

REVIEW ARTICLE

Nonallergic comorbidities of atopic eczema: an overview of systematic reviews

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Abstract

The aims of this overview are to synthesize the current evidence of published systematic reviews (SRs) on nonallergic comorbidities of atopic eczema (AE). EMBASE and MEDLINE were searched for SRs published from inception to November 2012. SRs were selected independently based on predefined inclusion criteria. Methodological quality of SRs included was assessed by two independent reviewers using the Revised Assessment of Multiple Systematic Reviews (R-AMSTAR) checklist. Nine SRs met all inclusion criteria. Six reviews addressing the association between AE and cancer suggest a decreased risk of glioma, meningioma, and acute lymphoblastic leukemia in patients with current or previous AE. One SR reported a consistent positive association of AE with attention-deficit hyperactivity disorder (ADHD). Diabetes mellitus type 1 and multiple sclerosis (MS) were not significantly related to AE in reviews based on cross-sectional and case-control studies. Patients with AE appear to be at decreased risk of brain tumors. The relationship of AE with Th1- and Th17-mediated (auto-)inflammatory conditions such as diabetes mellitus type 1 and MS should be clarified in prospective observational studies. Children with AE are at increased risk of ADHD. SRs on the risk of depression and Th17-mediated disorders such as inflammatory bowel disease of patients with AE are missing.

With prevalence rates ranging between 10 and 20 percent in Europe, atopic eczema (AE) is among the most frequent chronic inflammatory disorders in children and adolescents (1, 2). High proportions of patients with AE in early childhood are free of symptoms in adolescence. A long-term follow-up study of young Icelanders pointed out that the prevalence of AE decreased from 31% at the age of 18–23 months to 8% at the age of 21 years (3). Utilizing a population-based administrative healthcare database in Germany, 2–4 percent of adults suffer from prevalent AE (4). AE is considered a T helper cell (Th) 2-mediated disease, with a switch to a Th1 cell predominance during the chronic phase of the disease (5). The itchy lesions frequently induce sleeping problems, may have a negative impact on quality of life, create embarrassment, interfere with daily activities and employment opportunities, and cause feelings of stigmatization particularly if the face or hands are affected (6, 7).

It is well established that AE frequently constitutes the beginning of the atopic march (8). Beyond allergic comorbidities, however, the association of AE with cardiovascular risk

factors, with cancer, with other inflammatory and auto-inflammatory disorders, and with mental disorders has gained increasing interest. Recognizing the whole spectrum of morbidities related to AE is a prerequisite for patient-centered care. Understanding the underlying biological mechanisms of the relationship between AE and other somatic and/or mental disorders may be a key to increase our understanding of the pathophysiology of AE and eventually lead to the development of targeted preventive or curative interventions.

Overviews of systematic reviews (SR; synonymous with overviews and systematic review of systematic reviews) represent a relatively new methodological approach to summarize the evidence from more than one research synthesis (9). In comparison with SRs, evidence synthesis of overviews refers to published data of SRs instead of primary studies. Thus, overviews provide a unique opportunity to sum up relevant evidence for physicians, scientists, and patients. The methods applied to prepare an overview are analogues to traditional SRs (10, 11), which were originally developed and established by the Cochrane Collaboration (12).

We aimed to systematically summarize and critically appraise all SRs on nonallergic comorbidities of AE.

Methods

Inclusion and exclusion criteria

Besides the research question, inclusion and exclusion criteria (Table 1) were predefined for literature search and the study selection procedure. Only articles reporting on SRs with or without statistical meta-analysis (study design) summarizing the evidence on the associations between AE (population/exposure) and one or more other nonallergic (comorbid) disorders (outcome) were considered. We only included reviews on specific comorbidities (disorders) that are classifiable diagnosis according to the International Statistical Classification of Diseases and Health Related Problems (Tenth Revision, ICD-10) (13). Studies that assessed the relationship of AE with unspecific symptoms such as psychosocial distress or sleeping problems were excluded. To be considered a 'systematic review', the following five prespecified criteria were requested in accordance with evidence-based medicine techniques: (1) formulation of a concrete research question in terms of PICO: population, intervention/exposure, control (if applicable), and outcome, (2) definition of inclusion and exclusion criteria, (3) implementation of a systematic (electronic) literature search, (4) critical appraisal of relevant research, and (5) systematic and transparent data synthesis (14). The presented overview of SRs was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA statement) (15).

Literature search

Given the lack of an electronic database that contains all publications of all medical journals and the fact that the restriction of only one database could be associated with a systematic bias, it is necessary to combine multiple databases for a comprehensive literature search. For this reason, an electronic literature search was carried out in (1) EMBASE and (2) MEDLINE via Ovid interface, and (3) MEDLINE via PubMed interface for all articles published from inception to November 30, 2012. The search of MEDLINE via the PubMed

interface was performed to ensure that no SRs were missed using MEDLINE and EMBASE via the Ovid interface, especially as PubMed tends to be more up to date, and therefore better suitable for finding newer citations. Database specific search strings were developed and included search terms describing AE (population/exposure) and SRs (study design). To keep the database search sensitive, additional search terms for comorbidities (outcome criteria) were not considered. Instead, a combination of medical subject headings (MeSH) and keywords was used. For SRs, search terms developed and recommended by Scottish Intercollegiate Guidelines Network (SIGN) (<http://www.sign.ac.uk/methodology/filters.html>) were applied for our Ovid search in EMBASE and MEDLINE. The search of PubMed was carried out using Clinical Queries SR filter (http://www.nlm.nih.gov/bsd/pubmed_subsets/sysreviews_strategy.html). We did not use any language restrictions for study selection. Additional details on the search string are provided in Appendix S1 (Supporting Information).

Hand search comprised screening of the reference lists from the SRs included and key articles on this topic such as (systematic) reviews, overviews of SRs, and the Annual Evidence Update on Atopic Eczema from the British NHS, for example, Shams et al. (16) or Williams et al. (17).

Study selection

First, titles and abstracts of identified reviews were screened by two independent reviewers (SD, CK) to determine whether the SRs met the predefined eligibility criteria of the overview. Second, full texts of the remaining articles were independently retrieved for eligibility by the two reviewers (SD, CK). Full texts that did not fulfill the a priori defined inclusion criteria were excluded. Disagreements were solved by discussion between all reviewers (SD, CK, and JS); reasons for exclusion were documented for each article.

Data extraction and critical appraisal

Characteristics of the included SRs were abstracted independently by two reviewers (SD, CK), and disagreements were resolved by a third reviewer (JS). Abstracted data were entered into evidence tables and included information on search strategy, quality assessment, study design, population,

Table 1 Inclusion and exclusion criteria for literature search and study selection

	Inclusion criteria	Exclusion criteria
Population/exposure	Atopic eczema (synonyms: eczema, atopic dermatitis, neurodermatitis)	All others
Outcome	Nonallergic comorbidities of AE (e.g., inflammatory bowel disease, cancer, diabetes mellitus, ADHD, depression, multiple sclerosis) based on ICD-10 (13)	Allergic diseases (e.g., food allergy) Disease impact of AE (quality of life, sleep disruptions)
Design	Systematic review/meta-analysis in accordance with Cochrane Collaboration (14)	Overview of systematic reviews, narrative review, expert review, cohort study, case-control study, cross-sectional study

AE, atopic eczema; ADHD, attention-deficit hyperactivity disorder.

assessment of exposure, classification, and assessment of outcome as well as (pooled) relative risks (RR) or odds ratios (OR).

All SRs included were critically assessed by two authors (SD, CK) using the revised and previously validated Assessment of Multiple Systematic Reviews (R-AMSTAR) checklist, an 11-item tool developed to appraise the methodological quality of SRs (18). R-AMSTAR is currently the only validated instrument available for this purpose. The R-AMSTAR items are scored on a range of one to four points with higher scores indicating better methodological quality. The total score on R-AMSTAR is 44 and illustrates that all criteria of the SRs were excellently satisfied in each item. In contrast, the minimum score of 11 reveals that no criteria in each of the 11 items are sufficiently fulfilled. Any disagreement between the reviewers with regard to methodological quality of the studies included was resolved in a consensus-building discussion, if necessary by a third reviewer (JS).

There is currently no consensus whether and how meta-analysis should be performed on the basis of overviews. Because meta-analysis based on SRs could be associated with an information loss and furthermore because of multiple outcomes of this overview, we did not calculate pooled risk estimates.

Results

The review identification and selection procedures are outlined in Fig. 1. Of 752 initially identified search hits, 23 arti-

cles were read in full text; nine of these met the predefined eligibility criteria and were included. In total, six SRs addressed the relationship between AE and cancer (19–24), and one SR reviewed the association of AE with diabetes mellitus type 1 (25), multiple sclerosis (MS) (26), and attention-deficit hyperactivity disorder (ADHD) (27), respectively. All included SRs were published between 2003 and 2011. The SR on the association of AE with ADHD (27) included studies based on clinical diagnosis of ADHD and studies that assessed ADHD symptoms. The latter studies were not included in this overview in accordance with our eligibility criteria.

Reasons for excluding the remaining 14 full texts were no focus on AE ($n = 2$) (28, 29), investigation of symptoms rather than specific medical conditions, allergic conditions or risk factors of AE ($n = 8$) (30–37), and no SRs ($n = 4$) (38–41).

Methodological quality

Results of the critical appraisal using R-AMSTAR for individual reviews are presented in Table 2. The methodological quality of included SRs was assessed with an average score of 25. SRs with highest scores reached a total of 30 points (21, 22). The transparency of the whole search strategy was mostly not disclosed (e.g., missing search string, lacking information concerning excluded studies). Three of nine SRs assessed the methodological quality of the primary studies included with a checklist (see also Table 3) (21, 22, 26). In all

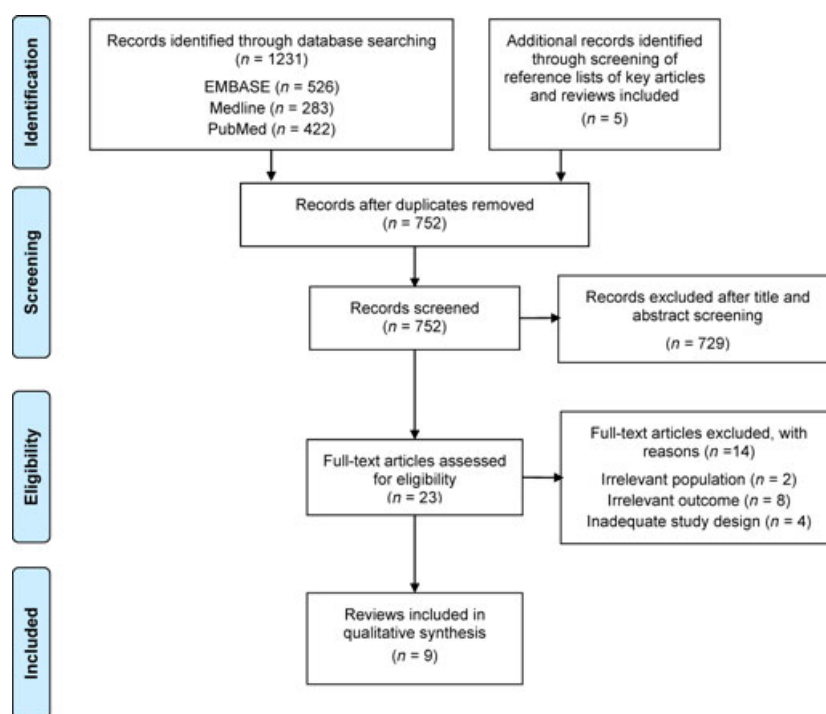


Figure 1 Flowchart of the systematic review selection procedure (according to the PRISMA statement) (15).

Table 2 Overview of quality assessment using R-AMSTAR

Reference	R-AMSTAR scoring*										
	Question 1	Question 2	Question 3	Question 4	Question 5	Question 6	Question 7	Question 8†	Question 9	Question 10	Question 11
Wang & Diepgen (20)	2	1	3	1	1	2	1	2	1	1	1
Wang & Diepgen (23)	3	1	2	1	2	1	2	1	1	1	1
Wang et al. (21)	3	4	4	1	2	2	2	3	4	1	1
Linos et al. (24)	3	2	3	1	4	1	2	3	4	2	2
Chen et al. (22)	3	4	4	1	4	2	2	3	3	2	2
Linabery et al. (19)	3	4	4	1	2	1	2	4	2	3	3
Cardwell et al. (25)	3	2	4	1	4	1	2	3	3	2	2
Monteiro et al. (26)	2	4	3	2	2	2	2	3	1	1	1
Schmitt et al. (27)	3	4	4	3	2	1	2	1	1	3	2
Mean	2.8	2.9	3.4	1.3	2.7	2.2	1.3	2.2	2.4	1.8	2.2
SD	0.44	1.36	0.73	0.70	1.32	0.67	0.50	0	1.13	1.30	0.83

SD, standard deviation.

1: Was an 'a priori' design provided? 2: Was there duplicate study selection and data extraction? 3: Was a comprehensive literature search performed? 4: Was the status of publication (i.e., gray literature) used as an inclusion criterion? 5: Was a list of studies (included and excluded) provided? 6: Were the characteristics of the included studies provided? 7: Was the scientific quality of the included studies assessed and documented? 8: Was the scientific quality of the included studies used appropriately in formulating conclusions? 9: Were the methods used to combine the findings of studies appropriate? 10: Was the likelihood of publication bias (a.k.a. 'file drawer' effect) assessed? 11: Was the conflict of interest stated?

*An R-AMSTAR score of 4 indicates that all criteria are satisfied for the specific question, whereas an R-AMSTAR score of 1 indicates that less criteria are satisfied (18).

†Within the domain 8, we considered the item 'this clinical consensus statement drives toward revision or confirmation of clinical practice guidelines?' as not applicable for the specific scope of this overview. To reach the maximum score of four points for this domain, only 3 instead of 4 criteria had to be fulfilled.

Table 3 Characteristics of reviews included on the association between atopic eczema and comorbidity

Reference	Search period	Assessment of methodological quality	Population (age, gender)*	Requirements of exposure assessment* (diagnostic criteria)	Outcome/comorbidity and requirements of assessment*
Wang & Diepgen (20)	January 1986 to April 2004	None	No predefined criteria	No predefined criteria	Pancreatic cancer, brain tumor, leukemia, non-Hodgkin lymphoma
Wang & Diepgen (23)	1985 to December 2004	None	No predefined criteria	No predefined criteria	Hematological malignancies, pancreatic cancer, brain tumors, skin cancer
Wang et al. (21)	January 1979 to October 2009	Yes	No predefined criteria	No predefined criteria	Meningioma, medically confirmed
Linos et al. (24)	1979 to February 2007	None	No predefined criteria	No predefined criteria	Primary glioma or meningioma, medically confirmed
Chen et al. (22)	January 1979 to October 2009	Yes	No predefined criteria	No predefined criteria	Glioma or meningioma, medically confirmed
Linabery et al. (19)	1952 to March 2009	None	Diagnosis of leukemia before the age of 19	No predefined criteria	Childhood/adolescent leukemia
Cardwell et al. (25)	Up to March 2003	None	No predefined criteria	No predefined criteria	Diabetes mellitus type 1
Monteiro et al., (26)	Up to July 2009	Yes	No restriction regarding sex, race, or age-group	Diagnosis of AE	Multiple sclerosis
Schmitt et al. (27)	Up to February 2010	None	No predefined criteria	No predefined criteria	ADHD, categorical assessment of ADHD and/or personal history

*Based on predefined inclusion and exclusion criteria of SRs included; AE, atopic eczema; ADHD, attention-deficit hyperactivity disorder.

these SRs, the standardized Newcastle Ottawa Scale (42) was applied. Furthermore, a ranking of quality of evidence was not conducted. Statistical tests on the likelihood of publication bias were performed in three of nine SRs (21, 22, 24), indicating a possible (21), an unlikely (24), and an unclear publication bias (22).

Summary of results of SRs included

Tables 3 and 4 summarize the characteristics and results of the SRs included. Several SRs reviewed more than ten primary studies on the association between AE and comorbidities, mainly retrospective studies. A total of 6 SRs

Table 4 Results of reviews included on the association between atopic eczema and comorbidity

Reference	Study design: no. of studies	Outcome (ICD-10 Code) (13)	Association between AE and outcome OR/RR (95% CI)*	Conclusions of SR authors
Wang & Diepgen (20)	CC: 5	Pancreatic cancer (C25)	Range: 0.2 (0.1–0.5) to 1.1 (0.7–1.9)	In spite of methodological problems, the studies conducted thus far seem to point toward a reduced risk of pancreatic cancer, childhood leukemia, and brain tumors
	CC: 4, C: 1	Brain tumor (C71)	Range: 0.2 (0.1–0.9) to 0.9 (0.5–1.4)	
	CC: 6	Leukemia (C90.1 to C95)	Range: 0.5 (0.3–0.7) to 1.7 (0.7–4.5)	
	CC: 5	Non-Hodgkin lymphoma, NHL (C82 to C85)	Range: 0.5 (0.3–0.7) to 1.9 (0.6–5.8)	
Wang & Diepgen (23)	CC: 11	Hematological malignancies (C81 to C96)	Range: 0.5 (0.3–0.7) to 1.9 (0.6–5.8)	The findings of the observational studies tend to support a lower risk of cancer among persons with a history of AE
	CC: 5	Pancreatic cancer (C25)	Range: 0.2 (0.1–0.5) to 1.1 (0.7–1.9)	
	CC: 4, C: 1	Brain tumors (C71)	Range: 0.2 (0.1–0.9) to 0.9 (0.3–2.5)	
	CC: 1, C: 1	Skin cancer (C43)	Range: 0.8 (0.6–1.0) to 1.8 (0.8–3.9)	
Wang et al. (21)	CC: 5, C: 1	Meningioma (C70)	Pooled OR: 0.75 (0.65–0.87)	AE is significantly associated with the occurrence of meningioma. Prospective cohort studies with adequate numbers of cases are needed to further confirm the observed association
Linós et al. (24)	CC: 6, C: 1	Glioma (C71)†	Pooled RR: 0.69 (0.58–0.82)	There is an inverse relationship between atopic disease and glioma that is unlikely to be explained by methodological bias alone
Chen et al. (22)	CC: 6, C: 1	Glioma (C71)†	Pooled OR: 0.69 (0.62–0.78)	Allergic conditions may significantly reduce the risk of glioma
Linabery et al. (19)	CC: 5	Acute lymphoblastic leukemia, ALL (C91.0)	Pooled OR: 0.74 (0.58–0.96)	Although the results of this meta-analysis indicate inverse association between atopy and childhood/adolescent, explanations other than a direct causal relation, such as reverse causality or recall bias, need to be ruled out
	CC: 2	Acute myeloid leukemia, AML (C92.0)	Pooled OR: 0.78 (0.53–1.15)	
Cardwell et al. (25)	CC: 17	Diabetes mellitus type 1 (E10)	Pooled OR: 0.82 (0.62–1.10)	Conclusion of inconsistent results for the association between eczema and diabetes mellitus type 1
	CS: 1			
Monteiro et al. (26)	CC: 2	Multiple sclerosis (G35)	Pooled OR: 0.93 (0.71–1.23)	The results showed that there is no evidence supporting an association between AE and asthma
	CS: 2			
Schmitt et al. (27)	CC: 1	Attention-deficit hyperactivity disorder, ADHD (F90)	Range: 1.47 (1.01–2.15) to 7.75 (1.65–40.45)	Studies consistently suggest a positive association between eczema and ADHD
	CS: 2			

CC, case-control study; C, cohort study; CS, cross-sectional study; AE, atopic eczema; ADHD, attention-deficit hyperactivity disorder.

*Range implicates SRs without meta-analysis, and pooled RR/OR indicates meta-analysis results.

†Results for the association between AE and meningioma not reported.

performed a meta-analysis (19, 21, 22, 24–26). In this case, pooled results (RR/OR with 95% confidence interval (CI)) are presented in Table 4. If no meta-analysis was performed, the range of RR or OR is reported.

Association between AE and cancer

The six cancer reviews assessed the association between AE and the following entities: brain tumors (i.e., glioma, meningioma) (20–24), leukemia (19, 20), non-Hodgkin lymphoma (NHL) (20), pancreatic cancer (20, 23), hematological malignancies (23), and skin cancer (23). These SRs summarized and appraised a total of 65 case-control studies and six cohort studies with substantial overlap between the different SRs in the original studies included regarding each entity.

Only the SR by Linabery et al. (19) used a predefined definition for the population and included primary studies that investigated patients with a diagnosis of leukemia before the age of 19 years. None of the cancer reviews defined requirements for AE assessment such as diagnostic criteria, disease severity, and physician diagnosis. Three of the included cancer reviews investigated explicitly studies where the outcome was defined as medically confirmed cases of cancer (21, 22, 24). The remaining three reviews (19, 20, 23) described no requirements for cancer assessment.

Current or previous AE was inversely associated with the risk of brain tumors. The observed RR/OR for brain tumor in general ranged from 0.2 (95% CI: 0.1–0.9) to 0.9 (95% CI: 0.3–2.5) (20, 23). For meningioma, the pooled OR was 0.75 (95% CI: 0.65–0.87) (21). AE was also associated with a decreased risk of glioma (pooled RR 0.69, 95% CI: 0.58–0.82 and pooled OR 0.69, 95% CI: 0.62–0.78) (22, 24). The authors of these SRs concluded a vague (20, 23) to a definite (21, 22, 24) risk reduction.

Acute lymphoblastic leukemia (ALL) was inversely related to AE (pooled OR: 0.74 (95% CI: 0.58–0.96)) in the SR published by Linabery et al. (19). No consistent associations were observed for the following entities: acute myeloid leukemia (AML) pooled OR 0.78 (95% CI: 0.53–1.15) (19), not further specified leukemia range of RR and OR: 0.7 (95% CI: 0.3–1.5) and 1.7 (95% CI: 0.7–4.5) (20), pancreatic cancer, NHL, hematological malignancies, and skin cancer (for more details on RR/OR and corresponding 95% CI, please refer to Table 4).

Association between AE and diabetes mellitus type 1

One SR with meta-analysis summarized the association between AE and childhood diabetes mellitus type 1 based on 17 case-control studies and one cross-sectional study (25). The authors did not use predefined inclusion criteria for patients with AE participating in primary observational studies. Further, concrete requirements for the assessment of AE and childhood diabetes mellitus type 1 were not defined. The pooled OR indicates a nonsignificant reverse association (OR 0.82; 95% CI: 0.62–1.10). The authors concluded inconsistent results for the association between AE and diabetes mellitus type 1.

Association between AE and multiple sclerosis

Monteiro et al. (26) reviewed two case-control and two cross-sectional studies on the relationship between AE and MS. The authors did not explicitly use restrictions for population characteristics such as age-groups or sex as inclusion criteria. Diagnostic criteria or requirements of assessment of AE or MS were not specified in this SR. The pooled OR showed no significant association between AE and MS (0.93; 95% CI: 0.71–1.23). The SR authors concluded that there is no evidence supporting an association between AE and MS.

Association between AE and attention-deficit hyperactivity disorder

One SR examined the relationship between AE and ADHD (27) including one case-control study and two cross-sectional studies. While one of these studies used secondary data concerning physician documentation of ADHD diagnosis (43), the other two studies were primary epidemiological studies (44, 45). We excluded three studies that were included in the review by Schmitt et al. (27), because the authors used non-categorical measures to assess ADHD or the description of the used measurement was not stated (46–48). The authors did not define specific inclusion criteria for population characteristics and requirements for AE assessment. In comparison, only studies that used categorical assessment and/or personal history of ADHD as outcome measure were included. The results exhibit a positive association between AE and ADHD. The OR ranged from 1.47 (95% CI: 1.01–2.15) to 7.75 (95% CI: 1.65–40.45). The OR was above four in one study and between 1 and 2 in two studies. The authors of the original SR concluded that the studies consistently suggested a positive association between AE and ADHD.

Discussion

Summary of main findings

Systematic reviews of observational studies suggest that patients with AE are at decreased risk of brain tumors such as glioma and meningioma. Children with AE appear to develop ALL less frequently than children without AE. For other cancers including AML, other hematological malignancies, skin cancer, and pancreatic cancer, no significant associations were observed with AE in a total of six SRs.

One SR (27) reported a consistent positive association of AE with ADHD. Additionally, one birth cohort study (46) that assessed ADHD with a dimensional measure and two additional studies (47, 48) with unclear methods indicate a positive association between AE and ADHD. The underlying pathophysiological mechanisms of this comorbidity are still unknown, but deserve further investigation. It has been speculated that the release of inflammatory cytokines due to AE may interfere with the maturation of the prefrontal cortex and neurotransmitter systems known to be involved in

ADHD pathology (49). Alternatively or additionally, AE and ADHD may not be causally related, but have one or more shared risk factors such as genetics and/or prenatal stress leading to the observed co-occurrence of both conditions. These alternative explanations of the findings from observational studies deserve further investigation to eventually develop targeted interdisciplinary primary prevention and treatment strategies (49, 50).

Published SRs did not observe a significant association between AE and diabetes mellitus type 1 (25) and between AE and MS (26). However, these two reviews are based only on cross-sectional and case-control studies, which both do not allow to deduce temporality or causality. Therefore, the relationship of AE with Th1-mediated auto-inflammatory conditions such as diabetes mellitus type 1 and MS deserves further clarification in prospective observational studies.

Systematic reviews on the risk of psychiatric morbidities and on cardiovascular risk factors and events of adults with AE are missing, but appear to be relevant in light of the known negative impact of AE on quality of life, the high prevalence of sleeping problems, and reports of embarrassment and feelings of stigmatization of patients with AE (6, 7).

Quality of evidence

The lacking methodological quality of SRs included is reflected in an overall low R-AMSTAR score (18). Only two SRs achieved 30 of possible 44 points (21, 22). The two SRs with the lowest quality score achieved 16 of 44 possible points (20, 23). Due to insufficient methodological quality, the presented evidence on the association of AE with comorbidities needs to be interpreted with caution. It was striking that only three SRs performed a quality assessment of included studies (21, 22, 26), which considered to be an essential step in the process of SR (14). We included SRs if a critical appraisal of relevant research was carried out; therefore, all included SRs discussed methodological problems. Nevertheless, a more rigorous, for example, transparent, independent, and standardized assessment of methodology study quality using validated and reliable tools should be made. Three of nine SRs did not search in more than one electronic database and also did not perform hand searching of relevant journals as the minimum criteria for a comprehensive literature search (20, 23, 26). The quality of evidence is also limited due to possible publication bias, which was the case in one SR (21). Only two further SRs identified an unlikely or unclear publication bias (Table 2) (22, 24). For the remaining six SRs, results could be biased which certainly limit the quality of evidence of included SRs. Neither the role of the severity of AE nor of the treatment of AE has been considered in the SRs included in this review. The absence of the application of validated case definitions or diagnostic criteria of AE and the comorbidities investigated may have introduced nondifferential misclassification bias with consecutive underestimation of the true positive or negative relationship of AE and the comorbidities under investigation.

Strengths and limitations

The methodological approach of overviews is to summarize the evidence of a specific research question. This procedure can be affected in accordance with the quality of included SRs with a certain information loss. Because it is not the aim of overviews to review and assess primary studies, this was not done by the authors of this overview.

Strengths of this overview include the comprehensive literature search using recommended search strings for SRs in three databases (MEDLINE, EMBASE, and PubMed), the independent title, abstract, and full text screening, quality assessment, and data abstraction with consensus finding. Additionally, we did not use any language restrictions for considering studies eligible. For the quality assessment of included SRs, we used R-AMSTAR, which is a validated tool (18). Although the original version of AMSTAR (51, 52) was prepared for SRs dealing with randomized controlled trials, the authors stated that AMSTAR can be applied to a wide variety of SRs (52). Therefore, we applied this checklist for observational studies. The Revised AMSTAR checklist allows quantification of the quality of SRs. The authors from R-AMSTAR (18) pointed out that question number 7A, which deals with a priori methods of assessment, for example, for placebo-controlled studies, needs alternative items for other types of studies. Given the fact that a validated checklist for SRs for observational studies is missing, we applied R-AMSTAR by rephrasing this item and predefined criteria for observational studies considering a priori methods for case definition and outcome assessment. Even though a higher overall R-AMSTAR score is indicating a better methodological quality in contrast to a lower overall R-AMSTAR score, a definite cutoff value is missing. Therefore, a clear interpretation is not possible, but differences in methodological quality can be illustrated.

To date, a principal methodological approach to conduct an overview does not exist. Hartling et al. (53) concluded in their descriptive analysis of overviews of SRs that methodological rigor and consistency in overviews, as well as empirical evidence to support the methods, are missing.

To avoid misclassification of the investigated comorbidities, this review focused on SRs on comorbidities of AE, which were classified according ICD-10 (13) rather than on symptoms. Therefore, a loss of information cannot be ruled out, for example, for depressive symptoms.

Implications for research

This overview clarifies whether SRs are available on non-allergic comorbidities of AE and whether these reviews provide complete and valid evidence. In this context, the necessity of more up to date SRs becomes obvious. This applies especially to the review on diabetes mellitus type 1 (25); hence, literature search was only performed till March 2003. An unsystematic literature search revealed that more recent, mainly case-control studies, for diabetes mellitus type 1 and AE, exist. There seems to be conflicting evidence, because two population-based case-control studies have

contradictive results. There is evidence for an inverse association between AE and the risk of diabetes mellitus type 1 (54), but also evidence for the opposite (55). This may be caused by study design, selection bias, or recall bias and should be clarified on the basis of a SR applying a critical appraisal of study quality. In case of insufficient number of prospective studies, cohort studies should be conducted in the future. In addition, the analysis of data from routine care could help investigating and understanding such associations.

In our opinion, a separate overview of SRs for allergic diseases considering food allergies, hay fever, and skin infections should be performed additionally.

Furthermore, our overview has detected a research gap regarding a systematic preparation of evidence, for example, for inflammatory bowels disease, rheumatoid arthritis, and psychiatric disorders other than ADHD. Further SRs and prospective cohort studies are needed to clarify the relevance of these diseases for patients with AE and their biological mechanisms.

Author contributions

Stefanie Deckert developed the search string, did the systematic electronic searches, identified relevant articles for inclu-

sion, abstracted data into evidence tables, performed study quality assessment, and drafted parts of the manuscript. Christian Kopkow identified relevant articles for inclusion, abstracted data into evidence tables, performed study quality assessment, and drafted parts of the manuscript. Jochen Schmitt resolved eligibility and quality assessment in case of disagreements and drafted parts of the manuscript. All authors were involved in the development of the study concept, critically reviewed the manuscript, and gave permission for publication.

Conflicts of interest

JS was the lead author of one of the systematic reviews (27) included in this overview. SD and CK declare no conflicts of interest.

Supporting Information

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

Appendix S1. Search strategy.

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