

REVIEW ARTICLE

Is atopic disease a risk factor for attention-deficit/hyperactivity disorder? A systematic review

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To cite this article: Schmitt J, Buske-Kirschbaum A, Roessner V. Is atopic disease a risk factor for attention-deficit/hyperactivity disorder? A systematic review. *Allergy* 2010; DOI: 10.1111/j.1398-9995.2010.02449.x.

Keywords

asthma; atopy; attention-deficit/hyperactivity disorder; eczema; systematic review.

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Accepted for publication 16 June 2010

DOI:10.1111/j.1398-9995.2010.02449.x

Edited by: Stephan Weidinger

Abstract

The increase in prevalence and burden of atopic diseases, i.e. eczema, rhinitis, and asthma over the past decades was paralleled by a worldwide increase in attention-deficit/hyperactivity disorder (ADHD) diagnoses. We systematically reviewed epidemiologic studies investigating the relationship between atopic diseases and ADHD. Electronic literature search in PubMed and PsycINFO (until 02/2010) supplemented by handsearch yielded 20 relevant studies totaling 170 175 individuals. Relevant data were abstracted independently by two reviewers. Six studies consistently reported a positive association between eczema and ADHD with one study suggesting effect modification by sleeping problems. Twelve studies consistently found a positive association between asthma and ADHD, which, however, appeared to be at least partly explained (confounded) by concurrent or previous eczema. Rhinitis and serum-IgE level were not related to ADHD symptomatology. We conclude that not atopic disease in general, but rather that eczema appears to be independently related to ADHD. Conclusions about temporality and whether the observed association constitutes a causal relationship are impossible, as most studies were cross-sectional ($n = 14$; 70%) or case-control studies without incident exposure measurement ($n = 5$; 25%). Another methodological concern is that the criteria to define atopic disease and ADHD were inadequate in most studies. A failure to adjust for confounders in the majority of studies was an additional limitation so that meta-analysis was not indicated. Future interdisciplinary high-quality prospective research is needed to better understand the mechanisms underlying the relationship between eczema and ADHD and to eventually establish targeted preventive and treatment strategies.

Background

Despite significant advances in disease prevention and treatment, there has been a steep increase in the prevalence of eczema, asthma, and rhinitis within the past decades (1). Eczema, asthma, and rhinitis are frequently referred to as 'atopic diseases', although only a subset of all individuals with eczema, asthma, and rhinitis is truly 'atopic', i.e. shows type I (immediate type) sensitizations to environmental allergens (2–4). With approximately one of four children being affected, the burden of atopic diseases has reached endemic dimensions. Eczema is the most prevalent chronic condition in early childhood (5) and a leading cause of sleeping problems in early life (6). Atopic diseases have a high impact on

the quality of everyday life of affected individuals and their families, constitute a significant economic burden, and represent a major public health concern with significant implications on adult health (7, 8). It is well accepted that in a substantial proportion of children different atopic diseases co-occur or develop sequentially (9). Eczema frequently constitutes the beginning of the atopic march: Approximately 50% of children with eczema develop type I (immediate type) sensitizations to environmental allergens. This subgroup often develops allergic rhinitis and/or asthma (2). A body of literature indicates that comorbidity of eczema, asthma, and rhinitis is not limited to allergic diseases. Atopic diseases may cause significant problems in everyday life (10–12). The rates of depression, stress-related disorders, and other mental

health disorders have been shown to be increased in adults with eczema and in children and adults with asthma (13–15). Patients with atopic diseases frequently experience high levels of social stress and anxiety (16–18). Additionally, many patients with eczema feel stigmatized because of itchy lesions on visible sites (19).

The increase in atopic disease was paralleled by increasing prevalences of mental health problems such as attention-deficit/hyperactivity disorder (ADHD) and depression (20–22).

With a worldwide prevalence rate of more than 5%, ADHD – characterized by increased inattention, hyperactivity, and impulsivity – is the most common behavioral disorder in children and adolescents (23, 24). The incidence of ADHD peaks at (pre-) school age. ADHD is highly impairing for the affected children, their families and social environment, and imposes a significant economic burden (24–27). Attention-deficit/hyperactivity disorder is associated with sleeping problems, disruption of family communication, social functioning, impaired school performance and significantly diminished quality of life (24, 28, 29). Left untreated, children with ADHD are at increased risk for antisocial and, addictive behavior as well as mood and anxiety disorders in early adulthood (30).

The relationship between atopic diseases and ADHD has been a matter of debate for quite a long time (31–34). In the 1980s, Geschwind and Behan hypothesized an association between left-handedness, immune dysfunctioning and dyslexia, mediated by prenatal exposure to testosterone (35, 36). To test this hypothesis, Biederman et al. investigated the co-existence between asthma (as an example of an immune disorder) and ADHD (which is frequently associated with dyslexia) and found no significant relationship (37). Other studies failed to demonstrate an association between atopic responsiveness and ADHD (38). Genetic investigations further indicated that asthma and ADHD are transmitted independently in families suggesting that there is no substantial etiological or pathophysiological relationship between the two conditions (39). Other recently published studies, however, observed a significant co-existence between eczema and ADHD (40, 41).

A better understanding of the relationship between atopic diseases and the development of ADHD is of significant public health relevance as it may lead to targeted treatments and improved preventive measures for those children with atopic disease who are at increased risk to develop ADHD.

Recognizing that previous investigations in this field focused on atopic airway diseases (i.e. asthma and rhinitis), while there is a lack of epidemiologic research on the relationship between eczema, eczema-related sleeping problems, and ADHD, we recently analyzed data from three epidemiological studies concerning the relationship between eczema and ADHD/ADHD symptoms (40–42).

To come to a conclusion about the co-existence of atopic disease and ADHD, this systematic review aims to give a comprehensive overview of the epidemiologic evidence on the prevalence of atopic disease in ADHD and vice versa.

In light of our own epidemiologic investigations on this issue (40–42), we hypothesized that

- there is a positive crude association between each atopic disease (eczema, asthma, rhinitis) and ADHD,
- this association is strongest for eczema and ADHD, while the association between atopic airway disease (asthma and rhinitis) and ADHD is explained (confounded) by comorbid or previous eczema, and that
- sleeping problems early in life caused by eczema increase the risk for the subsequent occurrence of ADHD.

A specific focus of the present review is the role of the characteristics and methodological quality of the individual studies as well as the criteria applied to define ADHD/ADHD symptoms as well as atopic disease in relation to the results.

Methods

Study design

We systematically reviewed original articles that report on epidemiological studies (i.e. cross-sectional studies, case-control studies, cohort studies) to investigate the relationship between atopic disease (i.e. eczema, asthma, rhinitis) and ADHD/ADHD symptoms.

For the purpose of this review, we use the term 'atopic disease' for eczema, asthma, and rhinitis, although we are aware that not all individuals with eczema, asthma, and rhinitis are truly atopic, i.e. have specific IgE antibodies against environmental allergens (43). However, an individual's phenotype of eczema, asthma, and rhinitis can switch from nonatopic to atopic over time (43). Our main rationale behind this broad (highly sensitive, but less specific) definition of 'atopic disease' including atopic and nonatopic eczema, allergic and nonallergic asthma, and allergic and nonallergic rhinitis was to include as many relevant papers as possible.

The presented systematic review was performed in accordance with the meta-analysis of observational studies in epidemiology (MOOSE) principles (44). All relevant procedures were fixed in a study protocol prior to beginning with the literature search.

Identification of articles

A systematic electronic literature search in PubMed and PsycINFO was made from inception until February 09, 2010. Aiming for a very sensitive search strategy, we extended the literature search beyond asthma, eczema, and rhinitis and also used allergy, urticaria, and IgE as search terms.

We searched for combinations of search terms for

- atopic disease, i.e. ('atopic dermatitis' OR 'eczema' OR 'asthma' OR 'rhinitis') OR 'allergy' OR 'urticaria' OR 'IgE'
- attention-deficit/hyperactivity disorder, i.e. 'ADHD' or 'attention-deficit/hyperactivity disorder' or 'hyperactivity' or 'impulsiveness' or 'inattention')
- the study type ('observational study' or 'cohort study' or 'case-control study' or 'cross-sectional study' or 'relative risk' or 'odds ratio' or 'attributable risk')

We limited the systematic literature search to papers in English and German language on humans and excluded reviews.

We also conducted a handsearch of the reference lists of eligible articles as well as those of review articles to identify additional studies.

Studies were selected for inclusion based on three primary criteria: (i) assessment of presence/absence and/or personal history of at least one atopic disease, i.e. eczema, asthma, rhinitis; (ii) dimensional assessment of ADHD symptoms (inattention, hyperactivity, impulsivity) and/or categorical assessment of presence/absence and/or personal history of ADHD; and (iii) quantitative information on the association between atopic disease and ADHD (directly or indirectly).

Data abstraction

We reviewed the abstracts of all 122 citations yielded by the electronic search, excluded 104 articles after title and abstract review because they did not meet the eligibility criteria, and identified additional 23 potentially eligible articles by handsearch. From the 41 articles retrieved for full text review, 20 papers met the predefined eligibility criteria and were included in the systematic review. (Fig. 1) Two investigators (JS, VR) independently searched, reviewed, and abstracted data. Disagreements were resolved by discussion between all authors.

Data were abstracted using a standardized data abstraction form that had been pilot tested for this systematic review. The form included information on study design, setting, data sources, country in which the study was completed, sample size and follow-up rate of participants, participant characteristics (age, sex, race), proportion of participants having at least one atopic disease stratified by disease entity, and proportion of participants with ADHD diagnosis or ADHD symptoms above a predefined cutoff

score. Detailed data were collected on the methods used for the measurement of ADHD symptoms as a dimensional construct and ADHD as a categorical construct, as well as diagnostic criteria applied to define cases with atopic disease.

According to both psychiatric diagnostic systems in place today [Diagnostic and Statistical Manual of Mental Disorders (DSM) IV and International Classification of Diseases (ICD) 10], a child must manifest a minimal threshold of presenting the core symptoms as well as a number of additional criteria e.g. related to age of onset to receive a diagnosis of ADHD. The reliability, validity, and clinical utility of categorically defined ADHD are very well established (45–47). However, there are also strong arguments for considering ADHD defined as a dimensional measure (48). Additionally, from a statistical perspective, this has the advantage of less attenuation and greater precision in estimates of effect sizes, and better ability to detect signals also in terms of questions concerning the coexistence of ADHD and atopy.

Study results were abstracted both verbally and quantitatively with the main outcome of interest being the association between each individual atopic condition and ADHD/ADHD symptoms.

Quantitative methods

If not reported in the paper, proportions of patients with atopic disease and with ADHD were calculated from the numbers presented in the paper. Following our hypothesis, we considered atopic diseases as the exposure and ADHD/ADHD symptoms as the outcome of interest. The main outcome of interest was the relationship between each individual atopic disease and ADHD presented as odds ratios (ORs). We abstracted crude ORs and maximally adjusted ORs and information whether adjustment was performed for important potential confounding factors, i.e. age, sex, socioeconomic status (SES), sleeping problems, and other atopic

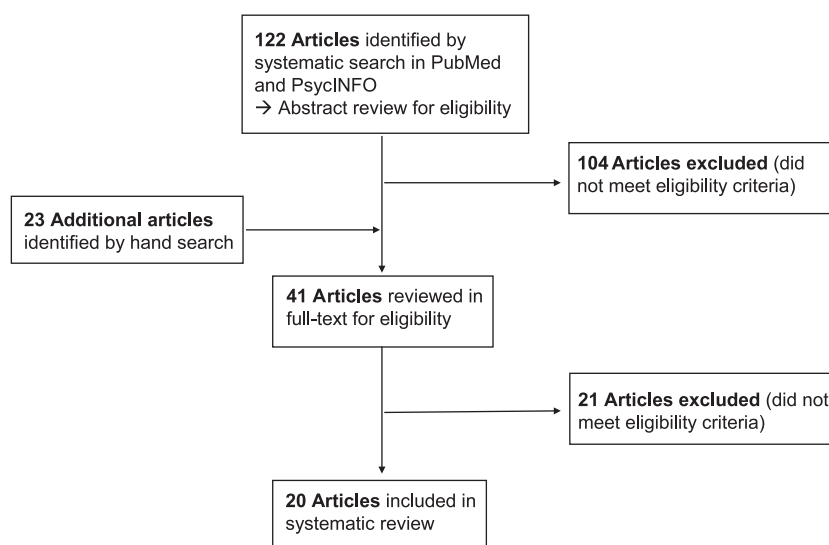


Figure 1 Flow chart of literature search and identification of relevant articles.

manifestations (49). If not reported in the paper, ORs were calculated from the numbers presented if possible.

We planned to pool the ORs of qualitatively homogeneous studies stratified by atopic disease entity (random effects models) and to perform sensitivity analyses based on study specific covariates by means of meta-regression (50).

All analyses were carried out using STATA, version 10 (STATA Corp., College Station, TX, USA).

Results

Figure 1 shows the study flow chart. Twenty studies (25, 37, 38, 40–42, 51–64) comprising a total of 170 175 individuals were included in the systematic review.

Study characteristics and study populations

Tables 1 and 2 summarize the study characteristics and the participant characteristics of the 20 individual studies included. We identified one (42) cohort study which followed newborns from birth until age 10 years and five case-control studies (37, 40, 58, 63, 64). The majority of identified studies ($n = 14$; 70%) were cross-sectional studies or cross-sectional analyses within cohort studies. Five studies (40–42, 63, 64) were performed in Germany, four in other parts of Europe (52–54, 57), nine in North America (25, 37, 38, 51, 55, 56, 58, 59, 61), one in Australia (60), and one in New Zealand (62). Ten studies (25, 40–42, 52, 55, 57, 59, 61, 62) were population-based investigations, four were performed in the setting of child- and adolescent psychiatry (56, 63), allergy (38) or pediatric outpatient clinics (37), or in other selected settings. (Table 1) All but one (58) study focused on children and adolescents. Three studies utilized exclusively secondary data from routine clinical practice (40, 58, 61), while the other 17 studies used parent interview and/or questionnaires alone or in combination with chart review, clinical examination, teacher questionnaire, or self-questionnaire. (Table 1) The proportion of participants included from all potential participants screened for eligibility varied considerably and ranged between 19% (61) and 100% (40) and was not reported in eight studies (37, 42, 54, 56, 59, 62–64).

Two studies (54, 60) included 100 participants or less, eight studies (37, 38, 51, 53, 56, 62–64) included between 100 and 1000 participants, and ten (25, 40–42, 52, 55, 57–59, 61) studies more than 1000 participants. One (58) study focused on adults aged 18–65 years whereas the other 19 studies included in this review investigated the association between atopic disease and ADHD/ADHD symptoms in pediatric populations. (Table 2) One study by Biederman (37) only included male participants, the other studies included both male and female participants with the proportion of females ranging from 12% to 60%. Ethnicity was rarely reported (Table 2). From the four studies including information about the participants' ethnicity, three included predominantly or exclusively white Caucasians (37, 56, 61) and one US study (51) focused on African Americans and other minorities.

Only five studies (40–42, 61, 62) reported data on the occurrence of all three atopic conditions, i.e. eczema, asthma,

and rhinitis. Twelve studies (25, 37, 51–55, 57–60, 64) only reported on the prevalence of one single atopic condition and failed to report on other atopic diseases. Three studies (38, 56, 63) reported on the prevalence of atopic disease in general without distinguishing between the specific clinical entities. Two case-control studies (40, 64) compared the rates of ADHD in participants with eczema vs controls without eczema. In the other studies reporting on eczema, the prevalence ranged between 13% and 41%. The reported prevalence of asthma and rhinitis ranged from 4% to 28% and from 4% to 29%, respectively (Table 2). The proportion of study participants with ADHD/ADHD symptoms was also very heterogeneous and ranged from 1, 2% in the study by Calam et al. (57) to over 20% in the studies by O'Callaghan et al. (60) and by Beyreiss et al. (64).

Assessment of ADHD and atopic disease

The methods to define presence/absence of atopic disease were generally inadequate (Table 3). Most studies (25, 37, 41, 42, 51, 52, 55, 57, 60, 62, 63) ($n = 11$; 55%) relied on parental reports to define presence or absence of atopic disease. Three studies (53, 61, 64) did not report at all on how atopic disease was defined. Chart review was performed in two studies (38, 56). From the three studies utilizing secondary data from routine clinical practice (40, 58, 61), only one (40) applied internal validation methods as proposed by methodological guidelines aiming to avoid misclassification bias (65–67). Only the study by Yuksel (54) applied validated diagnostic criteria to define allergic asthma. None of the studies utilized validated diagnostic criteria to define eczema (68) (Table 3).

There was significant heterogeneity in the methods used to define ADHD and ADHD symptoms (Table 3). Different and not necessarily comparable parent-, self-, and/or teacher-rated questionnaires on mental health problems more or less specific for ADHD symptoms were applied such as the Strength and Difficulties Questionnaire (SDQ) (69), the Child Behaviour Check List (CBCL) (70), the Development and Well-being Assessment (71), the ADHD rating scale of Du Paul (72), the Rutter Child Scales A and B (73), Conners Rating Scale (74), and the MacArthur Health and behavior questionnaire (75). (Table 3) Three studies (40, 58, 61) used secondary data concerning physician documentation of ADHD diagnosis according to ICD criteria, but only one (40) of these studies applied internal validation methods (65–67). Parent reports of physician diagnosis of ADHD/ADHD symptoms were used in three studies (41, 52, 55) to define the primary outcome, i.e. presence/absence of ADHD. A clinical diagnosis by a clinical expert according to DSM criteria (76) was included in only three studies (37, 56, 63) (15% of all studies identified) (Table 3).

Summary of main results of studies included in the review

Relationship between eczema and ADHD

Six studies (40–42, 60, 61, 64) investigated the relationship between eczema and ADHD and consistently found a positive association between eczema and ADHD reaching

Table 1 Characteristics of studies included in the systematic review

Reference	Time conducted	Country	Setting	Study design	Data source	Proportion included from all potential participants screened for eligibility (%)	Follow-up rate (cohort study) (%)
Cutuli 2010 (51)	2006–2007	USA	Emergency shelter for homeless families	Cross-sectional	Parent and teacher interview and questionnaire	85	n.a.
Schmitt 2010 (42)	1995–2008	Germany	General population	Prospective cohort study	Repeated clinical examinations and parent interviews	n.r.	49
Romanos 2010 (41)	2003–2006	Germany	General population	Cross-sectional	Parent interview	67	n.a.
Hysing 2009 (52)	2002	Norway	General population	Cross-sectional	Parent and teacher questionnaire	74	n.a.
Cuffe 2009 (25)	2001	USA	General population, National Health Interview Survey	Cross-sectional	Parent interview and questionnaire	81	n.a.
Schmitt 2009 (40)	2003–2004	Germany	General population	Case-control study	Population-based outpatient healthcare database	100	n.a.
deVries 2008 (53)	2006	the Netherlands	Outpatient clinic	Cross-sectional study	Parent questionnaire	57	n.a.
Yukse 2008 (54)	n.r.	Turkey	n.r.	Cross-sectional study	Parent questionnaire	n.r.	n.a.
Blackman 2007 (55)	2003–2004	USA	General population, National Survey of Children's Health	Cross-sectional	Parent interview	55	n.a.
Infante 2007 (56)	2001–2002	USA	Child & adolescent psychiatry outpatient clinic	Cross-sectional	Clinical evaluation, parent interview, chart review	n.r.	n.a.
Calam 2005 (57)	1999	UK	General population	Cross-sectional	Parent interview and parent, teacher and self-questionnaire; psychiatrist review	83	n.a.
Secnik 2005 (58)	1999–2001	USA	Secondary healthcare data from employed population	Case-control study	Medical claims database	100	n.a.
Leibson 2001 (59)	1987–1995	USA	General population	Cross-sectional analysis within cohort study	Review of school and medical records	n.r.	84%
Gaitens 1998 (38)	n.r.	Canada	Allergy outpatient clinic	Cross-sectional	Clinical evaluation, skin prick test, parent interview and questionnaire	31	n.a.
O'Callaghan 1997 (60)	n.r.	Australia	Extreme low birthweight children from neonatal ward	Cross-sectional analysis within cohort study	Parent and teacher questionnaire	97	70%
Flannery 1995 (61)	1959–1966	USA	General population	Cross-sectional analysis within cohort study	n.r.; presumably coded data from routine practice	19	n.a.

Table 1 (Continued)

Reference	Time conducted	Country	Setting	Study design	Data source	Proportion included from all potential participants screened for eligibility (%)	Follow-up rate (cohort study) (%)
Biederman 1995 (37)	n.r.	USA	Pediatric outpatient clinic	Cross-sectional study	Parent questionnaire and independent interviews with children and mothers	n.r.	n.a.
McGee 1993 (62)	1972–1991	New Zealand	General population	Cross-sectional analysis within cohort study	Parent and self-interview; parent, self-, and teacher questionnaire, clinical evaluation	n.r.	79%
Blank 1992 (63)	n.r.	Germany	Child & adolescent psychiatry outpatient clinic	Cross-sectional study	Clinical evaluation, skin prick test, parent interview and questionnaire	n.r.	n.a.
Beyreiss 1988 (64)	n.r.	Germany	n.r.	Cross-sectional study	Parent interview	n.r.	n.a.

n.a., not applicable; n.r., not reported.

statistical significance in four studies. The OR for the association between eczema and ADHD was above 4 in two studies (60, 64) and between 1 and 2 in four studies (40–42, 61) (for more details on ORs and corresponding 95% confidence intervals please refer to Table 4).

Three studies (40–42) focusing on the relationship between eczema and ADHD used multivariate logistic regression modeling methods to adjust for confounding factors including other atopic diseases, i.e. asthma and rhinitis. Each of these studies found a positive relationship between eczema and ADHD in the fully adjusted model reaching statistical significance in two studies (40, 41). One was a prospective cohort studies which found a statistically nonsignificant relationship between ever eczema and possible/probably hyperactivity/inattention at age 10 years (42). One was a population-based case-control study which observed a statistically significant association between ever eczema and ever ADHD (40). The third study was a population-based cross-sectional study which found a statistically significant association between eczema and ADHD modified by concurrent sleeping problems: Only children and adolescents with a lifetime history of eczema and sleeping problems were at increased risk for ADHD, whereas participants with eczema who did not report sleeping problems were not (41). The other studies did not consider sleeping problems as a potentially relevant variable. (Table 4) Interestingly, in all three multivariate-adjusted studies, there was a significant univariate association between asthma /rhinitis and ADHD, which disappeared in the multivariate model (40–42).

In their cross-sectional analysis within a cohort study including extreme low birthweight children from Australia O'Callaghan et al. observed a strong association between eczema and ADHD and reported that the overall health status and the number of physician visits were not related to eczema diagnosis (60).

Relationship between asthma and ADHD

All twelve studies (25, 37, 41, 51–55, 57–59, 61) that investigated the relationship between asthma and ADHD found a positive relationship with ORs ranging between 1.23 and 2.42. (Table 4) However, eleven of these twelve studies did not adjust for eczema so that it remains unclear whether the observed positive association between asthma and ADHD is explained (confounded) by comorbid eczema. In the study by Romanos et al., the crude association between asthma and ADHD disappeared almost completely after adjustment for concurrent eczema (41). Sleeping problems were not considered as a confounder or effect modifier in any of the included studies focusing on the relationship between asthma and ADHD. (Table 4) In contrast to the studies by Schmitt and by Romanos et al. (40–42), Flannery et al. (61) found that ADHD symptoms are significantly associated with asthma, but not with eczema in their cross-sectional analysis based on secondary data from routine clinical practice. Although they observed a statistically significant association between asthma and ADHD, Calam et al. (57) concluded that the percentage variance in hyperkinetic disorder explained by asthma is low, i.e. <1% so

Table 2 Summary of study population

Reference	Number of participants	Age, years (range)*	Female (%)*	Race* (%)	Atopic disease % affected†				ADHD % affected‡
					Eczema	Asthma	Allergic rhinitis		
Cutuli 2010 (51)	104	4–8	41	81 black 3 white 16 minorities	n.r.	28 ever	n.r.	n.r.	
Schmitt 2010 (42)	2916	Birth until age 10	50	n.r.	27 ever 17 at age 0–1 year	7 ever	13 ever	Hyperactivity/inattention 13, conduct problems 11	
Romanos 2010 (41)	13 318	3–17	50	n.r.	15	5 ever	12 ever	5	
Hysing 2009 (52)	7007	7–9	49	n.r.	n.r.	4	n.r.	n.r.	
Cuffe 2009 (25)	9830	9–17	47	n.r.	14% ever	n.r.	n.r.	3	
Schmitt 2009 (40)	1436 cases with eczema 1436 controls without eczema matched by age and sex	6–17	60	n.r.	1436 cases	7 current	29 current	4	
deVries 2008 (53)	Asthma treated with inhaled corticosteroids: <i>n</i> = 40; outpatient controls: <i>n</i> = 50; healthy controls: <i>n</i> = 183	1–7	51	n.r.	n.r.	Group 1 (<i>n</i> = 40)	n.r.	Children with known ADHD excluded	
Yuksel 2008 (54)	62 children with asthma 38 healthy controls (patients with known ADHD excluded)	7–12	43	n.r.	n.r.	62 cases	n.r.	n.r.	
Blackman 2007 (55)	101 778	0–17	n.r.	n.r.	n.r.	9 current	n.r.	6.8‡	
Infante 2007 (56)	184	4–20	55	94 white	n.r.	n.r.	n.r.	13 (externalizing disorder: ADHD, conduct disorder, oppositional defiant disorder)	
Calam 2005 (57)	9834	5–15	50	n.r.	n.r.	15 current	n.r.	1.2	
Secnik 2005 (58)	2252 ADHD cases; 2252 controls without ADHD, matched by age, sex, area	18–65	36	n.r.	n.r.	Cases 5 Controls 3	n.r.	2252 cases with ADHD	
Leibson 2001 (59)	4119	5–18	48	n.r.	n.r.	14	n.r.	8	

Table 2 (Continued)

Reference	Number of participants	Age, years (range)*	Female (%)*	Race* (%)	Atopic disease % affected†				ADHD % affected‡
					Eczema	Asthma	Allergic rhinitis		
Gaitens 1998 (38)	312	4–18	43	n.r.	n.r.	n.r.	n.r.	12 (attention problems)	
O'Callaghan 1997 (60)	87	8–17	64	n.r.	13%‡	n.r.	n.r.	24	
Flannery 1995 (61)	11 578	1–8	n.r.	100 white mothers	17%	6	4	3	
Biederman 1995 (37)	140 ADHD cases 120 controls without ADHD	6–17	0	100 Caucasian, non-Hispanic	n.r.	Cases 13 Controls 10	n.r.	140 cases with ADHD	
McGee 1993 (62)	815	9–13	n.r.	n.r.	41%	23	20	n.r.	
Blank 1992 (63)	104 cases with ADHD, 18 controls with other externalizing disorder	4–12	12	n.r.	n.r.	n.r.	n.r.	104 cases with ADHD	
Beyreiss 1988 (64)	81 children with eczema 81 controls without eczema	5–12	n.r.	n.r.	81 cases	n.r.	n.r.	51 cases; 20 controls	

CBCL, child behaviour check list; SDQ, Strengths and Difficulties Questionnaire; ADHD, attention-deficit/hyperactivity disorder; n.r., not reported; n.a., not applicable.

*Total sample.

†By group (in case-control and cohort studies) otherwise in total sample (i.e. in cross-sectional studies).

‡Calculated from data presented in paper.

Table 3 Measurement of ADHD (outcome) and atopic diseases (exposures)

Reference	Methods used for the measurement of ADHD/ADHD symptoms		Methods used for the measurement of atopic disease
Cutuli 2010 (51)	Dimensional	MacArthur Health and behavior questionnaire (parent and teacher rated)	Parent-reported asthma
	Categorical	n.r.	
Schmitt 2010 (42)	Dimensional	n.r.	Parent reports of physician diagnosis of asthma, eczema, rhinitis
	Categorical	SDQ-domain (parent rated) hyperactivity/inattention	
Romanos 2010 (41)	Dimensional	n.r.	Parent report of physician diagnosis of asthma, eczema, rhinitis
	Categorical	Parent report of physician or psychologist diagnosis	
Hysing 2009 (52)	Dimensional	SDQ-domain (parent rated) hyperactivity/inattention	Parent-reported asthma
	Categorical	n.r.	
Cuffe 2009 (25)	Dimensional	SDQ-domain (parent rated) hyperactivity/inattention	Parent-reported asthma
	Categorical	(a) SDQ-domain (parent rated) hyperactivity/inattention ≥ 7 (b) Difficulties in emotions, concentration, behavior, or being able to get along with other people being present longer than 6 months. (c) The difficulties interfere with the child's everyday life in at least two of the following areas: home life, friendships, classroom learning, and leisure activities	
Schmitt 2009 (40)	Dimensional	n.r.	ICD-10 codes used for eczema, allergic asthma, allergic rhinitis; internal validation methods applied
	Categorical	ICD-10 codes; internal validation methods applied	
deVries 2008 (53)	Dimensional	CBCL (1.5–5 years); DSM-IV oriented interview	Physician diagnosed asthma
	Categorical	n.r.	
Yuksel 2008 (54)	Dimensional	Conners Rating Scale (parent rated 48-item version): domains hyperactivity and attention-deficit	Physician diagnosed asthma according to the Global Strategy for Asthma Management and Prevention (GINA) 2006 criteria
	Categorical	n.r.	
Blackman 2007 (55)	Dimensional	n.r.	Parent-reported asthma
	Categorical	Parent report of physician / health professional diagnosis	
Infante 2007 (56)	Dimensional	n.r.	Chart review: medically documented diagnosis of asthma, allergic rhinitis, eczema, and/or urticaria; no differentiation between atopic conditions
	Categorical	Comprehensive clinical psychiatric evaluation of subject and parent(s) for DSM-IV diagnoses	
Calam 2005 (57)	Dimensional	SDQ-domain (parent-, self-, teacher-rated) hyperactivity/inattention	Parent-reported asthma
	Categorical	Child and adolescent psychiatrist reviewed SDQ-domain (parent-, self-, teacher-rated) hyperactivity/inattention and Development and Well-being Assessment	

Table 3 (Continued)

Reference	Methods used for the measurement of ADHD/ADHD symptoms		Methods used for the measurement of atopic disease
Secnik 2005 (58)	Dimensional Categorical	n.r. ICD-9 codes; no internal validation methods applied	ICD-9 codes used to define asthma; no internal validation methods applied
Leibson 2001 (59)	Dimensional Categorical	n.r. Retrospective review of information from multiple sources in accordance to DSM-IV criteria	Diagnosis of asthma documented by physician; diagnostic codes referred from billing data; no internal case validation measures performed
Gaitens 1998 (38)	Dimensional Categorical	CBCL (4–18 years) attention problems n.r.	Positive skin prick test
O'Callaghan 1997 (60)	Dimensional	ADHD rating scale of Du Paul based on DSM-III-R criteria (parent and teacher rated)	Parent-reported asthma and eczema
	Categorical	A cutoff of 8 or more symptoms based on the ADHD rating scale of Du Paul based on DSM-III-R criteria (parent and/or teacher rated)	
Flannery 1995 (61)	Dimensional Categorical	n.r. Unclear	Methods used to define eczema and asthma not reported
Biederman 1995 (37)	Dimensional Categorical	n.r. DSM-III R criteria (Kiddie SADS-E)	Parent-reported asthma
McGee 1993 (62)	Dimensional	Rutter Child Scales A and B Revised Behavior Problem Checklist (RBPC; parent rated) parent and teacher reports of ADHD based directly upon DSM-III criteria via questionnaires self-reported ADHD behaviors assessed using subscales derived from the Diagnostic Interview Schedule for Children (DISC-C)	Parent-reported asthma, eczema, and rhinitis
	Categorical	n.r.	
Blank 1992 (63)	Dimensional	CBCL (German version, 6–16 years) attention problems, Conners Rating Scale (parent rated 10-item version)	Parent-reported atopic condition; no differentiation between specific atopic conditions
	Categorical	Clinical diagnosis by child and adolescent psychiatrist	
Beyreiss 1988 (64)	Dimensional	Conners Rating Scale	Unclear
	Categorical	n.r.	

n.r., not reported; ADHD, attention-deficit/hyperactivity disorder; CBCL, Child Behaviour Check List; SDQ, Strength and Difficulties Questionnaire.

that the observed mean difference in ADHD symptoms between children with asthma and children without asthma is probably clinically not relevant. Hysing et al. (52) excluded all children with known eczema who did not have any other atopic disease from their study (but not children with asthma and comorbid eczema), found a statistically significant association between asthma and ADHD in the unadjusted analysis, and concluded that effect sizes were small and it is unclear whether the observed mean difference in ADHD score is clinically relevant. For more details on

the other studies evaluating the relationship between asthma and ADHD, please refer to Table 4.

Relationship between rhinitis and ADHD

The two epidemiologic studies identified that investigated the association between allergic rhinitis and ADHD found no association (40, 41) (Table 4).

Because of the observed heterogeneity between statistical methodology, study designs, criteria to define atopic disease as well as ADHD/ADHD symptoms, and baseline rates of

Table 4 Summary of study results

Reference	Main result	Association between allergic condition and ADHD (OR/RR; 95% CI)*			Variables included in adjusted model				
		Eczema	Allergic Asthma	Allergic rhinitis	Adjustment for potential confounders	Other allergies in model	Age	Sex	SES (e.g. income)
Cutuli 2010 (51)	Crude analysis: mean ADHD score sign. higher in children with asthma ($P < 0.05$) Adjusted analysis: tendency toward higher ADHD score in children with asthma ($P = 0.06$)						•	•	
Schmitt 2010 (42)	Significant association between infant onset eczema and hyperactivity/inattention ($P = 0.04$); after adjustment for confounders and comorbidities nonsignificant relationship ($P = 0.26$) Eczema only in infancy nonsignificantly associated with hyperactivity/inattention ($P = 0.12$) at age 10 controlling for confounders and comorbidities	Ever eczema 1.25 (0.97–1.61) Infant eczema 1.19 (0.88–1.61)	n.r.	n.r.	•	•	•	•	•
Romanos 2010 (41)	Eczema and ADHD significantly associated; association independent of allergic comorbidity, age and sex, socioeconomic status, environmental & lifestyle factors Significant effect modification by sleeping problems Asthma and allergic rhinitis not independently related to ADHD Compared to children without any chronic disease, mean hyperactivity/inattention score ($P < 0.001$) was significantly higher in children with asthma	1.54 (1.24–1.93)	1.23 (0.87–1.72)	0.82 (0.63–1.06)	•	•	•	•	•
Hysing 2009 (52)	Hyperactivity/inattention significantly associated with ever being diagnosed as having asthma Eczema and ADHD significantly associated; association independent of allergic comorbidity, healthcare utilization, age and sex	n.r.	n.r.	n.r.					
Cuffe 2009 (25)		n.r.	2.42 (1.83–3.18)†	n.r.					
Schmitt 2009 (40)		1.47 (1.01–2.15)	n.r.	n.r.	•	•	•	•	•

Table 4 (Continued)

Reference	Main result	Association between allergic condition and ADHD (OR/RR; 95% CI)*			Variables included in adjusted model				
		Eczema	Allergic Asthma	Allergic rhinitis	Adjustment for potential confounders	Other allergies in model	Age	Sex	SES (e.g. income)
deVries 2008 (53)	Asthma and allergic rhinitis not related to ADHD								
	Severity of eczema related to probability of ADHD								
Yuksel 2008 (54)	Median total ADHD score higher in children with asthma (all using inhaled corticosteroids) vs healthy controls ($P = 0.03$)	n.r.	n.r.	n.r.					
	No difference between children with asthma and outpatient controls in any ADHD parameter								
Blackman 2007 (55)	Mean attention-deficit score significantly higher in children with asthma compared to controls ($P = 0.01$)	n.r.	n.r.	n.r.					
	Mean hyperactivity score not significantly higher in children with asthma compared to controls ($P = 0.36$)								
Infante 2007 (56)	Association between asthma and ADHD ($P < 0.001$) but no association between asthma and ADHD treated pharmacologically	n.r.	Mild 1.61 (1.37–1.85) Moderate 2.45 (1.97–2.93) Severe 2.93 (1.92–3.94)	n.r.	•		•	•	•
	Children with externalizing disorders were not significantly more frequently diagnosed as having an atopic condition than children with other psychiatric conditions (enuresis, learning disorder, somatoform disorder, substance abuse) OR 1.24; 95% CI 0.42–3.67	n.r.	n.r.	n.r.					

Table 4 (Continued)

Reference	Main result	Association between allergic condition and ADHD (OR/RR; 95% CI)*			Variables included in adjusted model						
		Eczema	Allergic Asthma	Allergic rhinitis	Adjustment for potential confounders	Other allergies in model	Age	Sex	SES (e.g. income)	Sleeping problems	Other
Calam 2005 (57)	ADHD diagnoses and asthma significantly associated ($P = 0.004$) SDQ-domain hyperactivity/inattention significantly associated with allergic asthma ($P < 0.001$) ADHS and asthma significantly associated in employed adults	n.r.	1.82 (1.16–2.79)†	n.r.							
Secnik 2005 (58)	Significant association between ADHD and asthma	n.r.	1.66 (1.20–2.31)†	n.r.							
Leibson 2001 (59)	No statistically significant differences in mean ADHD score (CBCL Attention Problems) in children with and without atopy (i.e. positive vs negative skin prick test)	n.r.	1.88 (1.39–2.52)†	n.r.							
Gaitens 1998 (38)	No difference for previously diagnosed attention problems/hyperactivity reported by parents.	n.r.	n.r.	n.r.							
O'Callaghan 1997 (60)	Eczema and ADHD significantly associated ($P = 0.009$).	7.75 (1.65–40.45)†	n.r.	n.r.							
Flannery 1995 (61)	ADHD symptoms significantly associated with asthma, but not with eczema	1.09 (0.70–1.65)†	1.76 (1.13–2.64)†	n.r.							
Biederman 1995 (37)	No significant association between ADHD and asthma	n.r.	1.33 (0.57–3.17)†	n.r.							
McGee 1993 (62)	No significant differences in mean ADHD score in children with and without atopic disorder (no discrimination between atopic conditions)										

Table 4 (Continued)

Reference	Main result	Association between allergic condition and ADHD (OR/RR; 95% CI)*			Variables included in adjusted model				
		Eczema	Allergic Asthma	Allergic rhinitis	Adjustment for potential confounders	Other allergies in model	Age	Sex	SES (e.g. income)
Blank 1992 (63)	No significant association between serum-IgE level and mean ADHD score								
	Children with ADHD were more often diagnosed as having an atopic disorder than children with other externalizing disorders (OR 2.78; 95% CI 0.71–15.87† The ADHD subtype without concurrent conduct disorder was strongest related to atopic disorders. Children with atopic disorders had more likely only hyperactivity and inattention as ADHD symptoms, but were not at risk for Additional developmental problems and/or defiant behavior	n.r.	n.r.	n.r.					
Beyreiss 1988 (64)	Significant association between eczema and ADHD symptoms	4.16 (1.97–8.97)†	n.r.	n.r.					

n.r., not reported; •, yes; ADHD, attention-deficit/hyperactivity disorder; CBCL, Child Behaviour Check List; SDQ, Strength and Difficulties Questionnaire; SES, socioeconomic status; OR, odds ratios.

*maximally adjusted odds ratios.

†calculated from data presented in paper.

atopic disease and ADHD statistical meta-analysis was not indicated.

Discussion and conclusions

Main findings

We identified and systematically reviewed 20 epidemiologic studies investigating the relationship between atopic disease and ADHD/ADHD symptoms. These studies consistently suggest a positive association between eczema and ADHD (40–42, 60, 61, 64) and between asthma and ADHD (25, 37, 41, 51–55, 57–59, 61), whereas rhinitis and total IgE level was not related to ADHD in published studies.

Most studies identified for this review were cross-sectional or used a case–control design without incident exposure measurement. Despite the consistency in the results, we therefore cannot interpret the observed associations as a causal relationship. In the only prospective cohort study identified eczema was assessed repeatedly from birth until age 10 years, but ADHD symptoms were only assessed once at age 10 years so conclusions about temporality or causality are not possible (42, 67).

With regard to our hypotheses, it may be concluded that:

- Children with eczema and children with asthma are more frequently diagnosed as having ADHD than children without these chronic diseases. Two cross-sectional studies found a strong crude association between eczema and ADHD with ORs above 4. In the other studies, the relationship between eczema and ADHD was weak to moderately strong with ORs below 2. The association between asthma and ADHD was weak to moderately strong with ORs below 2.5 in all studies included in this review. Allergic rhinitis does not appear to be related to ADHD.

Remarkably, eczema and asthma are two chronic inflammatory conditions frequently, but not necessarily related with atopy, i.e. specific IgE-mediated hypersensitivity to environmental allergens (2, 3).

- Three studies (40–42) analyzing the relationship between eczema and ADHD adjusted for concurrent atopic airway disease and for a broad set of environmental and behavioral confounders. In these studies, the relationship between eczema and ADHD persisted after multivariate adjustment, whereas significant univariate associations between atopic airway disease and ADHD disappeared in the multivariate model (40–42). In contrast, none of the studies reporting a positive relationship between asthma and ADHD considered comorbid eczema or personal history of eczema as a confounding factor. These findings clearly suggest that the association between atopic airway disease and ADHD is at least partly explained by comorbid or previous eczema.

- Only a single epidemiologic study (41) considered sleeping problems as a potential modifier or confounder in the relationship between atopic disease and ADHD. This population-based cross-sectional study found eczema and ADHD to be strongly and independently associated in children and adolescents with sleeping problems, but not in children

without sleeping problems. This study, however, did not collect data on the reasons for sleeping problems and on temporal relationship between sleeping problems, occurrence and course of eczema and ADHD (41). Because of the limited data available, we conclude with regard to our third hypothesis that we do not know whether sleeping problems early in life caused by eczema increase the risk for the subsequent occurrence of ADHD. However, because pruritus caused by eczema is a leading cause of sleeping problems early in life (6, 28, 29) and because sleep inefficiency has been shown to trigger ADHD symptoms, prospective investigations on the role of sleeping problems in the relationship between eczema and ADHD are of utmost importance (49).

Association between eczema and ADHD – what are the mechanisms?

As highlighted earlier, we found consistent evidence for a positive association between eczema and ADHD/ADHD symptoms. This relationship was found to be independent of environmental and lifestyle factors such as breastfeeding, number of siblings, early daycare, of family history of eczema, and of concurrent or previous atopic airway disease.

As mentioned before, eczema is the most prevalent chronic disease in young children (5). The cumulative incidence of eczema within the first 2 years of life is about 20% (5). In contrast, ADHD is rarely diagnosed before the age of 4 years and generally, incidence peaks at school age (24). The current epidemiologic evidence does not allow drawing any conclusions about which of the both disorders, i.e. eczema or ADHD, develops first and subsequently, impacts the onset of the other. The natural history of eczema and ADHD, however, rather suggests that eczema precedes ADHD symptoms.

The underlying mechanisms how the manifestation and chronification of eczema may affect the development of ADHD later in life remain speculative. Two potential, not mutually exclusive pathways, can be envisioned that may explain why eczema in childhood may be correlated with an increased risk for ADHD in later life. There is broad acceptance that a hallmark of the pathology of eczema are immunologic irregularities such as – in the subgroup of children with truly atopic eczema (43) – hypersecretion of immunoglobulin-E (IgE), increased eosinophilic activity and a predominantly T helper type 2 (TH2) cytokine secretion (4). It becomes clear that the children with atopic eczema is imposed to increased levels of proinflammatory cytokines and mediators and further, that exposure to these mediators starts during early infancy. A growing number of studies suggest that inflammatory cytokines released during the atopic response may pass the blood brain barrier (77) and activate neuroimmune mechanisms that involve behaviorally and emotionally relevant circuits (78). For example, in animals, increased fear and reduced social behavior was found to be linked to the atopic reaction (79, 80). In humans, activation of prefrontal cortex regions during an atopic episode has been demonstrated using functional magnetic resonance (81).

The prefrontal cortex is known to subserve executive cognitive functions such as planned behavior, decision making, motivation and attention (82). Structural and functional alterations in prefrontal cortex regions have been linked to various cognitive disturbances including ADHD symptomatology. Thus, it may be argued that a sustained and exaggerated release of proinflammatory mediators impacts ADHD relevant brain circuits which may render the child vulnerable to develop ADHD later in life. Aside this neuroimmunologic pathway, other mechanisms such as stress may be involved. The misery of living with eczema is associated with high levels of psychological stress that may include dysfunctional mother-child relationship, sleep disturbances, less bodily contact, as well as later stigmatization and bullying by the peer group (83). This increased level of everyday stress starts early in infancy with the onset of eczema, mostly during the first month of life. Studies in animals and humans clearly suggest that during early life the brain is particularly sensitive to stress probably because of its profound developing changes during this period. Animal data show that adverse rearing behavior during infancy lead to increased fear behavior (84), an exaggerated startle response (85) or changes in prefrontal cortex regions (86). In humans, adverse experiences such as maltreatment or neglect, but as a low parental bonding has been shown to be associated with significant neuroendocrine dysfunctions such as a hyporeactivity of the hypothalamus–pituitary–adrenal axis, increased activity of the sympathetic nervous system or an elevated dopamine release in the striatum during stressful conditions (87–89). As stated before, sleep disturbances are common in the eczematous child and eczema is top of the list as being responsible for parental and infant sleep disruption (6). Sleep is vital for the brain development and normal sleep development has been found to be linked to higher mental developmental scores (90). For example, sleep quality was predictive for later temperament in that night waking and sleeplessness during early infancy were correlated with difficult temperament, higher irritability and lower approachability in childhood (91). Regarding these findings, it is tempting to speculate that increased stress exposure, i.e. adverse parenting or malfunctioning sleep patterns, during early infancy affects multiple neurotransmitter and neuroendocrine systems leading to long-term alterations of the behavioral and physiological repertoire in children with eczema increasing their vulnerability to psychopathological conditions, such as ADHD.

Theoretically, it may also be speculated that treatment of eczema may pharmacologically induce ADHD symptoms. One small study in 2–16-year-old children with severe asthma treated with higher (2 mg/kg) vs lower (1 mg/kg) doses of oral prednisolone found nonstatistically significant increased rates of hyperactivity in the high-dose group (92). The underlying pathophysiological mechanisms of this finding are unclear. The majority of children with eczema, however, is not treated with systemic, but exclusively with topical corticosteroids harboring lower risks for systemic adverse drug reactions. Investigations on adverse mental health effects of topical inflammatory treatment of eczema are miss-

ing and should be undertaken to clarify this issue. Similarly, we are not aware of relevant data on the effect of long-term use of sedating antihistamines in infancy and early childhood on brain development and mental health.

Strengths and limitations of the systematic review

Our study followed *a priori*-defined procedures that also met the criteria in the MOOSE checklist for performing a systematic review of epidemiological studies (44). Although we undertook a systematic electronic literature search supplemented by handsearch, we cannot guarantee that we identified all relevant articles on the issue.

One significant limitation of the studies included in this review is the failure to use appropriate, validated methods to define ADHD/ADHD symptoms and presence/absence of eczema, asthma, and rhinitis. Almost all studies relied on parent reports or on secondary data from routine practice. None of the studies on eczema used validated criteria for case definition such as the UK working party criteria (68), and only a single study (54) investigating the relationship between asthma and ADHD applied appropriate criteria to define asthma.

Analogously, they used quite heterogeneous and not satisfactory methods to define particularly the categorical diagnosis ADHD (45). Up to date the diagnosis of ADHD is made by careful clinical history (carried out only by 15% of studies included in the present review). On the other hand, most of the studies used well-established and validated questionnaires on behavioral and emotional problems that were more or less specific for ADHD symptoms and functioning (93). Although such rating scales are extremely helpful in documenting the individual profile of ADHD symptoms and e.g. assessing the response to treatments, it is important to emphasize that they should not be used for diagnosis without careful clinical confirmation and elicitation of the other criteria necessary for diagnosis of ADHD or coexisting disorders. Unfortunately, all studies did not control for the latter, although coexisting disorders (e.g. conduct disorder, depression) are very common in ADHD (94) and might bias the present findings. Nevertheless, there are also strong arguments for considering ADHD defined as a dimensional measure (48). Additionally, from a statistical perspective, this has the advantage of less attenuation and greater precision in estimates of effect sizes and better ability to detect signals also in terms of questions concerning the coexistence of ADHD and atopy.

Another limitation of the majority of the study included was the failure to consider behavioral and environmental factors and for atopic comorbidity as potential confounding factors. This increased the degree of methodological heterogeneity between studies so that quantitative meta-analysis could not be performed (95).

Implications for future research

Both eczema and ADHD are highly prevalent in childhood, frequently persist into adulthood, and are associated with

considerable problems in everyday life of affected children and their families. If treatment is required, the costs incurred are substantial. (1, 5–8, 20–22, 24–27).

Eczema and ADHD are complex multifactorial traits with a substantial genetic component (4, 24, 96, 97). The possibility of shared vulnerability genes in patients with eczema and ADHD is an attractive hypothesis that should be investigated in future studies. Future studies should also consider complex gene $\times$ environment interactions as possible explanations of the observed comorbidity.

Assuming an approximately 1.5-fold increased risk for ADHD attributable to eczema as suggested by multi-adjusted analyses (40, 41), the population attributable risk of eczema in relation to later ADHD symptoms is assumed to be approximately 9%. A better understanding of the biologic mechanisms explaining the association of infant eczema and psychological development in children with eczema would therefore be of great public health significance, as targeted

preventive measures for children with eczema may help to decrease the burden of ADHD in children and adolescents.

Ideally, adequately powered, interdisciplinary, prospective controlled studies utilizing a within-subject repeated measurements design, applying validated and sensitive methods to measure ADHD symptoms and eczema symptoms (98) including sleeping inefficiency should be undertaken to increase our understanding of the biologic underpinnings of the observed association between eczema and ADHD.

Funding

None.

Competing interests

JS: none; AB: none; VR: Advisory board and honoraria from Lilly, and from Novartis.

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