depending on specialty or diagnostic practice of the physician. On the other hand, in our study, one-third of the ADHD cases received ADHD medication, which is slightly higher than in a nationally representative German sample, but we also found the same gender differences: Boys are treated more often than girls (37% vs. 23%) (19). In addition, the cumulative incidence of parent-reported ADHD diagnosis in our study compares well to nationally representative data in Germany, suggesting good generalizability (12).

We directly assessed physicians' reports of AE diagnosis in addition to parental reports. Physicians reported substantially more often a diagnosis of AE than parents with only fair agreement between both reports. Among those with a physician-reported AE diagnosis, only 36% reported flexural eczema. For those with parental reports, this figure was 61%, possibly suggesting overdiagnosis or misclassification by physicians. We do not have additional data that could clarify this difference in reporting between parents and physicians, especially no data on specialty or diagnostic practices of the responding physicians. But similar to ADHD, the cumulative incidence of parent-reported AE in our study is in line with nationally representative data in Germany (20). Furthermore, associations of a strict definition of early AE based on parental and physicians' reports with ADHD did not deviate substantially from associations based on parental reports only. We thus have no reason to believe that the results based on parental reports are seriously biased.

There are several explanations for the observed comorbidity between AE and ADHD. First, both diseases could be causally linked through neuroimmune pathways, which is supported by some experimental evidence (9). Indeed, the effect of allergic inflammatory cytokines on ADHD-relevant brain circuits may be more pronounced in early life when the brain is still immature (9). This may be reflected in our observation that the association of early AE seems stronger than the association of late eczema with subsequent ADHD. On the contrary, the association between AE and ADHD was independent of other allergic disease. In addition, we did not observe an association between rhinoconjunctivitis and ADHD among subjects without AE, which contradicts the hypothesis of mediation by allergic inflammation. We did not investigate asthma or wheeze because asthma is difficult to diagnose before 6 yr of age and early wheeze is less likely to be of allergic origin. Still, we did not objectively measure allergic inflammation, and the lack of association may be due to misclassification.

Second, ADHD could be a behavioral response to the discomforts of itching skin and associated psychological processes (9). The decrease in the association with time since diagnosis of AE could support this explanation as children may outgrow AE or be treated effectively and thus loose the trigger for the behavioral response. Although we ascertained itchy rash throughout childhood, we neither assessed severity of this condition, nor treatment, nor did we have sufficient numbers to investigate temporal patterns of itchy symptoms.

Third, ADHD is closely related to other mental disorders for which comorbidity with AE exists. On the one hand, this is supported by a previous cross-sectional study showing associations of AE with depression, anxiety, conduct disorder, and with autism, even after adjustment for ADHD (4). On the other hand, this observational study did not present the

association of AE with ADHD adjusting for the other mental disorders (4). Another cross-sectional study adjusted for psychiatric comorbidities and found an association between AE and ADHD (5). There is debate about diagnostic criteria and the existence of ADHD as an identifiable disease (21). Children with symptoms of ADHD are very likely to meet criteria for other disorders, such as oppositional defiant disorder or conduct disorder (21). While we did not assess data on other mental disorders, it is questionable whether observational studies can disentangle the effects on mental disorders with highly overlapping case definitions.

In conclusion, the observed comorbidity between AE and ADHD may indicate vulnerability to develop ADHD symptoms in response to AE symptoms or through a common underlying mechanism. This vulnerability seems to decrease with time since AE onset and may be greater in early life. These temporal relationships should be considered in future research investigating mechanisms linking both diseases and in clinical efforts to screen for and prevent ADHD symptoms in children with AE.

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References

1. Schmitt J, Buske-Kirschbaum A, Roessner V. Is atopic disease a risk factor for attention-deficit/hyperactivity disorder? A systematic review *Allergy* 2010: **65**: 1506–24.
2. Chou P-H, Lin C-C, Lin C-H, Loh E-W, Chan C-H, Lan T-H. Prevalence of allergic rhinitis in patients with attention-deficit/hyperactivity disorder: a population-based study. *Eur Child Adolesc Psychiatry* 2013: **22**: 301–7.
3. Shyu C-S, Lin H-K, Lin C-H, Fu L-S. Prevalence of attention-deficit/hyperactivity disorder in patients with pediatric allergic disorders: a nationwide, population-based study. *J Microbiol Immunol Infect* 2012: **45**: 237–42.
4. Yaghmaie P, Koudelka CW, Simpson EL. Mental health comorbidity in patients with atopic dermatitis. *J Allergy Clin Immunol* 2013: **131**: 428–33.
5. Chen M-H, Su T-P, Chen Y-S, et al. Attention deficit hyperactivity disorder, tic disorder, and allergy: is there a link? A nationwide population-based study. *J Child Psychol Psychiatry* 2013: **54**: 545–51.
6. Tsai J-D, Chang S-N, Mou C-H, Sung F-C, Lue K-H. Association between atopic diseases and attention-deficit/hyperactivity disorder in childhood: a population-based case-control study. *Ann Epidemiol* 2013: **23**: 185–8.
7. Camfferman D, Kennedy JD, Gold M, Martin AJ, Winwood P, Lushington K. Eczema, sleep, and behavior in children. *J Clin Sleep Med* 2010: **6**: 581–8.
8. Schmitt J, Chen C-M, Apfelbacher C, et al. Infant eczema, infant sleeping problems, and mental health at 10 years of age: the prospective birth cohort study LISAplus. *Allergy* 2011: **66**: 404–11.
9. Buske-Kirschbaum A, Schmitt J, Plessow F, Romanos M, Weidinger S, Roessner V. Psychoendocrine and psychoneuro-immunological mechanisms in the comorbidity of atopic eczema and attention deficit/hyperactivity disorder. *Psychoneuroendocrinology* 2013: **38**: 12–23.
10. Schmitt J, Apfelbacher C, Chen C-M, et al. Infant-onset eczema in relation to mental health problems at age 10 years: results from a prospective birth cohort study (German Infant Nutrition Intervention plus). *J Allergy Clin Immunol* 2010: **125**: 404–10.
11. Snyder SM, Hall JR, Cornwell SL, Quintana H. Review of clinical validation of ADHD behavior rating scales. *Psychol Rep* 2006: **99**: 363–78.
12. Schlack R, Hölling H, Kurth B-M, Huss M. The prevalence of attention-deficit/hyperactivity disorder (ADHD) among children and adolescents in Germany. Initial results from the German Health Interview and Examination Survey for Children and Adolescents (KiGGS). *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz* 2007: **50**: 827–35.
13. Rothenbacher D, Weyermann M, Beermann C, Brenner H. Breastfeeding, soluble CD14 concentration in breast milk and risk of atopic dermatitis and asthma in early childhood: birth cohort study. *Clin Exp Allergy* 2005: **35**: 1014–21.
14. Asher MI, Keil U, Anderson HR, et al. International Study of Asthma and Allergies in Childhood (ISAAC): rationale and methods. *Eur Respir J* 1995: **8**: 483–91.
15. Zou G. A modified poisson regression approach to prospective studies with binary data. *Am J Epidemiol* 2004: **159**: 702–6.
16. Woerner W, Becker A, Rothenberger A. Normative data and scale properties of the German parent SDQ. *Eur Child Adolesc Psychiatry* 2004: **13** (Suppl. 2): II3–10.
17. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition, Text Revision. Washington DC, American Psychiatric Association, 2000.
18. Biederman J, Faraone SV. Attention-deficit hyperactivity disorder. *Lancet* 2005: **366**: 237–48.
19. Knopf H, Hölling H, Huss M, Schlack R. Prevalence, determinants and spectrum of attention-deficit hyperactivity disorder (ADHD) medication of children and adolescents in Germany: results of the German Health Interview and Examination Survey (KiGGS). *BMJ Open* 2012: **2**: e000477. doi:10.1136/bmjopen-2011-000477.
20. Schlaud M, Atzpodien K, Thierfelder W. Allergic diseases. Results from the German Health Interview and Examination Survey for Children and Adolescents (KiGGS). *Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz* 2007: **50**: 701–10.
21. Furman LM. Attention-deficit hyperactivity disorder (ADHD): does new research support old concepts? *J Child Neurol* 2008: **23**: 775–84.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Data S1. Methods.