Article Type: From the Academy

Title: Guidelines of care for the primary prevention of atopic dermatitis and awareness of comorbid conditions in pediatric atopic dermatitis

Robert Sidbury, MD, MPH (Co-Chair)[a], Ali Alikhan, MD[b], Lionel Bercovitch, MD[c], David E. Cohen, MD, MPH[d], Jennifer M. Darr, LCSW[e], Aaron M. Drucker, MD, ScM[f, g], Lawrence F. Eichenfield, MD[h], Lindsy Frazer-Green, PhD[i], Amy S. Paller, MD[j], Kathryn Schwarzenberger, MD[k], Jonathan I. Silverberg, MD, PhD, MPH[l], Anne Marie Singh, MD[m], Peggy A. Wu, MD, MPH[n], Dawn M.R. Davis, MD (Co-Chair)[o]

Division of Dermatology, Department of Pediatrics, University of Washington School of Medicine and Seattle Children's Hospital, Seattle, Washington[a]; Department of Dermatology, Sutter Medical Foundation, Sacramento, California[b]; Department of Dermatology, Warren Alpert Medical School of Brown University, Providence, Rhode Island[c]; The Ronald O. Perelman Department of Dermatology, New York University Grossman School of Medicine, New York[d]; Department of Pediatrics, National Jewish Health, Denver, Colorado[e]; Division of Dermatology, Department of Medicine, University of Toronto, Toronto, Ontario, Canada[f]Research and Innovation Institute and Department of Medicine, Women's College Hospital, Toronto, Ontario, Canada[g]; Departments of Dermatology and Pediatrics, University of California San Diego and Rady Children's Hospital San Diego, San Diego, California[h]; American Academy of Dermatology, Rosemont, Illinois[i]; Departments of Dermatology and Pediatrics, Northwestern University Feinberg School of Medicine, Chicago, Illinois[j]; Department of Dermatology, Oregon Health and Science University, Portland, Oregon[k]; Department of Dermatology, The George Washington University School of Medicine and Health Sciences, Washington, DC[l]; Department of Pediatrics, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin[m]; Department of Dermatology, University of California, Davis, Sacramento, California[n]; Departments of Dermatology and Pediatrics, Mayo Clinic, Rochester, Minnesota[o]

Corresponding author:
Lindsy Frazer-Green, PhD
American Academy of Dermatology
9500 Bryn Mawr Avenue, Suite 500
Rosemont, IL 60018
Email: lfrazer-green@aad.org

Funding sources: This study was funded in total by internal funds from the American Academy of Dermatology.

Conflicts of Interest: Listed in text.

Supplementary files are available on:
Reprint Requests: No reprints available.

Manuscript word count: words [excluding abstract, references, figures, tables, appendix]
Abstract word count:

References:
Figures:
Online Supplementary figures:

Keywords: atopic dermatitis, prevention, comorbidities, allergies, cardiovascular disease, dermatology, diabetes, guidelines, mental health, metabolic syndrome, obesity, skin infection, osteoporosis

Publishable Conflict of Interest Statement

The American Academy of Dermatology (AAD) strives to produce clinical guidelines that reflect the best available evidence supplemented with the judgment of expert clinicians. Significant efforts are taken to minimize the potential for conflicts of interest to influence guideline content. The management of conflict of interest for this guideline complies with the Council of Medical Specialty Societies' Code of Interactions with Companies. Funding of guideline production by medical or pharmaceutical entities is prohibited, full disclosure is obtained and evaluated for all guideline contributors throughout the guideline development process, and recusal is used to manage identified relationships. The AAD conflict of interest policy summary may be viewed at www.aad.org.

Disclaimer

Adherence to these guidelines will not ensure successful treatment in every situation. Furthermore, these guidelines should not be interpreted as setting a standard of care or be deemed inclusive of all proper methods of care, nor exclusive of other methods of care reasonably directed to obtaining the same results. The ultimate judgment regarding the propriety of any specific therapy must be made by the physician and the patient in light of all the circumstances presented by the individual patient, and the known variability and biologic behavior of the disease. This guideline reflects the best available data at the time the guideline was prepared. The results of future studies may require revisions to the recommendations in this guideline to reflect new data.

Abstract

Background: Pediatric atopic dermatitis (AD) is a common, chronic inflammatory skin disorder that significantly impacts the quality of life of affected children and their families. In addition to skin-related symptoms, AD in pediatric patients may be associated with a range of comorbid conditions

Objective: To provide evidence-based recommendations on primary prevention of AD and to appraise evidence of the association between AD and comorbidities among pediatric patients.

Methods: A multidisciplinary workgroup conducted a systematic review and applied the GRADE approach for assessing the certainty of evidence and formulating and grading recommendations.

Results: The workgroup developed 14 evidence-based recommendations on primary prevention of AD and 29 statements on the association between pediatric AD and comorbid conditions.

Limitations: This analysis is based on the best available evidence at the time it was conducted. This guideline does not make recommendations for screening or management of comorbidities in children with AD.

Conclusions: We make a conditional recommendation for moisturizing skin care to reduce the occurrence of AD and conditional recommendations against early food introduction, human milk consumption, and probiotic or vitamin D supplementation for the primary prevention of AD. Clinicians should be aware of comorbidities associated with pediatric AD, but further research is needed to optimize screening and/or management of comorbidities.

Abbreviations Used

AA: Alopecia areata

AAD: American Academy of Dermatology

AC: Allergic conjunctivitis

AD: Atopic dermatitis

ADHD: Attention deficit hyperactivity disorder

AE: Adverse event

AR: Allergic rhinitis

ASD: Autism spectrum disorder

CDLQI: Children's Dermatology Life Quality Index

CI: Confidence interval

EASI: Eczema Area and Severity Index

EoE: Eosinophilic esophagitis

FA: food allergies

FDA: Food and Drug Administration

HR: Hazard ratio

IGA: Investigator Global Assessment

MD: Mean difference

OR: Odds ratio

POEM: Patient Oriented Eczema Measure

QoL: Quality of life

RCT: Randomized controlled trial

RR: Risk ratio

SAE: Serious adverse event

SCORAD: Scoring of Atopic Dermatitis

Scope and Objectives

Atopic dermatitis (AD) is a chronic inflammatory skin condition affecting 10 to 20% of children worldwide.[1-4] It often begins in infancy and is associated with appreciable morbidity and healthcare burden. In addition to skin-related symptoms, AD in pediatric patients may be associated with a range of comorbidities, including allergic rhinitis, asthma, food allergies, and mental health disorders. The objective of these guidelines is twofold: (1) to provide evidence-based recommendations for the primary prevention of AD, and (2) to present evidence-informed statements on the associations between AD and pediatric comorbidities. These guidelines aim to support healthcare professionals, caregivers, and policymakers in implementing preventive measures and in understanding the broader health implications of pediatric AD. Children under 18 years of age with AD of any severity in any healthcare setting or context are the target population of these guidelines. Importantly, these guidelines do not make recommendations for screening or management of comorbidities in adults with AD.

Methods

A multidisciplinary workgroup developed these guidelines using a systematic evidence review process, which included (i) identifying and prioritizing clinical questions and outcomes (**Table I**), (ii) systematic retrieval and assessment of evidence, and (iii) assessment of the certainty of the evidence and formulation of recommendations or statements of association using GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) (**Tables II & III**).

Table I. Clinical questions and scope

Clinical Questions	
1.How do infant-focused skin care, dietary, microbiome, environmental, and other interventions affect the risk of developing AD, and do primary AD prevention interventions cause undesirable effects?	
2. Are the following comorbidities associated with AD in children and adolescents: mental and behavioral health disorders, allergic conditions, skin infections, asthma, lifestyle choices, alopecia areata, bone fractures, osteoporosis, cardiovascular disease, metabolic syndrome?	
Outcomes of interest	
Primary Prevention	Incidence, occurrence, or rate of AD at 6 months to 3 years of age
	Serious adverse events(as defined by studies)
	Adverse events of interest (specific to each intervention defined a priori)
Comorbidities	Incidence of select comorbid conditions
	Prevalence of select comorbid conditions
Scope for prevention	
Characteristic	**Inclusion Criteria**
Population	Healthy full-term (≤ 37 weeks' gestation) infants ≤12 months without pre-existing atopic dermatitis from high-risk or general populations
Intervention	Infant-directed interventions intended to prevent development of AD. Including skincare, environmental, dietary, microbiome, and other interventions
Study Design	Published RCTs
Scope for comorbidities	
Characteristic	**Inclusion Criteria**
Population	Children and adolescents (<18 years old) with clinically diagnosed AD of any severity
Exposure	Diagnosis of atopic dermatitis
Study Design	Non-randomized studies (cohort, case-control, cross-sectional)

Specific to the clinical question addressing the association between pediatric AD and comorbid conditions, the GRADE for prognosis approach was used to assess the overall certainty of the evidence for each outcome.[5, 6] The GRADEPro Guideline Development Tool was used to create evidence profiles that categorized the overall quality of the body of evidence for each outcome into one of four categories: high, moderate, low, or very low. Each category represents the confidence in the estimate of effect for an outcome (**Table III**).

Table II. Strength of recommendation and certainty of evidence for primary prevention recommendations

Strength of Recommendation	Wording	Implication[7-9]
Strong recommendation *for* the use of an intervention	"We recommend…"	Benefits clearly outweigh risks and burdens; recommendation applies to most patients in most circumstances.
Strong recommendation *against* the use of an intervention	"We recommend against…"	Risk and burden clearly outweigh benefits; the recommendation applies to most patients in most circumstances.
Good Practice Statement	"We recommend…"	Guidance was viewed by the Work Group as imperative to clinical practice and developed when the supporting evidence was considerable but indirect, and the certainty surrounding an intervention's impact was high with the benefits clearly outweighing the harms (or vice versa). Good Practice Statements are strong recommendations as the certainty surrounding the impact of the recommended intervention is high. Implementation of these strong recommendations is considered to clearly result in beneficial outcomes.[9]
Conditional recommendation *for* the use of an intervention	"Evidence suggests benefit…"	Benefits are closely balanced with risks and burdens; recommendation applies to most patients, but the most appropriate action may differ depending on the patient or other stakeholder values.
Conditional recommendation *against* the use of an intervention	"Evidence suggests no benefit…"	Risks and burden closely balanced with benefits; recommendation applies to most patients, but the most appropriate action may differ depending on the patient or other stakeholder values
Insufficient evidence statement	"There is insufficient evidence to recommend…"	The available evidence is inadequate to make a reliable determination about the effectiveness or lack thereof of an intervention
Certainty of Evidence	**Wording**	**Implication[7, 8]**
High	"high certainty evidence"	Very confident that the true effect lies close to that of the estimate of the effect.
Moderate	"moderate certainty evidence"	Moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	"low certainty evidence"	Confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect
Very Low	"very low certainty evidence"	The estimate of effect is very uncertain; the true effect may be substantially different from the estimate of effect

Table III . Strength of statements of association and supporting evidence: Wording & implications

Statement Wording	Overall certainty of Supporting Evidence	Implication
Is associated	High or Moderate	Clear evidence of an important large effect
Is not associated	High or Moderate	Clear evidence of no association
Probably associated	High or Moderate	Evidence of a moderate effect
Probably not associated	High or Moderate	Evidence of small or unimportant effect
May be associated	Low	Evidence of a large, moderate, or small effect based on low quality evidence.
May not be associated	Low	Evidence of no association based on low quality evidence.
Uncertain association	Any Quality	Evidence of any magnitude of effect from very low quality evidence or imprecise or inconsistent effect estimates from evidence of any quality.
Strength of Evidence	**Wording**	**Implication[6-8]**
High	"high quality evidence"	Very confident that the true magnitude of association lies close to that of the estimate.
Moderate	"moderate quality evidence"	Moderately confident in the estimate of association, but there is a possibility that it is substantially different.

Low	“low quality evidence”	Confidence in the estimate is limited; the true magnitude of association may be substantially different from the estimate.
Very Low	"very low quality evidence"	The estimate is very uncertain; the true magnitude of association may be substantially different from the estimate.

For detailed methodology, see **Supplemental Appendix 1**.

Definition

AD, also known as atopic eczema, is a chronic, pruritic inflammatory skin disease that occurs with highest prevalence in children. It follows a relapsing course. AD is often associated with a personal or family history of atopy.

PRIMARY PREVENTION

A range of interventions from skin care to nutritional modifications were explored for their potential for primary prevention of AD. This section of the guideline evaluates the data on infant-focused primary AD prevention interventions to support evidence-based clinical practice recommendations (**Table IV**).

Table IV. Recommendations for primary AD prevention interventions

Statement	Strength	Certainty of Evidence	Evidence
Skincare interventions			
Evidence suggests regular use of moisturizing skin care before the age of 2 years in children at risk for atopic dermatitis may reduce the risk of developing atopic dermatitis. *Remark*: The evidence does not support a protective benefit with the use of moisturizing skincare in the general population.	Conditional	Low	10-23
Environmental interventions (water softening, allergen avoidance)			
There is insufficient evidence to recommend water softening or dust mite avoidance interventions before the age of 2 years in children at risk of developing atopic dermatitis.	NA	Very low	24-26
Dietary interventions			
Evidence suggests no benefit to early food introduction for the prevention AD.	Conditional	Very low	20, 27

Evidence suggests no benefit of the consumption of human milk for the prevention of AD.	Conditional	Very low	[28]
Evidence suggests no benefit from probiotic supplementation for the prevention of AD.	Conditional	Low	[29-37]
Evidence suggests no benefit from vitamin D supplementation for the prevention of AD.	Conditional	Low	[38]
There is insufficient evidence to recommend prebiotic supplementation for the prevention of AD.	NA	Very low	[39-42]
There is insufficient evidence to recommend synbiotic supplementation for the prevention of AD.	NA	Low	[43]
There is insufficient evidence to recommend the consumption of goat milk for the prevention of AD.	NA	Very low	[44, 45]
There is insufficient evidence to recommend fatty acid supplementation for the prevention of AD.	NA	Very low	[25, 46-48]
There is insufficient evidence to recommend an enriched formula for the prevention of AD.	NA	Low	[49]
There is insufficient evidence to recommend partially hydrolyzed whey formula for the prevention of AD.	NA	Very low	[50-58]
There is insufficient evidence to recommend the short-term early consumption of hydrolyzed formula.	NA	Very low	[53]
There is insufficient evidence to recommend soy formula for the prevention of AD.	NA	Low	[51, 54]

Skin care interventions

Regular use of moisturizing skin care before 2 years of age in children at risk for AD may reduce the development of AD,[10-12, 14-19, 21-23] (**Supplemental Table 1**). There is great heterogeneity among applicable studies, in terms of age at intervention, duration of intervention, washout periods, age at assessment, intervention composition timing and frequency, and comparator group. The evidence does not support a protective benefit with the use of moisturizing skin care in the general population.[13, 20] However, providers should educate caregivers about the potential for exposure to allergens in personal care products, though adverse events (AEs) with regular moisturizing skin care appears rare and comparable to standard care.[12-14, 19, 22]

Environmental interventions

There is insufficient evidence to recommend dust mite avoidance interventions before the age of 2 years in children at risk of developing AD (**Supplemental Table 2**).[24] Due to the underpowered

sample in the study by Jabbar-Lopez et al, there is also insufficient evidence to recommend water-softening interventions before the age of 2 years in children at risk of developing AD (**Supplemental Table 3**).[26]

Dietary interventions

Available evidence suggests no benefit to early complementary feeding for the prevention of AD (**Supplemental Table 4**).[20, 27] Although early food introduction may reduce the risk of food allergy, it does not alter the occurrence or severity of AD.[59, 60]

Available evidence suggests no benefit from human milk consumption,[28] probiotic supplementation,[29, 31-33, 35-37] or vitamin D supplementation[38] for the prevention of AD (**Supplemental Tables 5-7**). Furthermore, due to limited, underpowered data, there is insufficient evidence to recommend prebiotic supplementation,[39, 40, 42] synbiotic (combined probiotic and prebiotic) supplementation, [43] goat milk consumption (note, it may cause gastrointestinal distress and iron-deficiency anemia),[44, 45] fatty acid supplementation,[46-48, 61] enriched formula,[49] partially hydrolyzed whey formula,[50-58] short-term early consumption of hydrolyzed formula,[53] or soy formula[51, 54] for the prevention of AD (**Supplemental Tables 8-15**).

COMORBIDITIES

AD detrimentally impacts quality of life (QoL) and overall health, increasing health care utilization.[62, 63] Comorbidities further increase the individual- and population-level burdens of AD, and AD in children is associated with a wide variety of systemic comorbidities, particularly atopic and allergic conditions (**Table III**). This section of the guidelines appraises the evidence

of the association between pediatric AD and comorbid conditions to increase awareness and understanding of AD and its potential associations with the aim of helping providers deliver more holistic care and prevent long-term health consequences and reductions in QoL for these patients.

Table III. Pediatric AD comorbidities statements of association

Statement of Association	Certainty of Evidence	Evidence
Atopic & Allergic Conditions		
The association between AD in children and allergic conjunctivitis is uncertain.	Low	64-66
AD in children is associated with allergic rhinitis.	Moderate	64, 65, 67-93
AD in children is associated with eosinophilic esophagitis.	High	65, 70, 85, 94-99
AD in children is associated with food allergies. *Remark:* The majority of studies used strict definitions of IgE-mediated food allergy (including symptoms plus evidence of allergic sensitization and/or oral food challenge).	Moderate	65, 70, 78, 80, 82, 83, 88, 92, 100-140
Greater AD severity in children may be associated with increasing food allergy prevalence	Low	80, 117, 120, 127, 136
AD in children is associated with asthma	Moderate	65, 67-70, 73, 75, 76, 78, 80, 82-85, 87-92, 117, 119, 125, 132, 136, 141-174
Greater AD severity in children may be associated with increasing asthma prevalence	Moderate	68, 90, 136
Immune-mediated Conditions		
AD in children may be associated with alopecia areata.	Low	70, 76, 82, 175-181
AD in children is associated with urticaria	Moderate	66, 68, 70, 75, 76, 80, 82, 85, 182-187
Mental Health & Substance Use		
AD in children is probably associated with anxiety	Moderate	64, 65, 68-70, 82, 83, 90, 188-193
The association between AD in children and depression is uncertain	Very low	64, 68, 69, 76, 82, 90, 188, 190-194
AD in children is probably *not* associated with suicide	Moderate	64, 90, 195-198
AD in children is probably *not* associated with drinking alcohol	Moderate	199-203
AD in children is probably *not* associated with cigarette smoking	Moderate	199-201, 204-206
AD in children is probably *not* associated with illicit drug use	Moderate	69, 199
ADHD & Autism Spectrum Disorders		
AD in children is associated with ADHD	Moderate	64, 65, 69, 70, 82, 83, 90, 188, 190, 192, 207-225
The association between AD in children and autism spectrum disorder is uncertain	Low	64, 82, 83, 90, 188, 190, 210, 211, 220, 221, 226-229
Cardiovascular Diseases		
AD in children may be associated with hypertension *Remark:* The evidence suggests a small magnitude of association between AD and hypertension in children.	Low	69, 70, 76, 230, 231

The association between AD in children and ischemic heart disease is uncertain.	Low	69, 76
AD in children is probably *not* associated with peripheral vascular disease.	Moderate	69
AD in children is probably *not* associated with cardiac arrhythmia.	Moderate	69, 82
AD in children is probably *not* associated with congestive heart failure.	Moderate	69
Metabolic Disorders		
AD in children is probably associated with obesity	Moderate	69, 70, 76, 144, 230, 232-242
AD in children may be associated with metabolic syndrome	Moderate	70, 242
AD in children may *not* be associated with dyslipidemia	Low	69, 70, 76, 230, 236
AD in children is probably *not* associated with diabetes	Moderate	69, 70, 76, 230, 237
Bone Health		
The association between AD in children and fractures is uncertain	Low	70, 82, 243, 244
AD in children may *not* be associated with osteoporosis	Low	69
Skin Infection		
AD in children is associated with bacterial, viral, and fungal skin infections	Moderate	66, 68, 70, 152, 231, 245-254

Allergic conditions

Allergic Conjunctivitis

The association between AD in children and allergic conjunctivitis (AC) is uncertain, due to the absence of consistent evidence, with estimates varying widely across the available studies (**Supplemental Table 16**). Pooled prevalence of AC in children with AD over 3 studies (n = 41,169) was 10.2% (0, 22.0),[64-66] and one study found higher adjusted odds of AC in children with AD compared to those without AD (adjusted Odds Ratio[aOR] 1.99 [95% Confidence Interval[CI] 1.59, 2.49]).[66]

Allergic Rhinitis

Allergic rhinitis is a recognized common comorbidity of AD, and our systematic review found moderate certainty evidence that AD in children is associated with AR (**Supplemental Table 17**). It is important to note that several studies used in the analysis had high risk for bias and relied on unvalidated exposure and/or outcome assessments. In a pooled analysis of 5 studies,[67, 69, 70, 72, 75] children with AD, compared to those without AD, had a high aOR of AR (3.59 [95%CI: 2.19,

5.88]). Furthermore, the association and prevalence of AR may be higher in children with more severe AD.[68, 90] Additionally, in a pooled analysis of 8 studies,[77, 78, 81, 82, 85-87, 89, 91] children with AD, compared to those without AD, had higher odds of a subsequent diagnosis of AR (aOR 2.20 [95% CI 1.88, 2.59]).

Eosinophilic Esophagitis

The available evidence suggests AD in children is associated with eosinophilic esophagitis (EoE) (**Supplemental Table 18**). Evaluating 6 studies, the pooled prevalence of AD in children with EoE was 21.8% (95% CI 7.8, 35.8).[65, 94-96, 98, 99] A retrospective analysis of health care claims data suggested higher odds of EoE in children with AD compared to those without AD,[70] while two other studies demonstrated an increased risk of EoE in children with AD.[85, 97]

Food Allergies

Most studies in our systematic review used strict definitions of IgE-mediated food allergies (FA) (including symptoms plus evidence of allergic sensitization and/or oral food challenge) to distinguish food allergy from allergic sensitization to food. With moderate certainty, we concluded that AD in children is associated with FA (**Supplemental Table 19**). Including 18 studies (n = 682,736), of both caregiver-reported and clinically-confirmed FA, the pooled prevalence of FA in children with AD is 23.6% (95% CI 21.7, 25.4).[65, 80, 83, 88, 104, 110, 113, 116, 118-120, 122, 125-127, 129, 131, 132] Furthermore, five studies described increasing FA prevalence with increasing AD severity,[80, 88, 120, 127, 136] while two did not.[126, 129] Examining the association between FA and AD demonstrated similar findings – the pooled analysis of six studies found children with AD, compared to those without AD, had higher adjusted odds of FA (aOR 6.53 [95% CI 3.89,

299 10.96])[70, 100, 101, 105, 110, 113] , and Mailhol et al. found an association with FA and AD severity in a
300 cohort of 386 children with AD.[104] The association with AD in children and specific FA (i.e.,
301 eggs, peanut, cow's milk) is less clear with limited data. Moreover, while studies are limited,
302 children with AD may have higher odds of subsequent diagnosis of FA. While there are many
303 studies examining the link between AD in children and FA, several relied on unvalidated and/or
304 self-reported exposure and/or outcome assessments so are of a high risk of bias.
305
306 *Asthma*
307 Atopic dermatitis in children is associated with asthma. (**Supplemental Table 20**). In the pooled
308 adjusted analysis of nine studies, children with AD had higher odds of asthma [aOR 3.03 (95%
309 CI 2.30, 4.01)];[69, 70, 73, 75, 141, 142, 146, 151, 152]. The pooled unadjusted analysis of 5 additional studies
310 demonstrated similar results.[76, 90, 148, 149, 153] Several studies demonstrate children with a prior
311 diagnosis of AD have higher odds and higher risk of a subsequent diagnosis of asthma.[67, 78, 82, 85,
312 87, 89, 91, 156, 159, 163, 164, 170, 173]
313 The pooled prevalence of asthma in children with AD (n = 955, 098) is 21.4% (95% CI 19.6,
314 23.1).[65, 69, 75, 76, 78, 80, 82-85, 88, 90, 91, 117, 119, 125, 132, 146, 148, 149, 151, 153, 155, 157, 160-162, 166-169, 171, 172] There is
315 evidence that asthma prevalence increases by AD severity. Gerner et al. reported increasing
316 asthma prevalence in children with clear/almost clear, mild, moderate and severe AD: 22.9%,
317 26.5%, 35.7%, and 35.7%, respectively.[68] Prevalence estimates varied widely across studies, in
318 part related to variability by geography.
319
320 **Immune-mediated Conditions**
321 *Alopecia areata*

Evidence of the association between AD in children and AA is of low certainty (**Supplemental Table 21**). In the pooled analysis of two studies, children with AD, compared to those without, have higher unadjusted odds of AA (OR 3.17 [95% CI 1.71, 5.86]).[70, 76] There are few studies examining this association, which generally rely on unvalidated or self-reported exposure and outcome assessments, with high risk of bias.

Urticaria

AD in children is associated with urticaria (**Supplemental Table 22**). The pooled prevalence of urticaria in children with AD (n =54,360) is 9.5% (95% CI 7.2, 11.8),[66, 68, 75, 76, 80, 182] and a pooled analysis of three studies suggests higher adjusted odds of urticaria in children with AD compared to those without [aOR 2.98 (95% CI 2.84, 3.14)].[66, 70, 75] Furthermore, a pooled analysis of two studies suggests an increased risk of subsequent urticaria in children with AD [adjusted Hazard Ratio[aHR] of 1.76 (95% CI 1.42, 2.18)];[82, 85] Kitsioulis et al. also found higher odds of subsequent AD in children with chronic urticaria, suggesting the relationship may be bidirectional.[186]

Attention Deficit Hyperactivity Disorder and Autism Spectrum Disorders

Attention deficit hyperactivity disorder

The pooled prevalence of ADHD in children with AD (n = 158,832) is 8.2% (95% CI 6.4, 10.0),[64, 65, 69, 83, 209-211, 214-216, 219, 224] but prevalence rates varied widely across studies ranging from 1.2% to 23.7%; this may be secondary to various measures used to assess outcomes across studies (**Supplemental Table 23**). The pooled analysis of nine studies examining the association between ADHD and AD demonstrated children with AD, compared to those without AD, have

higher odds of ADHD (aOR 1.43 [95% CI 1.26, 1.63]).[69, 70, 188, 190, 209-212, 214] Studies examining the occurrence of ADHD in early onset AD (under 4 years of age) and AD in general were mixed – some suggest an association with early onset AD and AD in general[218, 220-223] while others do not,[82, 90, 217, 219] and some suggest a greater association with more severe AD cases,[192] while others do not.[90]

Autism spectrum disorder

The association between AD in children and autism spectrum disorder (ASD) is uncertain (**Supplemental Table 24**). This was due to low certainty of evidence and conflicting results across studies, as well as a small magnitude of association. In a pooled analysis of four studies, children with AD, compared to those without AD, had higher odds of ASD (aOR 2.12[95%CI 1.35, 3.33]).[188, 190, 210, 211] Conversely, a pooled analysis of two studies found ASD in children was not associated with AD (aOR 1.27 [95%CI 0.90, 1.79]).[208, 227] Prevalence rates of ASD in children with AD varied widely across studies, and rates were both lower and greater than expected rates.[64, 83, 190, 211, 226, 227, 229] Additionally, Wan et al. did not find severity of AD to be associated with increased risk of subsequent ASD diagnosis.[90]

Mental health and substance use

Substance use

While it is important for all providers to look for signs of substance use in their pediatric patients, AD in children is probably not associated with drinking alcohol, cigarette smoking, or illicit drug use based on available data (**Supplemental Tables 25-27**).[69, 199-202, 204-206]

Nonetheless, age is an important consideration as adolescents with AD may be more likely to engage in substance use than younger children.

Mental health

Although AD in children is probably associated with anxiety, the association between pediatric AD and depression is uncertain (**Supplemental Tables 28-29**). In the pooled analysis of four studies, children with AD, compared to those without, have increased odds of anxiety [aOR 1.33 (95% CI 1.14, 1.57)],[69, 70, 189, 190] and a study by Yaghmaie et al. found increasing odds of anxiety with increasing AD severity as reported by caregivers [mild AD aOR 1.44 (95% CI 1.01, 2.05), moderate AD aOR 2.18 (95% CI 1.47, 3.23), severe AD aOR 2.81 (95% CI 1.28, 6.17)].[190] Alternatively, the pooled analysis of two studies suggests no association between AD and a diagnosis of depression [aOR 1.45 (95% CI 0.77, 2.73)].[69, 190] However, Yaghmaie et al. suggested the frequency of depression in children with AD increased with increasing AD severity as reported by caregivers (mild AD 5.4%, moderate AD 7.2%, severe AD 14.1%), and increasing self-reported AD severity may be associated with increased odds of depression.[190]

Atopic dermatitis in children is probably not associated with suicide, though the data are limited and mixed. Some studies suggest suicide and suicidal ideation/attempts are not associated with AD,[90] while the pooled analysis of two studies suggests children with AD, compared to those without AD, have higher adjusted odds of suicidal ideation [aOR 1.15 (95% CI 1.02, 1.30)] (**Supplemental Table 30**).[197, 198] As with substance abuse above, age is an important consideration as adolescent patients may be more likely to present with anxiety, depression and suicidal ideation than their younger counterparts.

Metabolic disorders

Obesity

AD in children is probably associated with obesity with the pooled analysis of nine studies demonstrating children with AD had higher adjusted odds of obesity than did controls without AD [aOR 1.35 (95% CI 1.15, 1.58)] (**Supplemental Table 31**). [69, 70, 144, 230, 232, 234, 236, 238, 242] The pooled unadjusted analysis of five studies also suggests higher odds of obesity in children with AD.[76, 233, 238-240] One study suggests the odds of obesity are higher in children with moderate-to-severe AD compared to children with mild AD [aOR 2.59 (95% CI 1.64, 4.10)].[238]

Dyslipidemia

Atopic dermatitis in children may not be associated with dyslipidemia based on available evidence (**Supplemental Table 32**). A study of 30,354 patients reports the prevalence of hyperlipidemia in children with AD is 0.71%.[76] Two studies suggest dyslipidemia is not associated with AD in children: one study found hypercholesterolemia is not associated with AD, while two other studies suggested increased odds of hyperlipidemia in children with AD.[69, 70, 76, 236]

Diabetes and metabolic syndrome

There are few studies examining the association between AD in children and diabetes. The available data are limited and mixed, suggesting AD in children is probably not associated with diabetes (**Supplemental Table 33**). Included studies varied in assessment and definition of diabetes and most do not distinguish between type 1 and type 2 diabetes. A retrospective analysis of 86,969 pediatric patients with AD and 116,564 matched controls, demonstrated the odds of

metabolic syndrome may be increased in children with AD [aOR 1.61 (95% CI 1.28, 2.01)] (**Supplemental Table 34**). An additional body of literature suggests an inverse association between AD and type I diabetes.[255-258]

Cardiovascular disease

AD in children may be associated with hypertension (small magnitude), though the evidence is limited (**Supplemental Table 35**). This association may be multifactorial and influenced by lifestyle factors (e.g. obesity, diet, physical activity). In the pooled analysis of three studies, children with AD, compared to those without AD, had higher adjusted odds of hypertension (aOR 1.20 [95% CI 1.03, 1.39]),[69, 70, 230] but an unadjusted analysis reported no association.[76] The association between AD in children and ischemic heart disease is uncertain – an adjusted analysis reported no association between AD and ischemic heart disease,[69] but an unadjusted analysis reported higher odds of ischemic heart disease in children with AD.[76] Additionally, our analysis showed no association between AD and peripheral vascular disease, cardiac arrhythmia, and congestive heart failure.

Fractures and Osteoporosis

One study found no association between pathologic fracture and AD,[70] while another suggested AD is associated with a small increase in the risk of any bone fracture [adjusted Risk Ratio (RR) 1.08 (95% CI 1.05, 1.10)(**Supplemental Tables 36-37**).[243] Similarly, a pooled estimate from two studies suggests a small increase in the subsequent risk of fracture in children with AD compared to those without AD; furthermore, the risk of fracture increased with increasing AD severity [mild AD: aHR 1.12 (95% CI 1.11, 1.14) versus moderate-to-severe: aHR 1.23 (95% CI 1.20,

1.26)].[82, 244] Only one study met inclusion criteria regarding osteoporosis, with wide confidence intervals precluding conclusions about an association with AD [aOR 2.15 (95% CI 0.78, 5.92)].

Skin infections

It is well known that AD predisposes to skin infections (**Supplemental Tables 38-41**). Ren and Silverberg reported higher odds of skin infections in children with AD compared to those without AD [aOR 2.23 (95% CI 2.16, 2.31) p<0.0001] and Narla and Silverberg, using multivariable models to control for age, race, sex and insurance status, reported AD was associated with cutaneous infections.[245, 246] This association between pediatric AD and skin infection includes: 1) bacterial infections (bacterial impetigo,[66, 70, 250] bacterial cellulitis,[70] and *S. aureus* skin infection[249]), 2) viral infections (molluscum contagiosum infections,[66, 70, 250] warts,[66, 70, 152, 250] coxsackie viral infection,[70] and herpes simplex infection[250]), and 3) fungal infections.[66, 70, 250]

Gaps in Research

While genetic factors may predispose a child to AD, early exposures and environmental factors likely contribute to pathogenesis. More studies on AD prevention will be useful – the ability to reduce the incidence of AD would be very impactful; we know that the disease is difficult to manage for patients and their caregivers and can affect their ability to perform well in school and adapt socially.

Larger studies examining associations, particularly as they relate to the severity of AD and more data about the association of AD with mental disorders, autism, and ADHD could help providers target these patients earlier and make appropriate referrals. Additionally, these guidelines do not make recommendations for screening or management of comorbidities in children with AD.

Rather, the evidence for the association between pediatric AD and comorbid conditions, including allergic conditions, alopecia areata (AA), attention deficit and hyperactivity disorder (ADHD), cardiovascular disease, and fractures among others, was evaluated with the aim of improving awareness and understanding among dermatologists and other clinicians.

Conclusions

These guidelines provide evidence-based recommendations for the primary prevention of AD in favor of regular use of moisturizer and to date insufficient evidence or no benefit to environmental or dietary interventions. There are also associations between pediatric AD and other atopic and allergic conditions, immune mediated conditions such as urticaria, anxiety, ADH, skin infection, and some metabolic disorders.

References

1. Laughter MR, Maymone MBC, Mashayekhi S, Arents BWM, Karimkhani C, Langan SM et al. The global burden of atopic dermatitis: lessons from the Global Burden of Disease Study 1990–2017. British Journal of Dermatology 2021;184:304-9.
2. Odhiambo JA, Williams HC, Clayton TO, Robertson CF , Asher MI. Global variations in prevalence of eczema symptoms in children from ISAAC Phase Three. J Allergy Clin Immunol 2009;124:1251-8.e23.
3. Deckers IA, McLean S, Linssen S, Mommers M, van Schayck CP , Sheikh A. Investigating international time trends in the incidence and prevalence of atopic eczema 1990-2010: a systematic review of epidemiological studies. PLoS One 2012;7:e39803.
4. Choragudi S , Yosipovitch G. Trends in the Prevalence of Eczema Among US Children by Age, Sex, Race, and Ethnicity From 1997 to 2018. JAMA Dermatol 2023;159:454-6.
5. Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol 2011;64:401-6.
6. Foroutan F, Guyatt G, Zuk V, Vandvik PO, Alba AC, Mustafa R et al. GRADE Guidelines 28: Use of GRADE for the assessment of evidence about prognostic factors: rating certainty in identification of groups of patients with different absolute risks. J Clin Epidemiol 2020;121:62-70.
7. Andrews J, Guyatt G, Oxman AD, Alderson P, Dahm P, Falck-Ytter Y et al. GRADE guidelines: 14. Going from evidence to recommendations: the significance and presentation of recommendations. J Clin Epidemiol 2013;66:719-25.
8. Andrews JC, Schunemann HJ, Oxman AD, Pottie K, Meerpohl JJ, Coello PA et al. GRADE guidelines: 15. Going from evidence to recommendation-determinants of a recommendation's direction and strength. J Clin Epidemiol 2013;66:726-35.
9. Guyatt GH, Alonso-Coello P, Schunemann HJ, Djulbegovic B, Nothacker M, Lange S et al. Guideline panels should seldom make good practice statements: guidance from the GRADE Working Group. J Clin Epidemiol 2016;80:3-7.
10. Chalmers JR, Haines RH, Bradshaw LE, Montgomery AA, Thomas KS, Brown SJ et al. A randomised controlled trial of daily emollient during infancy for preventing eczema-results of the beep trial. Acta dermato-venereologica 2021;101:7-8.
11. Chaoimh CN, Lad D, Nico C, Puppels GJ, Wong X, Murray DM et al. Early initiation of short-term emollient use for the prevention of atopic dermatitis in high-risk infants—The STOP-AD randomised controlled trial. Allergy 2022.
12. Horimukai K, Morita K, Narita M, Kondo M, Kitazawa H, Nozaki M et al. Application of moisturizer to neonates prevents development of atopic dermatitis. J Allergy Clin Immunol 2014;134:824-30.e6.
13. Dissanayake E, Tani Y, Nagai K, Sahara M, Mitsuishi C, Togawa Y et al. Skin Care and Synbiotics for Prevention of Atopic Dermatitis or Food Allergy in Newborn Infants: A 2 × 2 Factorial, Randomized, Non-Treatment Controlled Trial. Int Arch Allergy Immunol 2019;180:202-11.
14. Harder I, Stölzl D, Sander N, Hartmann J, Rodriguez E, Mazur C et al. Effects of Early Emollient Use in Children at High Risk of Atopic Dermatitis: A German Pilot Study. Acta dermato-venereologica 2023;103:adv5671.

15. Kottner J, Hillmann K, Fastner A, Conzade R, Heidingsfelder S, Neumann K , Blume-Peytavi U. Effectiveness of a standardized skin care regimen to prevent atopic dermatitis in infants at risk for atopy: a randomized, pragmatic, parallel-group study. J Eur Acad Dermatol Venereol 2022.
16. Lowe AJ, Su JC, Allen KJ, Abramson MJ, Cranswick N, Robertson CF et al. A randomized trial of a barrier lipid replacement strategy for the prevention of atopic dermatitis and allergic sensitization: the PEBBLES pilot study. Br J Dermatol 2018;178:e19-e21.
17. McClanahan D, Wong A, Kezic S, Samrao A, Hajar T, Hill E , Simpson EL. A randomized controlled trial of an emollient with ceramide and filaggrin-associated amino acids for the primary prevention of atopic dermatitis in high-risk infants. J Eur Acad Dermatol Venereol 2019;33:2087-94.
18. Ng PSM, Wee LWY, Ho VPY, Tan WC, Bishnoi P, Alagappan U et al. Moisturisers from birth in at-risk infants of atopic dermatitis - a pragmatic randomised controlled trial. Australas J Dermatol 2021;62:e539-e45.
19. Simpson EL, Chalmers JR, Hanifin JM, Thomas KS, Cork MJ, McLean WH et al. Emollient enhancement of the skin barrier from birth offers effective atopic dermatitis prevention. J Allergy Clin Immunol 2014;134:818-23.
20. Skjerven HO, Rehbinder EM, Vettukattil R, LeBlanc M, Granum B, Haugen G et al. Skin emollient and early complementary feeding to prevent infant atopic dermatitis (PreventADALL): a factorial, multicentre, cluster-randomised trial. Lancet 2020;395:951-61.
21. Techasatian L , Kiatchoosakun P. Effects of an emollient application on newborn skin from birth for prevention of atopic dermatitis: a randomized controlled study in Thai neonates. J Eur Acad Dermatol Venereol 2022;36:76-83.
22. Thitthiwong P. The Good Skin Care Practices and Emollient Use since Early Infancy as the Primary Prevention of Infantile Atopic Dermatitis among Infants at Risk: a Randomized Controlled Trial. Siriraj Medical Journal 2020;72:41-6.
23. Simpson EL, Michaels LC, Ramsey K, Fagnan LJ, Nease DE, Henningfield M et al. Emollients to Prevent Pediatric Eczema: A Randomized Clinical Trial. JAMA Dermatol 2025.
24. Horak F, Jr., Matthews S, Ihorst G, Arshad SH, Frischer T, Kuehr J et al. Effect of mite-impermeable mattress encasings and an educational package on the development of allergies in a multinational randomized, controlled birth-cohort study -- 24 months results of the Study of Prevention of Allergy in Children in Europe. Clin Exp Allergy 2004;34:1220-5.
25. Mihrshahi S, Peat JK, Marks GB, Mellis CM, Tovey ER, Webb K et al. Eighteen-month outcomes of house dust mite avoidance and dietary fatty acid modification in the Childhood Asthma Prevention Study (CAPS). Journal of Allergy and Clinical Immunology 2003;111:162-8.
26. Jabbar-Lopez ZK, Ezzamouri B, Briley A, Greenblatt D, Gurung N, Chalmers JR et al. Randomized controlled pilot trial with ion-exchange water softeners to prevent eczema (SOFTER trial). Clin Exp Allergy 2022;52:405-15.
27. Palmer DJ, Sullivan TR, Gold MS, Prescott SL , Makrides M. Randomized controlled trial of early regular egg intake to prevent egg allergy. J Allergy Clin Immunol 2017;139:1600-7.e2.

28. Güngör D, Nadaud P, LaPergola CC, Dreibelbis C, Wong YP, Terry N et al. Infant milk-feeding practices and food allergies, allergic rhinitis, atopic dermatitis, and asthma throughout the life span: a systematic review. The American Journal of Clinical Nutrition 2019;109:772S-99S.
29. Berni Canani R, Di Costanzo M, Bedogni G, Amoroso A, Cosenza L, Di Scala C et al. Extensively hydrolyzed casein formula containing Lactobacillus rhamnosus GG reduces the occurrence of other allergic manifestations in children with cow's milk allergy: 3-year randomized controlled trial. J Allergy Clin Immunol 2017;139:1906-13.e4.
30. Cabana MD, McKean M, Caughey AB, Fong L, Lynch S, Wong A et al. Early Probiotic Supplementation for Eczema and Asthma Prevention: a Randomized Controlled Trial. Pediatrics 2017;140.
31. He JH, Zhao XG, Sun F, Peng WQ, Li HY , Li H. Clinical study on prevention of atopic dermatitis by oral administration of probiotics in infants. Arch Med Sci 2023;19:101-6.
32. Lau S, Gerhold K, Zimmermann K, Ockeloen CW, Rossberg S, Wagner P et al. Oral application of bacterial lysate in infancy decreases the risk of atopic dermatitis in children with 1 atopic parent in a randomized, placebo-controlled trial. J Allergy Clin Immunol 2012;129:1040-7.
33. Prescott SL, Wiltschut J, Taylor A, Westcott L, Jung W, Currie H , Dunstan JA. Early markers of allergic disease in a primary prevention study using probiotics: 2.5-year follow-up phase. Allergy 2008;63:1481-90.
34. Rautava S, Arvilommi H , Isolauri E. Specific probiotics in enhancing maturation of IgA responses in formula-fed infants. Pediatr Res 2006;60:221-4.
35. Soh SE, Aw M, Gerez I, Chong YS, Rauff M, Ng YP et al. Probiotic supplementation in the first 6 months of life in at risk Asian infants--effects on eczema and atopic sensitization at the age of 1 year. Clin Exp Allergy 2009;39:571-8.
36. West CE, Hammarström ML , Hernell O. Probiotics during weaning reduce the incidence of eczema. Pediatr Allergy Immunol 2009;20:430-7.
37. Bellomo AR, Rotondi G, Rago P, Bloise S, Di Ruzza L, Zingoni A et al. Effect of Bifidobacterium bifidum Supplementation in Newborns Born from Cesarean Section on Atopy, Respiratory Tract Infections, and Dyspeptic Syndromes: A Multicenter, Randomized, and Controlled Clinical Trial. Microorganisms 2024;12.
38. Rueter K, Jones AP, Siafarikas A, Lim EM, Bear N, Noakes PS et al. Direct infant UV light exposure is associated with eczema and immune development. J Allergy Clin Immunol 2019;143:1012-20.e2.
39. Arslanoglu S, Moro GE, Schmitt J, Tandoi L, Rizzardi S , Boehm G. Early dietary intervention with a mixture of prebiotic oligosaccharides reduces the incidence of allergic manifestations and infections during the first two years of life. J Nutr 2008;138:1091-5.
40. Boyle RJ, Tang ML, Chiang WC, Chua MC, Ismail I, Nauta A et al. Prebiotic-supplemented partially hydrolysed cow's milk formula for the prevention of eczema in high-risk infants: a randomized controlled trial. Allergy 2016;71:701-10.
41. Grüber C, van Stuijvenberg M, Mosca F, Moro G, Chirico G, Braegger CP et al. Reduced occurrence of early atopic dermatitis because of immunoactive prebiotics among low-atopy-risk infants. J Allergy Clin Immunol 2010;126:791-7.

42. Ranucci G, Buccigrossi V, Borgia E, Piacentini D, Visentin F, Cantarutti L et al. Galacto-Oligosaccharide/Polidextrose Enriched Formula Protects against Respiratory Infections in Infants at High Risk of Atopy: A Randomized Clinical Trial. Nutrients 2018;10.
43. Rozé JC, Barbarot S, Butel MJ, Kapel N, Waligora-Dupriet AJ, De Montgolfier I et al. An α-lactalbumin-enriched and symbiotic-supplemented v. a standard infant formula: a multicentre, double-blind, randomised trial. Br J Nutr 2012;107:1616-22.
44. Zhou SJ, Sullivan T, Gibson RA, Lönnerdal B, Prosser CG, Lowry DJ , Makrides M. Nutritional adequacy of goat milk infant formulas for term infants: a double-blind randomised controlled trial. Br J Nutr 2014;111:1641-51.
45. Xu M, Wang Y, Dai Z, Zhang Y, Li Y , Wang J. Comparison of growth and nutritional status in infants receiving goat milk-based formula and cow milk-based formula: a randomized, double-blind study. Food & nutrition research 2015;59.
46. Birch EE, Khoury JC, Berseth CL, Castañeda YS, Couch JM, Bean J et al. The impact of early nutrition on incidence of allergic manifestations and common respiratory illnesses in children. J Pediatr 2010;156:902-6.e1.
47. Lucas A, Stafford M, Morley R, Abbott R, Stephenson T, MacFadyen U et al. Efficacy and safety of long-chain polyunsaturated fatty acid supplementation of infant-formula milk: a randomised trial. The Lancet 1999;354:1948-54.
48. van Gool CJ, Thijs C, Henquet CJ, van Houwelingen AC, Dagnelie PC, Schrander J et al. Gamma-linolenic acid supplementation for prophylaxis of atopic dermatitis--a randomized controlled trial in infants at high familial risk. Am J Clin Nutr 2003;77:943-51.
49. Li F, Wu SS, Berseth CL, Harris CL, Richards JD, Wampler JL et al. Improved Neurodevelopmental Outcomes Associated with Bovine Milk Fat Globule Membrane and Lactoferrin in Infant Formula: A Randomized, Controlled Trial. J Pediatr 2019;215:24-31 e8.
50. Chan YH, Shek LP, Aw M, Quak SH , Lee BW. Use of hypoallergenic formula in the prevention of atopic disease among Asian children. J Paediatr Child Health 2002;38:84-8.
51. Chandra RK , Hamed A. Cumulative incidence of atopic disorders in high risk infants fed whey hydrolysate, soy, and conventional cow milk formulas. Ann Allergy 1991;67:129-32.
52. Chirico G, Gasparoni A, Ciardelli L, De Amici M, Colombo A , Rondini G. Immunogenicity and antigenicity of a partially hydrolyzed cow's milk infant formula. Allergy 1997;52:82-8.
53. Juvonen P, Månsson M, Andersson C , Jakobsson I. Allergy development and macromolecular absorption in infants with different feeding regimens during the first three days of life. A three-year prospective follow-up. Acta paediatrica 1996;85:1047-52.
54. Lowe AJ, Hosking CS, Bennett CM, Allen KJ, Axelrad C, Carlin JB et al. Effect of a partially hydrolyzed whey infant formula at weaning on risk of allergic disease in high-risk children: a randomized controlled trial. J Allergy Clin Immunol 2011;128:360-5.e4.
55. Mallet E , Henocq A. Long-term prevention of allergic diseases by using protein hydrolysate formula in at-risk infants. J Pediatr 1992;121:S95-100.
56. Nicolaou N, Pancheva R, Karaglani E, Sekkidou M, Marinova-Achkar M, Popova S et al. The Risk Reduction Effect of a Nutritional Intervention With a Partially Hydrolyzed Whey-Based Formula on Cow's Milk Protein Allergy and Atopic Dermatitis in High-Risk Infants Within the First 6 Months of Life: The Allergy Reduction Trial (A.R.T.), a Multicenter Double-Blinded Randomized Controlled Study. Front Nutr 2022;9:863599.

57. Vandenplas Y, Hauser B, Van den Borre C, Clybouw C, Mahler T, Hachimi-Idrissi S et al. The long-term effect of a partial whey hydrolysate formula on the prophylaxis of atopic disease. Eur J Pediatr 1995;154:488-94.
58. von Berg A, Koletzko S, Grübl A, Filipiak-Pittroff B, Wichmann HE, Bauer CP et al. The effect of hydrolyzed cow's milk formula for allergy prevention in the first year of life: the German Infant Nutritional Intervention Study, a randomized double-blind trial. J Allergy Clin Immunol 2003;111:533-40.
59. Abrams EM, Shaker M, Stukus D, Mack DP , Greenhawt M. Updates in Food Allergy Prevention in Children. Pediatrics 2023;152.
60. Perkin MR, Logan K, Tseng A, Raji B, Ayis S, Peacock J et al. Randomized Trial of Introduction of Allergenic Foods in Breast-Fed Infants. N Engl J Med 2016;374:1733-43.
61. Mihrshahi S, Peat JK, Marks GB, Mellis CM, Tovey ER, Webb K et al. Eighteen-month outcomes of house dust mite avoidance and dietary fatty acid modification in the Childhood Asthma Prevention Study (CAPS). J Allergy Clin Immunol 2003;111:162-8.
62. Drucker AM, Wang AR, Li WQ, Sevetson E, Block JK , Qureshi AA. The Burden of Atopic Dermatitis: Summary of a Report for the National Eczema Association. J Invest Dermatol 2017;137:26-30.
63. Silverberg JI, Garg NK, Paller AS, Fishbein AB , Zee PC. Sleep disturbances in adults with eczema are associated with impaired overall health: a US population-based study. J Invest Dermatol 2015;135:56-66.
64. Ahn H-J, Shin MK, Seo J-K, Jeong SJ, Cho AR, Choi S-H , Lew B-L. Cross-sectional study of psychiatric comorbidities in patients with atopic dermatitis and nonatopic eczema, urticaria, and psoriasis. Neuropsychiatr Dis Treat 2019;15:1469-78.
65. Paller AS, Guttman-Yassky E, Schuttelaar MLA, Irvine AD, Baselga E, Kataoka Y et al. Disease characteristics, comorbidities, treatment patterns and quality of life impact in children <12 years old with atopic dermatitis: Interim results from the PEDISTAD Real-World Registry. J Am Acad Dermatol 2022;87:1104-8.
66. Pols DHJ, Bohnen AM, Nielen MMJ, Korevaar JC , Bindels PJE. Risks for comorbidity in children with atopic disorders: an observational study in Dutch general practices. BMJ Open 2017;7:e018091.
67. Chiu CY, Yang CH, Su KW, Tsai MH, Hua MC, Liao SL et al. Early-onset eczema is associated with increased milk sensitization and risk of rhinitis and asthma in early childhood. J Microbiol Immunol Infect 2020;53:1008-13.
68. Gerner T, Haugaard JH, Vestergaard C, Deleuran M, Jemec GB, Mortz CG et al. Disease severity and trigger factors in Danish children with atopic dermatitis: a nationwide study. J Eur Acad Dermatol Venereol 2021;35:948-57.
69. Gilaberte Y, Pérez-Gilaberte JB, Poblador-Plou B, Bliek-Bueno K, Gimeno-Miguel A , Prados-Torres A. Prevalence and Comorbidity of Atopic Dermatitis in Children: A Large-Scale Population Study Based on Real-World Data. J Clin Med 2020;9.
70. Huang AH, Roh YS, Sutaria N, Choi J, Williams KA, Canner JK et al. Real-world comorbidities of atopic dermatitis in the pediatric ambulatory population in the United States. J Am Acad Dermatol 2021;85:893-900.

71. Ibáñez MD, Valero AL, Montoro J, Jauregui I, Ferrer M, Dávila I et al. Analysis of comorbidities and therapeutic approach for allergic rhinitis in a pediatric population in Spain. Pediatr Allergy Immunol 2013;24:678-84.
72. Kelbore AG, Alemu W, Shumye A , Getachew S. Magnitude and associated factors of Atopic dermatitis among children in Ayder referral hospital, Mekelle, Ethiopia. BMC Dermatol 2015;15:15.
73. Shreberk-Hassidim R, Hassidim A, Gronovich Y, Dalal A, Molho-Pessach V , Zlotogorski A. Atopic Dermatitis in Israeli Adolescents from 1998 to 2013: Trends in Time and Association with Migraine. Pediatr Dermatol 2017;34:247-52.
74. Sultesz M, Horvath A, Molnar D, Katona G, Mezei G, Hirschberg A , Galffy G. Prevalence of allergic rhinitis, related comorbidities and risk factors in schoolchildren. Allergy, Asthma and Clinical Immunology 2020;16.
75. Werner-Busse A, Kostev K, Heine G , Worm M. Impact of comorbidities on the treatment of atopic dermatitis in clinical practice. Int J Clin Pharmacol Ther 2014;52:726-31.
76. Augustin M, Radtke MA, Glaeske G, Reich K, Christophers E, Schaefer I , Jacobi A. Epidemiology and Comorbidity in Children with Psoriasis and Atopic Eczema. Dermatology 2015;231:35-40.
77. Ballardini N, Bergström A, Böhme M, van Hage M, Hallner E, Johansson E et al. Infantile eczema: Prognosis and risk of asthma and rhinitis in preadolescence. J Allergy Clin Immunol 2014;133:594-6.
78. Goksör E, Loid P, Alm B, Åberg N , Wennergren G. The allergic march comprises the coexistence of related patterns of allergic disease not just the progressive development of one disease. Acta Paediatr 2016;105:1472-9.
79. Izquierdo-Dominguez A, Jauregui I, Del Cuvillo A, Montoro J, Davila I, Sastre J et al. Allergy rhinitis: similarities and differences between children and adults. Rhinology 2017;55:326-31.
80. Jeon YH, Ahn K, Kim J, Shin M, Hong SJ, Lee SY et al. Clinical Characteristics of Atopic Dermatitis in Korean School-Aged Children and Adolescents According to Onset Age and Severity. J Korean Med Sci 2022;37:e30.
81. Kang X, Tu H, Tian T, Huang Z, Luo L, Shen L , Ye J. Home environment and diseases in early life are associated with allergic rhinitis. Int J Pediatr Otorhinolaryngol 2019;118:47-52.
82. Kim JH, Lee E, Ha EK, Shin J, Lee GC, Rha YH , Han MY. Cascade of atopic dermatitis comorbidities in children after birth for 15 years. Allergy 2024;79:153-63.
83. Mora T, Sánchez-Collado I, Mullol J, Muñoz-Cano R, Ribó P , Valero A. Prevalence of atopic dermatitis in the adolescent population of Catalonia (Spain). Allergol Immunopathol (Madr) 2023;51:101-9.
84. Nakamura T, Haider S, Fontanella S, Murray CS, Simpson A , Custovic A. Modelling trajectories of parentally reported and physician-confirmed atopic dermatitis in a birth cohort study. Br J Dermatol 2022;186:274-84.
85. Paller AS, Mina-Osorio P, Vekeman F, Boklage S, Mallya UG, Ganguli S et al. Prevalence of type 2 inflammatory diseases in pediatric patients with atopic dermatitis: Real-world evidence. J Am Acad Dermatol 2022;86:758-65.
86. Schoos AM, Chawes BL, Bønnelykke K, Stokholm J, Rasmussen MA , Bisgaard H. Increasing severity of early-onset atopic dermatitis, but not late-onset, associates with

development of aeroallergen sensitization and allergic rhinitis in childhood. Allergy 2022;77:1254-62.
87. Shen CY, Lin MC, Lin HK, Lin CH, Fu LS , Fu YC. The natural course of eczema from birth to age 7 years and the association with asthma and allergic rhinitis: a population-based birth cohort study. Allergy Asthma Proc 2013;34:78-83.
88. Somanunt S, Chinratanapisit S, Pacharn P, Visitsunthorn N , Jirapongsananuruk O. The natural history of atopic dermatitis and its association with Atopic March. Asian Pac J Allergy Immunol 2017;35:137-43.
89. Tran MM, Lefebvre DL, Dharma C, Dai D, Lou WYW, Subbarao P et al. Predicting the atopic march: Results from the Canadian Healthy Infant Longitudinal Development Study. J Allergy Clin Immunol 2018;141:601-7.e8.
90. Wan J, Shin DB, Syed MN, Abuabara K, Lemeshow AR , Gelfand JM. Atopic dermatitis and risk of major neuropsychiatric disorders in children: A population-based cohort study. J Eur Acad Dermatol Venereol 2022.
91. Wang LC , Chiang BL. Early-onset-early-resolving atopic dermatitis does not increase the risk of development of allergic diseases at 3 Years old. J Formos Med Assoc 2020;119:1854-61.
92. Choi UE, Deng J, Parthasarathy V, Liao V, D'Amiano A, Taylor M et al. Risk factors and temporal associations of progression of the atopic march in children with early-onset atopic dermatitis. J Am Acad Dermatol 2025;92:732-40.
93. Marques G, Amaral AFS, Passos VL, Weber P, Oliveira PD, Menezes AMB et al. Prevalence of allergic rhinitis, atopic dermatitis, and wheezing at 15 and 22 years of age: the 1993 Pelotas (Brazil) Birth Cohort Study. J Bras Pneumol 2024;50:e20240317.
94. Capucilli P, Cianferoni A, Grundmeier RW , Spergel JM. Comparison of comorbid diagnoses in children with and without eosinophilic esophagitis in a large population. Ann Allergy Asthma Immunol 2018;121:711-6.
95. Chadha SN, Wang L, Correa H, Moulton D , Hummell DS. Pediatric eosinophilic esophagitis: the Vanderbilt experience. Ann Allergy Asthma Immunol 2014;113:445-51.
96. Chehade M, Jones SM, Pesek RD, Burks AW, Vickery BP, Wood RA et al. Phenotypic Characterization of Eosinophilic Esophagitis in a Large Multicenter Patient Population from the Consortium for Food Allergy Research. J Allergy Clin Immunol Pract 2018;6:1534-44.e5.
97. Hill DA, Grundmeier RW, Ramos M , Spergel JM. Eosinophilic Esophagitis Is a Late Manifestation of the Allergic March. J Allergy Clin Immunol Pract 2018;6:1528-33.
98. Vernon N, Shah S, Lehman E , Ghaffari G. Comparison of atopic features between children and adults with eosinophilic esophagitis. Allergy Asthma Proc 2014;35:409-14.
99. Witmer CP, Susi A, Min SB , Nylund CM. Early Infant Risk Factors for Pediatric Eosinophilic Esophagitis. J Pediatr Gastroenterol Nutr 2018;67:610-5.
100. de Jong NW, Elbert NJ, Mensink-Bout SM, van der Valk JPM, Pasmans S, Jaddoe VWV et al. Parental and child factors associated with inhalant and food allergy in a population-based prospective cohort study: the Generation R Study. Eur J Pediatr 2019;178:1507-17.
101. Gaspar-Marques J, Carreiro-Martins P, Papoila AL, Caires I, Pedro C, Araújo-Martins J et al. Food allergy and anaphylaxis in infants and preschool-age children. Clin Pediatr (Phila) 2014;53:652-7.

773 102. Kawada S, Futamura M, Hashimoto H, Ono M, Akita N, Sekimizu M et al. Association
774 between sites and severity of eczema and the onset of cow's milk and egg allergy in
775 children. PLoS One 2020;15:e0240980.
776 103. Keet C, Pistiner M, Plesa M, Szelag D, Shreffler W, Wood R et al. Age and eczema
777 severity, but not family history, are major risk factors for peanut allergy in infancy. J Allergy
778 Clin Immunol 2021;147:984-91.e5.
779 104. Mailhol C, Giordano-Labadie F, Lauwers-Cances V, Ammoury A, Paul C , Rance F.
780 Point prevalence and risk factors for food allergy in a cohort of 386 children with atopic
781 dermatitis attending a multidisciplinary dermatology/paediatric allergy clinic. Eur J
782 Dermatol 2014;24:63-9.
783 105. Martin PE, Eckert JK, Koplin JJ, Lowe AJ, Gurrin LC, Dharmage SC et al. Which infants
784 with eczema are at risk of food allergy? Results from a population-based cohort. Clin Exp
785 Allergy 2015;45:255-64.
786 106. McGowan EC, Bloomberg GR, Gergen PJ, Visness CM, Jaffee KF, Sandel M et al.
787 Influence of early-life exposures on food sensitization and food allergy in an inner-city birth
788 cohort. J Allergy Clin Immunol 2015;135:171-8.
789 107. Miceli Sopo S, Monaco S, Giorgio V, Calvani M, Tripodi S , Onesimo R. Risk of adverse
790 IgE-mediate reaction at the first egg ingestion in children with atopic dermatitis. Results of
791 a case-control study. Allergol Immunopathol (Madr) 2014;42:96-101.
792 108. Samady W, Warren C, Kohli S, Jain R, Bilaver L, Mancini AJ , Gupta R. The prevalence of
793 atopic dermatitis in children with food allergy. Ann Allergy Asthma Immunol 2019;122:656-
794 7.e1.
795 109. Sasaki M, Peters RL, Koplin JJ, Field MJ, McWilliam V, Sawyer SM et al. Risk Factors for
796 Food Allergy in Early Adolescence: The SchoolNuts Study. J Allergy Clin Immunol Pract
797 2018;6:496-505.
798 110. Sasaki M, Yoshida K, Adachi Y, Furukawa M, Itazawa T, Odajima H et al. Environmental
799 factors associated with childhood eczema: Findings from a national web-based survey.
800 Allergol Int 2016;65:420-4.
801 111. Shoda T, Futamura M, Yang L, Yamamoto-Hanada K, Narita M, Saito H , Ohya Y. Timing
802 of eczema onset and risk of food allergy at 3 years of age: A hospital-based prospective
803 birth cohort study. J Dermatol Sci 2016;84:144-8.
804 112. Suaini NHA, Loo EX, Peters RL, Yap GC, Allen KJ, Van Bever H et al. Children of Asian
805 ethnicity in Australia have higher risk of food allergy and early-onset eczema than those in
806 Singapore. Allergy 2021;76:3171-82.
807 113. Bilaver LA, Kanaley MK, Fierstein JL , Gupta RS. Prevalence and Correlates of Food
808 Allergy Among Medicaid-Enrolled United States Children. Acad Pediatr 2021;21:84-92.
809 114. Blaiss MS, Meadows JA, Yu S, Robison DR, Hass SL, Norrett KE et al. Economic burden
810 of peanut allergy in pediatric patients with evidence of reactions to peanuts in the United
811 States. J Manag Care Spec Pharm 2021;27:516-27.
812 115. Akarsu A, Ocak M, Köken G, Şahiner Ü M, Soyer Ö , Şekerel BE. IgE mediated food
813 allergy in Turkey: different spectrum, similar outcome. Turk J Pediatr 2021;63:554-63.
814 116. Akelma Z, Köse S , Özmen S. The risk factors for food allergy in infants with atopic
815 dermatitis. Turk J Pediatr 2023;65:235-44.

117. Al S, Asilsoy S, Atay O, Kangallı O, Atakul G, Tezcan D , Uzuner N. Transepidermal water loss in allergic diseases. Allergy Asthma Proc 2023;44:186-92.
118. Al S, Asilsoy S, Atay Ö, Kangallı Ö , Uzuner N. Does the severity of atopic dermatitis change with allergic sensitization? Is it real or a myth? Allergol Immunopathol (Madr) 2023;51:66-71.
119. Amat F, Saint-Pierre P, Bourrat E, Nemni A, Couderc R, Boutmy-Deslandes E et al. Early-onset atopic dermatitis in children: which are the phenotypes at risk of asthma? Results from the ORCA cohort. PLoS One 2015;10:e0131369.
120. Cansever M , Oruç Ç. What plays a role in the severity of atopic dermatitis in children? Turk J Med Sci 2021;51:2494-501.
121. Chokshi NY, Maskatia Z, Miller S, Guffey D, Minard CG , Davis CM. Risk factors in pediatric shrimp allergy. Allergy Asthma Proc 2015;36:65-71.
122. Chousein A, Duman Senol H, Ece Özdoğru E, Eren Akarcan S , Tuncel T. The clinical and laboratory findings of infants with atopic dermatitis during diagnosis and follow-up. Eur Ann Allergy Clin Immunol 2024;56:71-8.
123. Cousin M, Verdun S, Seynave M, Vilain AC, Lansiaux A, Decoster A , Sauvage C. Phenotypical characterization of peanut allergic children with differences in cross-allergy to tree nuts and other legumes. Pediatr Allergy Immunol 2017;28:245-50.
124. Deschildre A, Elegbédé CF, Just J, Bruyère O, Van der Brempt X, Papadopoulos A et al. Peanut-allergic patients in the MIRABEL survey: characteristics, allergists' dietary advice and lessons from real life. Clin Exp Allergy 2016;46:610-20.
125. Gabryszewski SJ, Dudley J, Shu D, Faerber JA, Grundmeier RW, Fiks AG , Hill DA. Patterns in the Development of Pediatric Allergy. Pediatrics 2023;152.
126. Geat D, Giovannini M, Barlocco G, Pertile R, Pace M, Mori F et al. Assessing patients' characteristics and treatment patterns among children with atopic dermatitis. Ital J Pediatr 2021;47:92.
127. Gray CL, Levin ME, Zar HJ, Potter PC, Khumalo NP, Volkwyn L et al. Food allergy in South African children with atopic dermatitis. Pediatr Allergy Immunol 2014;25:572-9.
128. Kotsapas C, Nicolaou N, Haider S, Kerry G, Turner PJ, Murray CS et al. Early-life predictors and risk factors of peanut allergy, and its association with asthma in later-life: Population-based birth cohort study. Clin Exp Allergy 2022;52:646-57.
129. Li JC, Arkin LM, Makhija MM , Singh AM. Prevalence of food allergy diagnosis in pediatric patients with atopic dermatitis referred to allergy and/or dermatology subspecialty clinics. J Allergy Clin Immunol Pract 2022;10:2469-71.
130. Mahr TA, Lieberman JA, Haselkorn T, Damle V, Ali Y, Chidambaram A et al. Characteristics of Peanut Allergy Diagnosis in a US Health Care Claims Database (2011-2017). J Allergy Clin Immunol Pract 2021;9:1683-94.e5.
131. Mavroudi A, Karagiannidou A, Xinias I, Cassimos D, Karantaglis N, Farmaki E et al. Assessment of IgE-mediated food allergies in children with atopic dermatitis. Allergol Immunopathol (Madr) 2017;45:77-81.
132. Peters RL, Koplin JJ, Gurrin LC, Dharmage SC, Wake M, Ponsonby AL et al. The prevalence of food allergy and other allergic diseases in early childhood in a population-based study: HealthNuts age 4-year follow-up. J Allergy Clin Immunol 2017;140:145-53.e8.

133. Pettersson ME, Koppelman GH, Flokstra-de Blok BMJ, Kollen BJ , Dubois AEJ. Prediction of the severity of allergic reactions to foods. Allergy 2018;73:1532-40.
134. Protudjer JL, Vetander M, Kull I, Hedlin G, van Hage M, Wickman M , Bergström A. Food-Related Symptoms and Food Allergy in Swedish Children from Early Life to Adolescence. PLoS One 2016;11:e0166347.
135. Sicherer SH, Wood RA, Vickery BP, Jones SM, Liu AH, Fleischer DM et al. The natural history of egg allergy in an observational cohort. J Allergy Clin Immunol 2014;133:492-9.
136. Silverberg JI , Simpson EL. Association between severe eczema in children and multiple comorbid conditions and increased healthcare utilization. Pediatr Allergy Immunol 2013;24:476-86.
137. Taylor-Black S , Wang J. The prevalence and characteristics of food allergy in urban minority children. Ann Allergy Asthma Immunol 2012;109:431-7.
138. Ünsal H, Dal ST, Akarsu A, Şahiner Ü M, Soyer Ö , Şekerel BE. Phenotypes of persistent hen`s egg allergy in children and adolescents. Turk J Pediatr 2023;65:3-12.
139. Venkataraman D, Soto-Ramírez N, Kurukulaaratchy RJ, Holloway JW, Karmaus W, Ewart SL et al. Filaggrin loss-of-function mutations are associated with food allergy in childhood and adolescence. J Allergy Clin Immunol 2014;134:876-82.e4.
140. Yamamoto-Hanada K, Suzuki Y, Yang L, Saito-Abe M, Sato M, Mezawa H et al. Persistent eczema leads to both impaired growth and food allergy: JECS birth cohort. PLoS One 2021;16:e0260447.
141. Abuabara K, Ye M, Margolis DJ, McCulloch CE, Mulick AR, Silverwood RJ et al. Patterns of Atopic Eczema Disease Activity From Birth Through Midlife in 2 British Birth Cohorts. JAMA Dermatol 2021;157:1191-9.
142. Barnish MS, Tagiyeva N, Devereux G, Aucott L , Turner S. Diverging prevalences and different risk factors for childhood asthma and eczema: a cross-sectional study. BMJ Open 2015;5:e008446.
143. Beridze V, Bakhtadze T, Beridze S, Phagava K, Chkhaidze I, Brożek GM , Zejda JE. Coexistence of asthmatic and non-respiratory allergic symptoms in children of Batumi Region, Georgia: occurrence and association with known diagnosis of asthma. Cent Eur J Public Health 2021;29:23-7.
144. James S, Pezic A, Ponsonby AL, Lafferty A, Glasgow N, Ciszek K et al. Obesity and asthma at school entry: co-morbidities and temporal trends. J Paediatr Child Health 2013;49:E273-80.
145. Jang Y , Shin A. Sex-Based Differences in Asthma among Preschool and School-Aged Children in Korea. PLoS One 2015;10:e0140057.
146. Kuo CL, Chen TL, Liao CC, Yeh CC, Chou CL, Lee WR et al. Birth month and risk of atopic dermatitis: a nationwide population-based study. Allergy 2016;71:1626-31.
147. Lødrup Carlsen KC, Mowinckel P, Hovland V, Håland G, Riiser A , Carlsen KH. Lung function trajectories from birth through puberty reflect asthma phenotypes with allergic comorbidity. J Allergy Clin Immunol 2014;134:917-23.e7.
148. Misery L, Ansolabehere X, Grandfils N, Georgescu V , Taieb C. Nine-year follow-up of children with atopic dermatitis by general practitioners. Dermatology 2014;228:344-9.

149. Mortz CG, Andersen KE, Dellgren C, Barington T , Bindslev-Jensen C. Atopic dermatitis from adolescence to adulthood in the TOACS cohort: prevalence, persistence and comorbidities. Allergy 2015;70:836-45.
150. Nordlund B, Melén E, Schultz ES, Grönlund H, Hedlin G , Kull I. Risk factors and markers of asthma control differ between asthma subtypes in children. Pediatr Allergy Immunol 2014;25:558-64.
151. Silverberg JI. Association between childhood atopic dermatitis, malnutrition, and low bone mineral density: a US population-based study. Pediatr Allergy Immunol 2015;26:54-61.
152. Silverberg JI , Silverberg NB. Childhood atopic dermatitis and warts are associated with increased risk of infection: a US population-based study. J Allergy Clin Immunol 2014;133:1041-7.
153. Takeuchi S, Esaki H, Furusyo N, Hayashida S, Yamamura K, Tsuji G et al. Incidence, serum IgE and TARC/CCL17 levels in atopic dermatitis associated with other allergic diseases: an update from the Ishigaki cohort. Acta dermato-venereologica 2015;95:480-4.
154. Tang SP, Liu YL, Wang SB, Weng SF, Chen S, Zhang MJ et al. Trends in prevalence and risk factors of childhood asthma in Fuzhou, a city in Southeastern China. J Asthma 2015;52:10-5.
155. Af Klinteberg M, Winberg A, Andersson M, Rönmark E , Hedman L. Decreasing prevalence of atopic dermatitis in Swedish schoolchildren: three repeated population-based surveys. Br J Dermatol 2024;190:191-8.
156. Ali Z, Ulrik CS, Egeberg A, Thyssen JP , Thomsen SF. Association of Childhood Atopic Dermatitis With a Higher Risk of Health Care Utilization and Drug Use for Asthma: A Nationwide Cohort Study. Dermatitis 2022;33:257-63.
157. Antonietti C, Angles MV, Giachetti A, Diaz MS, Gloser D, Juszkiewicz E et al. Atopic dermatitis in children and adolescents seen at a general hospital in the City of Buenos Aires. Arch Argent Pediatr 2023;121:e202202639.
158. Aschalew A, Kebed RA, Demie TG , Weldetsadik AY. Assessment of level of asthma control and related factors in children attending pediatric respiratory clinics in Addis Ababa, Ethiopia. BMC Pulm Med 2022;22:70.
159. Chiesa Fuxench ZC, Mitra N, Del Pozo D, Hoffstad O, Shin DB , Margolis DJ. Risk of atopic dermatitis and the atopic march paradigm in children of mothers with atopic illnesses: A birth cohort study from the United Kingdom. J Am Acad Dermatol 2024;90:561-8.
160. Färdig M, Hoyer A, Almqvist C, Bains KES, Carlsen KCL, Gudmundsdóttir HK et al. Infant lung function and early skin barrier impairment in the development of asthma at age 3 years. Allergy 2024;79:667-78.
161. Huang C, Liu W, Cai J, Weschler LB, Wang X, Hu Y et al. Breastfeeding and timing of first dietary introduction in relation to childhood asthma, allergies, and airway diseases: A cross-sectional study. J Asthma 2017;54:488-97.
162. Kim M, Yoo J, Kim J, Park J, Han E, Jang W et al. Association of FLG single nucleotide variations with clinical phenotypes of atopic dermatitis. PLoS One 2017;12:e0190077.

163. Lowe AJ, Angelica B, Su J, Lodge CJ, Hill DJ, Erbas B et al. Age at onset and persistence of eczema are related to subsequent risk of asthma and hay fever from birth to 18 years of age. Pediatr Allergy Immunol 2017;28:384-90.
164. Luukkonen TM, Kiiski V, Ahola M, Mandelin J, Virtanen H, Pöyhönen M et al. The Value of FLG Null Mutations in Predicting Treatment Response in Atopic Dermatitis: An Observational Study in Finnish Patients. Acta dermato-venereologica 2017;97:456-63.
165. Machluf Y, Farkash R, Rotkopf R, Fink D , Chaiter Y. Asthma phenotypes and associated comorbidities in a large cohort of adolescents in Israel. J Asthma 2020;57:722-35.
166. Park YM, Lee SY, Kim WK, Han MY, Kim J, Chae Y et al. Risk factors of atopic dermatitis in Korean schoolchildren: 2010 international study of asthma and allergies in childhood. Asian Pac J Allergy Immunol 2016;34:65-72.
167. Schmitz R, Atzpodien K , Schlaud M. Prevalence and risk factors of atopic diseases in German children and adolescents. Pediatr Allergy Immunol 2012;23:716-23.
168. Sehgal VN, Srivastava G, Aggarwal AK, Saxena D, Chatterjee K , Khurana A. Atopic Dermatitis: A Cross-Sectional (Descriptive) Study of 100 Cases. Indian J Dermatol 2015;60:519.
169. Thorsteinsdottir S, Stokholm J, Thyssen JP, Nørgaard S, Thorsen J, Chawes BL et al. Genetic, Clinical, and Environmental Factors Associated With Persistent Atopic Dermatitis in Childhood. JAMA Dermatol 2019;155:50-7.
170. Vermeulen EM, Koplin JJ, Dharmage SC, Gurrin LC, Peters RL, McWilliam V et al. Food Allergy Is an Important Risk Factor for Childhood Asthma, Irrespective of Whether It Resolves. J Allergy Clin Immunol Pract 2018;6:1336-41.e3.
171. Wan J, Mitra N, Hoffstad OJ, Gelfand JM, Yan AC , Margolis DJ. Variations in risk of asthma and seasonal allergies between early- and late-onset pediatric atopic dermatitis: A cohort study. J Am Acad Dermatol 2017;77:634-40.
172. Wananukul S, Chatproedprai S, Tempark T, Phuthongkamt W , Chatchatee P. The natural course of childhood atopic dermatitis: a retrospective cohort study. Asian Pac J Allergy Immunol 2015;33:161-8.
173. Wen HJ, Chiang TL, Lin SJ , Guo YL. Predicting risk for childhood asthma by pre-pregnancy, perinatal, and postnatal factors. Pediatr Allergy Immunol 2015;26:272-9.
174. Wypych-Ślusarska A, Grot M, Kujawińska M, Nigowski M, Krupa-Kotara K, Oleksiuk K et al. Respiratory Symptoms, Allergies, and Environmental Exposures in Children with and without Asthma. Int J Environ Res Public Health 2022;19.
175. Conic RZ, Tamashunas NL, Damiani G, Fabbrocini G, Cantelli M , Bergfeld WF. Comorbidities in pediatric alopecia areata. J Eur Acad Dermatol Venereol 2020;34:2898-901.
176. Ghaffari J, Rokni GR, Kazeminejad A , Abedi H. Association among Thyroid Dysfunction, Asthma, Allergic Rhinitis and Eczema in Children with Alopecia Areata. Open access Macedonian journal of medical sciences 2017;5:305-9.
177. Narla S , Silverberg JI. Association between atopic dermatitis and autoimmune disorders in US adults and children: A cross-sectional study. J Am Acad Dermatol 2019;80:382-9.

178. Campos-Alberto E, Hirose T, Napatalung L , Ohyama M. Prevalence, comorbidities, and treatment patterns of Japanese patients with alopecia areata: A descriptive study using Japan medical data center claims database. J Dermatol 2023;50:37-45.
179. de Lusignan S, Alexander H, Broderick C, Dennis J, McGovern A, Feeney C , Flohr C. Atopic dermatitis and risk of autoimmune conditions: Population-based cohort study. J Allergy Clin Immunol 2022;150:709-13.
180. Wohlmuth-Wieser I, Osei JS, Norris D, Price V, Hordinsky MK, Christiano A , Duvic M. Childhood alopecia areata-Data from the National Alopecia Areata Registry. Pediatr Dermatol 2018;35:164-9.
181. Lu YY, Wu MK, Lu CC, Wang WT , Wu CH. Atopic diseases and the risk of alopecia areata among pre-teens and teenagers in Taiwan. Indian J Dermatol Venereol Leprol 2025;91:294-9.
182. Brüske I, Standl M, Weidinger S, Klümper C, Hoffmann B, Schaaf B et al. Epidemiology of urticaria in infants and young children in Germany--results from the German LISAplus and GINIplus Birth Cohort Studies. Pediatr Allergy Immunol 2014;25:36-42.
183. Celiksoy MH, Ozmen AH , Topal E. Prevalence of atopic diseases in children with papular urticaria. Allergol Immunopathol (Madr) 2021;49:62-7.
184. Rosman Y, Hershko AY, Meir-Shafrir K, Kedem R, Lachover-Roth I, Mekori YA , Confino-Cohen R. Characterization of chronic urticaria and associated conditions in a large population of adolescents. J Am Acad Dermatol 2019;81:129-35.
185. Cetinkaya PG, Soyer O, Esenboga S, Sahiner UM, Teksam O , Sekerel BE. Predictive factors for progression to chronicity or recurrence after the first attack of acute urticaria in preschool-age children. Allergol Immunopathol (Madr) 2019;47:484-90.
186. Kitsioulis NA, Papadopoulos NG, Kostoudi S, Manousakis E, Douladiris N , Xepapadaki P. Assessment of atopic dermatitis as a risk factor for chronic spontaneous urticaria in a pediatric population. Allergy Asthma Proc 2018;39:445-8.
187. Lachover-Roth I, Rabie A, Cohen-Engler A, Rosman Y, Meir-Shafrir K , Confino-Cohen R. Chronic urticaria in children - New insights from a large cohort. Pediatr Allergy Immunol 2021;32:999-1005.
188. Garg N , Silverberg JI. Association between childhood allergic disease, psychological comorbidity, and injury requiring medical attention. Ann Allergy Asthma Immunol 2014;112:525-32.
189. Hsu DY, Smith B , Silverberg JI. Atopic Dermatitis and Hospitalization for Mental Health Disorders in the United States. Dermatitis 2019;30:54-61.
190. Yaghmaie P, Koudelka CW , Simpson EL. Mental health comorbidity in patients with atopic dermatitis. J Allergy Clin Immunol 2013;131:428-33.
191. Cheng CM, Hsu JW, Huang KL, Bai YM, Su TP, Li CT et al. Risk of developing major depressive disorder and anxiety disorders among adolescents and adults with atopic dermatitis: a nationwide longitudinal study. J Affect Disord 2015;178:60-5.
192. Vittrup I, Andersen YMF, Droitcourt C, Skov L, Egeberg A, Fenton MC et al. Association between hospital-diagnosed atopic dermatitis and psychiatric disorders and medication use in childhood. Br J Dermatol 2021;185:91-100.

193. Mann C, Wollenberg A, Ständer S, Staubach P, Thaçi D , Zirpel H. Risk of developing sleep disorders and psychologic comorbidity in children with inflammatory skin diseases-A population-based study. J Am Acad Dermatol 2025;92:1261-8.
194. Teichgräber F, Jacob L, Koyanagi A, Shin JI, Seiringer P , Kostev K. Association between skin disorders and depression in children and adolescents: A retrospective case-control study. J Affect Disord 2021;282:939-44.
195. Kyung Y, Choi MH, Jeon YJ, Lee JS, Lee JH, Jo SH , Kim SH. Association of atopic dermatitis with suicide risk among 788,411 adolescents: A Korean cross-sectional study. Ann Allergy Asthma Immunol 2020;125:55-64.
196. Kyung Y, Lee JS, Lee JH, Jo SH , Kim SH. Health-related behaviors and mental health states of South Korean adolescents with atopic dermatitis. J Dermatol 2020;47:699-706.
197. Lee S , Shin A. Association of atopic dermatitis with depressive symptoms and suicidal behaviors among adolescents in Korea: the 2013 Korean Youth Risk Behavior Survey. BMC Psychiatry 2017;17:3.
198. Noh HM, Cho JJ, Park YS , Kim JH. The relationship between suicidal behaviors and atopic dermatitis in Korean adolescents. J Health Psychol 2016;21:2183-94.
199. Drucker AM, Field AE, Li WQ, Cho E, Li T, Corliss HL , Qureshi AA. Childhood Atopic Dermatitis and Risk of Problematic Substance Use. Dermatitis 2018;29:168-70.
200. Kong S, Koo J , Lim SK. Associations between Stress and Physical Activity in Korean Adolescents with Atopic Dermatitis Based on the 2018-2019 Korea Youth Risk Behavior Web-Based Survey. Int J Environ Res Public Health 2020;17.
201. Kwon JA, Park E-C, Lee M, Yoo K-B , Park S. Does stress increase the risk of atopic dermatitis in adolescents? results of the Korea Youth Risk Behavior Web-based Survey (KYRBWS-VI). PLoS One 2013;8:e67890-e.
202. Lee KS, Rha YH, Oh IH, Choi YS , Choi SH. Socioeconomic and sociodemographic factors related to allergic diseases in Korean adolescents based on the Seventh Korea Youth Risk Behavior Web-based Survey: a cross-sectional study. BMC Pediatr 2016;16:19.
203. Manjunath J , Silverberg JI. Childhood Atopic Dermatitis Is Not Associated With Maternal Alcohol Use During Pregnancy or Adolescent Alcohol Use. Dermatitis 2021;32:e92-e4.
204. Kim SY, Sim S , Choi HG. Atopic dermatitis is associated with active and passive cigarette smoking in adolescents. PLoS One 2017;12:e0187453.
205. Lee JS, Kim JM, Seok J , Kim BJ. Correlation between socio-economic status and atopic dermatitis in Korean adults: the Korea national health and nutrition examination survey (2007-2014). J Eur Acad Dermatol Venereol 2017;31:1509-15.
206. Manjunath J, Silverberg NB , Silverberg JI. Association of atopic dermatitis with delinquent behaviors in US children and adolescents. Arch Dermatol Res 2022;314:975-82.
207. Akmatov MK, Ermakova T , Bätzing J. Psychiatric and Nonpsychiatric Comorbidities Among Children With ADHD: An Exploratory Analysis of Nationwide Claims Data in Germany. J Atten Disord 2021;25:874-84.
208. Chen MH, Su TP, Chen YS, Hsu JW, Huang KL, Chang WH et al. Comorbidity of Allergic and Autoimmune Diseases Among Patients With ADHD. J Atten Disord 2017;21:219-27.

209. Horev A, Freud T, Manor I, Cohen AD , Zvulunov A. Risk of Attention-Deficit/Hyperactivity Disorder in Children with Atopic Dermatitis. Acta Dermatovenerol Croat 2017;25:210-4.
210. Hou A , Silverberg JI. Predictors and age-dependent pattern of psychologic problems in childhood atopic dermatitis. Pediatr Dermatol 2021;38:606-12.
211. Qu X, Lee LC, Ladd-Acosta C, Hong X, Ji Y, Kalb LG et al. Association between atopic diseases and neurodevelopmental disabilities in a longitudinal birth cohort. Autism Res 2022;15:740-50.
212. Strom MA, Fishbein AB, Paller AS , Silverberg JI. Association between atopic dermatitis and attention deficit hyperactivity disorder in U.S. children and adults. Br J Dermatol 2016;175:920-9.
213. Wang LJ, Yu YH, Fu ML, Yeh WT, Hsu JL, Yang YH et al. Attention deficit-hyperactivity disorder is associated with allergic symptoms and low levels of hemoglobin and serotonin. Sci Rep 2018;8:10229.
214. Yang CF, Yang CC , Wang IJ. Association between allergic diseases, allergic sensitization and attention-deficit/hyperactivity disorder in children: A large-scale, population-based study. J Chin Med Assoc 2018;81:277-83.
215. Atefi N, Rohaninasab M, Shooshtari M, Behrangi E, Mehran G, Goodarzi A et al. The Association between Attention-Deficit/Hyperactivity Disorder and Atopic Dermatitis: A Study among Iranian Children. Indian J Dermatol 2019;64:451-5.
216. Catal F, Topal E, Soylu N, Ozel Ozcan O, Celiksoy MH, Babayiğit A et al. Psychiatric disorders and symptoms severity in preschool children with atopic eczema. Allergol Immunopathol (Madr) 2016;44:120-4.
217. Genuneit J, Braig S, Brandt S, Wabitsch M, Florath I, Brenner H , Rothenbacher D. Infant atopic eczema and subsequent attention-deficit/hyperactivity disorder--a prospective birth cohort study. Pediatr Allergy Immunol 2014;25:51-6.
218. Hak E, de Vries TW, Hoekstra PJ , Jick SS. Association of childhood attention-deficit/hyperactivity disorder with atopic diseases and skin infections? A matched case-control study using the General Practice Research Database. Ann Allergy Asthma Immunol 2013;111:102-6.e2.
219. Johansson EK, Ballardini N, Kull I, Bergström A , Wahlgren CF. Association between preschool eczema and medication for attention-deficit/hyperactivity disorder in school age. Pediatr Allergy Immunol 2017;28:44-50.
220. Lee CY, Chen MH, Jeng MJ, Hsu JW, Tsai SJ, Bai YM et al. Longitudinal association between early atopic dermatitis and subsequent attention-deficit or autistic disorder: A population-based case-control study. Medicine (Baltimore) 2016;95:e5005.
221. Liao TC, Lien YT, Wang S, Huang SL , Chen CY. Comorbidity of Atopic Disorders with Autism Spectrum Disorder and Attention Deficit/Hyperactivity Disorder. J Pediatr 2016;171:248-55.
222. Tsai JD, Chang SN, Mou CH, Sung FC , Lue KH. Association between atopic diseases and attention-deficit/hyperactivity disorder in childhood: a population-based case-control study. Ann Epidemiol 2013;23:185-8.

223. van der Schans J, Pleiter JC, de Vries TW, Schuiling-Veninga CC, Bos JH, Hoekstra PJ , Hak E. Association between medication prescription for atopic diseases and attention-deficit/hyperactivity disorder. Ann Allergy Asthma Immunol 2016;117:186-91.
224. Yu H , Zhang W. Prevalence and Related Factors of Attention Deficit Hyperactivity Disorder in School-age Children With Atopic Dermatitis. Altern Ther Health Med 2024;30:13-7.
225. Boemanns L, Staab J , Meyer T. Associations of attention-deficit/hyperactivity disorder with inflammatory diseases. Results from the nationwide German Health Interview and Examination Survey for Children and Adolescents (KiGGS). Neuropsychiatr 2024;38:182-8.
226. Chen M-H, Su T-P, Chen Y-S, Hsu J-W, Huang K-L, Chang W-H et al. Comorbidity of allergic and autoimmune diseases in patients with autism spectrum disorder: A nationwide population-based study. Research in Autism Spectrum Disorders 2013;7:205–12.
227. Zerbo O, Leong A, Barcellos L, Bernal P, Fireman B , Croen LA. Immune mediated conditions in autism spectrum disorders. Brain Behav Immun 2015;46:232-6.
228. Alexeeff SE, Yau V, Qian Y, Davignon M, Lynch F, Crawford P et al. Medical Conditions in the First Years of Life Associated with Future Diagnosis of ASD in Children. J Autism Dev Disord 2017;47:2067-79.
229. Neumeyer AM, Anixt J, Chan J, Perrin JM, Murray D, Coury DL et al. Identifying Associations Among Co-Occurring Medical Conditions in Children With Autism Spectrum Disorders. Acad Pediatr 2019;19:300-6.
230. Silverberg JI. Atopic disease and cardiovascular risk factors in US children. J Allergy Clin Immunol 2016;137:938-40.e1.
231. Ma Y, Chachin M, Hirose T, Nakamura K, Shi N, Hiro S , Imafuku S. Prevalence and incidence of comorbidities in patients with atopic dermatitis, psoriasis, alopecia areata, and vitiligo using a Japanese claims database. J Dermatol 2025;52:841-54.
232. Kim SY, Choi SH, Kim JD, Sol IS, Kim MJ, Kim YH et al. Korean Youth with Comorbid Allergic Disease and Obesity Show Heightened Psychological Distress. J Pediatr 2019;206:99-104.e4.
233. Lei Y, Yang H , Zhen L. Obesity is a risk factor for allergic rhinitis in children of Wuhan (China). Asia Pac Allergy 2016;6:101-4.
234. Lin MH, Hsieh CJ, Caffrey JL, Lin YS, Wang IJ, Ho WC et al. Fetal Growth, Obesity, and Atopic Disorders in Adolescence: a Retrospective Birth Cohort Study. Paediatr Perinat Epidemiol 2015;29:472-9.
235. Manjunath J , Silverberg JI. Association of obesity in early childhood with atopic dermatitis in late childhood and adolescence. J Am Acad Dermatol 2022;87:426-7.
236. Seong MK , Shin M. Low-Density Lipoprotein Cholesterol Is Associated with Atopic Dermatitis in Korean Adolescents. Int Arch Allergy Immunol 2023;184:1230-6.
237. Silverberg JI, Becker L, Kwasny M, Menter A, Cordoro KM , Paller AS. Central obesity and high blood pressure in pediatric patients with atopic dermatitis. JAMA Dermatol 2015;151:144-52.
238. Silverberg JI , Simpson EL. Association between obesity and eczema prevalence, severity and poorer health in US adolescents. Dermatitis 2014;25:172-81.

239. Song N, Shamssain M, Zhang J, Wu J, Fu C, Hao S et al. Prevalence, severity and risk factors of asthma, rhinitis and eczema in a large group of Chinese schoolchildren. J Asthma 2014;51:232-42.
240. Sybilski AJ, Raciborski F, Lipiec A, Tomaszewska A, Lusawa A, Samel-Kowalik P et al. Epidemiology of atopic dermatitis in Poland according to the Epidemiology of Allergic Disorders in Poland (ECAP) study. J Dermatol 2015;42:140-7.
241. Lim MS, Lee CH, Sim S, Hong SK , Choi HG. Physical Activity, Sedentary Habits, Sleep, and Obesity are Associated with Asthma, Allergic Rhinitis, and Atopic Dermatitis in Korean Adolescents. Yonsei Med J 2017;58:1040-6.
242. Reddy P, Mahajan R, Mehta H, De D, Bhatia A, Kumar R , Handa S. Increased prevalence of metabolic syndrome and non-alcoholic fatty liver disease in children with atopic dermatitis: A case-control study from northern India. Pediatr Dermatol 2024;41:421-7.
243. Ha EK, Kim JH, Kwak JH, Lee S, Cha HR, Chung EH , Han MY. Association of clinical and social factors with risk of fracture in children with atopic dermatitis. Pediatr Allergy Immunol 2022;33:e13712.
244. Lee SW, Shin YH, Shin JI, Kang SM, Abuabara K, Hwang J et al. Fracture incidence in children after developing atopic dermatitis: A Korean nationwide birth cohort study. Allergy 2023;78:871-5.
245. Narla S , Silverberg JI. Association between childhood atopic dermatitis and cutaneous, extracutaneous and systemic infections. Br J Dermatol 2018;178:1467-8.
246. Ren Z , Silverberg JI. Association of Atopic Dermatitis With Bacterial, Fungal, Viral, and Sexually Transmitted Skin Infections. Dermatitis 2020;31:157-64.
247. Darbà J , Marsà A. Atopic dermatitis in specialized centers in Spain: a retrospective analysis of incidence and costs (2000-2017). Expert Rev Pharmacoecon Outcomes Res 2021;21:737-42.
248. Sandhu JK, Salame N, Ehsani-Chimeh N , Armstrong AW. Economic burden of cutaneous infections in children and adults with atopic dermatitis. Pediatr Dermatol 2019;36:303-10.
249. Hobbs MR, Grant CC, Thomas MG, Berry S, Morton SMB, Marks E , Ritchie SR. Staphylococcus aureus colonisation and its relationship with skin and soft tissue infection in New Zealand children. Eur J Clin Microbiol Infect Dis 2018;37:2001-10.
250. Langan SM, Abuabara K, Henrickson SE, Hoffstad O , Margolis DJ. Increased Risk of Cutaneous and Systemic Infections in Atopic Dermatitis-A Cohort Study. J Invest Dermatol 2017;137:1375-7.
251. Bocchini CE, Mason EO, Hulten KG, Hammerman WA , Kaplan SL. Recurrent community-associated Staphylococcus aureus infections in children presenting to Texas Children's Hospital in Houston, Texas. Pediatr Infect Dis J 2013;32:1189-93.
252. Basdag H, Rainer BM , Cohen BA. Molluscum contagiosum: to treat or not to treat? Experience with 170 children in an outpatient clinic setting in the northeastern United States. Pediatr Dermatol 2015;32:353-7.
253. McCollum AM, Holman RC, Hughes CM, Mehal JM, Folkema AM, Redd JT et al. Molluscum contagiosum in a pediatric American Indian population: incidence and risk factors. PLoS One 2014;9:e103419.

254. Olsen JR, Piguet V, Gallacher J , Francis NA. Molluscum contagiosum and associations with atopic eczema in children: a retrospective longitudinal study in primary care. Br J Gen Pract 2016;66:e53-8.
255. Cardwell CR, Shields MD, Carson DJ , Patterson CC. A meta-analysis of the association between childhood type 1 diabetes and atopic disease. Diabetes Care 2003;26:2568-74.
256. Olesen AB, Juul S, Birkebaek N , Thestrup-Pedersen K. Association between atopic dermatitis and insulin-dependent diabetes mellitus: a case-control study. Lancet 2001;357:1749-52.
257. Rosenbauer J, Herzig P , Giani G. Atopic eczema in early childhood could be protective against Type 1 diabetes. Diabetologia 2003;46:784-8.
258. Stene LC, Rønningen KS, Bjørnvold M, Undlien DE , Joner G. An inverse association between history of childhood eczema and subsequent risk of type 1 diabetes that is not likely to be explained by HLA-DQ, PTPN22, or CTLA4 polymorphisms. Pediatr Diabetes 2010;11:386-93.