American Academy of Dermatology Association

Supplemental Material

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

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Supplemental Appendix 1: Detailed Methodology

Expert Work Group Composition and Disclosures of Interest

The co-chairs of the Work Group (D.D. and R.S.) were reviewed for potential disclosures of interest (DOIs) and approved by the AAD's Clinical Guidelines Committee (CGC). Additional Work Group members were nominated by the co-chairs based on their expertise related to the clinical questions. All Work Group nominees were reviewed for potential DOIs by the CGC. The majority (at least 51%) of the Work Group was required to be free of financial DOIs relevant to the topic of the guideline. Nominees found to have no relevant financial DOIs were approved, whereas nominees found to have potentially relevant financial DOIs were approved with management. Work Group members approved with management were prohibited from discussions on and voting for recommendations in which they had relevant DOIs. Work Group members completed a DOI form that was periodically updated and reviewed for potential relevant DOIs throughout guideline development and used to ensure management terms were observed. The multidisciplinary Work Group consisted of the co-chairs, 10 members, an additional member serving as a methodologist, and a patient representative. The Work Group was supported by an AAD guidelines staff member (L.F.G) with health research methodology expertise.

Formulation of Questions and Rating the Importance of Outcomes

Based on the aim of the guideline to appraise the evidence on infant-focused primary prevention interventions and the association between AD in pediatric patients and select comorbidities, the expert Work Group identified two clinical questions, using the Population, Intervention, Comparator, Outcome (PICO) or PECO format, as applicable (**Table I**).

Specific to the clinical question addressing primary prevention of atopic dermatitis, the Work Group defined the objective of the systematic review to assess the effects of infant-focused skincare, dietary, environmental, and microbiome interventions for the primary prevention of atopic dermatitis.

Specific to the clinical question addressing the association between pediatric AD and comorbid conditions, the expert Work Group defined the objective of the systematic review to synthesize the evidence on associations between AD and comorbid conditions and established the outcomes of interest as incidence and prevalence of various comorbid conditions. After defining the research aims, the Work Group identified selected comorbid conditions considered critical or important to the clinical management of AD. Potential comorbid conditions were identified via a survey of AD literature, consultation with expert Work Group members, and review of conditions included in commonly used comorbidity indices.[1-3] The Work Group ranked the importance of each identified condition with respect to its relevance for clinical management of AD via anonymous online voting using a 9-point scale (a ranking of 7-9 was assigned to conditions considered critically relevant, 4-6 for conditions considered of important relevancy, and 1-3 for conditions of limited relevancy). All conditions achieving a mean ranking of critical or important were included in the review of comorbidities of interest (**Table 1**).

Table 1. Prioritized comorbidities

Among pediatric patients, what is the association between AD and…			
Atopic and allergic conditions		Mental health and substance use	
Asthma	Allergic conjunctivitis	Depression	Cigarette smoking
Food allergy	Eosinophilic esophagitis	Anxiety	ADHD
Allergic rhinitis		Suicide	Autism spectrum disorders
		Alcohol use disorders	
Immune-mediated conditions		Bone health	
Alopecia areata		Osteoporosis	
Urticaria		Bone fractures	
Cardiovascular disease		Metabolic disorders	

Coronary artery disease Congestive heart failure Peripheral artery disease Hypertension	Thromboembolic disease Myocardial infarction Stroke Cardiovascular death	Diabetes Dyslipidemia Obesity Metabolic syndrome
Skin infections		

Next, the Work Group identified outcomes considered important for making clinical decisions regarding: 1) infant-focused primary prevention interventions and 2)the potential association between pediatric AD and select comorbid conditions (see above) through discussion and review of the core outcome set for AD trials developed by the Harmonizing Outcome Measures for Eczema (HOME) initiative (**Table 2**).[4] The Work Group ranked the importance of each primary outcome for decision-making via anonymous online voting using a 9-point scale (a ranking of 7-9 was assigned to outcomes critical for decision-making, 4-6 for outcomes important for decision-making, and 1-3 for outcomes of limited importance for decision-making).[5] Results of voting were used to categorize outcomes as "critical", "important", or "not important".

Table 2. Primary Outcomes

Primary Outcome	Importance Ranking
Primary prevention interventions	
Incidence, occurrence, or rate of AD at 6 months to 3 years of age	Critical
Serious adverse events	Critical
Adverse events of interest (specific to each intervention defined a priori)	Important
Comorbidities	
Incidence or prevalence of comorbid conditions	Critical

Evidence Search and Review

A search of the literature for all PICO questions using MEDLINE (via PubMed), CENTRAL, and the Cochrane Database of Systematic Reviews was conducted starting April 15th, 2024, and periodically updated through July 20th, 2025. Existing systematic reviews published within the previous 10 years and meeting all eligibility criteria were identified (**Table 3**). If systematic reviews were not available or the identified systematic reviews did not include an intervention of interest a review was commissioned by an expert systematic review group or a de novo review was conducted by the Work Group with the assistance of AAD staff. The evidence review workflow is detailed in **Table 4**. All systematic reviews supporting this analysis met or followed standard methodology including development of PICO questions, explicit inclusion criteria, systematic literature searches, and vetted risk of bias assessment procedures.

Table 3. Eligibility Criteria for systematic review questions by guideline section

Category	Criteria
Association between pediatric AD and comorbid conditions	
Population	Children and adolescents (<18 years old) with clinically diagnosed AD of any severity
Exposure	Diagnosis of atopic dermatitis
Comparator	Children and adolescents without a diagnosis of atopic dermatitis
Outcomes	Incidence, prevalence, or rate of selected comorbid conditions
Study Design	Observational studies (cohort, case-control, cross-sectional)
Other	English language studies
Primary prevention of atopic dermatitis	
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 (moisturizers/emollients; bathing products, bathing practices, water softener), environmental (ultraviolet light exposure, reduction in dust mites, tobacco smoke avoidance, other modifiable environmental factors), dietary (vitamin D, infant formula (whey-based, casein-based, partially hydrolysed/hydrolyzed, soy), exclusive breastfeeding, dietary restrictions, dietary supplements, omega 3 & 6 oil, fish oil, early introduction of allergenic foods, complementary feeding), microbiome (probiotics, prebiotics, synbiotics, and other (Bacille Calmette-Guerin vaccine/Bacillus Calmette-Guérin, pertussis vaccine, pentavalent vaccine, bacterial lysate) interventions
Comparator	Standard care/practice, placebo, attention control, or no treatment
Outcomes	incidence/occurrence/rate of AD at 6 months-3 years old, adverse events during the intervention period, serious adverse events (as defined by the studies); specific AEs of interest per intervention type: emollients (slippage, skin infection, skin reactions), vaccination (injection site reactions, scarring), bacterial lysate (gastrointestinal issues), dietary interventions (gastrointestinal issues, growth, nutrition adequacy)
Study Design	Published randomized trials
Other	English language

For de novo reviews, studies retrieved by the literature searches were reviewed for relevance over two rounds of study selection. Two reviewers independently screened citations. All citations deemed relevant by one or both reviewers were obtained as full text. Two independent reviewers screened full text citations against a priori established eligibility criteria (**Table 3**); discrepancies were resolved through discussion. Data extraction using structured data abstraction spreadsheets was initially performed by an independent reviewer with subsequent quality control performed by a second reviewer. Risk of bias was assessed for all included studies using the Cochrane Collaboration's tool for assessing risk of bias in randomized trials (ROB2), the Newcastle Ottawa Scale for assessing the quality of nonrandomized studies in meta-analyses[6], or a modified Newcastle Ottawa Scale for assessing the quality of cross-sectional studies[7] based on study design.[8]

Table 4. Evidence Review Workflow

Clinical Topic Area	Evidence Review Workflow
Comorbidities	Updated a de novo systematic review conducted in May 2020 to support the development of the AAD's guidelines on comorbidities of adult atopic dermatitis.[9] Searches updated specific to pediatric AD through May July 2025.
Primary prevention	For skincare interventions human milk consumption existing high quality systematic reviews by Kelleher 2022[10] and Gungor 2019[11] were updated with searches through June 2024; For microbiome, dietary (excluding human milk consumption), environmental, and other interventions, a de novo systematic review was conducted with a literature searches run from inception through June 2024.

Assessing the Overall Certainty of the Body of Evidence

The GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach was used to assess the overall certainty of the evidence from systematic reviews for each critical or important outcome.[12] The GRADEPro Guideline Development Tool was used to create evidence profiles that categorized the overall certainty 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 5**).

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.[12,13] 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 6**).

Table 5. Certainty of Evidence Ratings

Certainty of the Evidence	Confidence in the Estimate of Effect

High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are 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	Our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect
Very Low	We have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Table 6 . Levels of Evidence for Comorbidities Evidence

Level of Evidence	Confidence in the Estimate of Effect[13]
High	We are very confident that the association lies close to that of the estimate.
Moderate	We are moderately confident that the association is close to that of the estimate, but there is a possibility that it is substantially different.
Low	Our confidence in the estimate is limited; the true association may be substantially different from the estimate.
Very Low	We have very little confidence in the estimate; the true association is likely to be substantially different from the estimate.

Formulating and Grading Recommendations

For the clinical questions regarding prevention, the Work Group drafted recommendations using the evidence profiles and considering the following: the balance of desirable and undesirable consequences of an intervention, the overall certainty of the evidence, patient values and preferences, and feasibility.[14] GRADE evidence-to-decision (EtD) frameworks were compiled for each clinical question to facilitate recommendation drafting. Structured searches were conducted for evidence of patient values and preferences, resource use, and feasibility to inform the EtD process. The workgroup also included a patient representative to provide input on preferences and values.

In accordance with the GRADE approach, recommendations were either “strong” or “conditional”.[15] The implications of each strength of recommendation are summarized in **Table 7**. Recommendations were also graded according to the GRADE approach.[15] In situations in which the supporting evidence for a recommendation was indirect only, but the certainty surrounding an intervention’s impact was high and the benefits of the intervention clearly outweigh the harms (or vice versa), a Good Practice Statement was developed.[16] Good Practice Statements are strong recommendations as the certainty surrounding the impact of the recommended intervention is high.

Table 7. Strength of Recommendation Implications

Strength	Implication
Strong	Benefits clearly outweigh risks and burden, or risks and burden clearly outweigh the benefits
Conditional	Benefits finely balanced with risks and burden

For the clinical question on the association between AD and comorbid conditions, the Work Group member drafted statements of association using the evidence profiles and considering the following: the strength of the estimated association between AD and a selected comorbid condition and the overall quality of the evidence of association. The implications of the wording of statements of association as a reflection of the strength of association and certainty of the evidence are summarized in **Table 8**. Remarks were drafted to accompany selected statements when the Work Group considered the additional information essential to the interpretation of the statement.

Table 8. Strength of statements of association and supporting evidence: Wording and 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**[13-15]
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.

Manuscript Review and Currency Statement

This guideline was developed in accordance with the AAD/AAD Association Administrative Regulations for Evidence-Based Clinical Practice Guidelines (March 2021), which includes the opportunity for review and comment by the entire AAD membership and final review and comment by the AAD Board of Directors.[17] This guideline will be considered current for a period of 5 years from the date of publication unless reaffirmed, updated, or retired before that time.

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Table. 1 Skincare Interventions

Moisturizing skin care compared to standard skin care for primary prevention of AD

Patient or population: healthy, full-term infants aged 12 months or younger
Setting: primary prevention
Intervention: Regular moisturizing skin care
Comparison: Standard skin care without regular moisturizer/emollient use

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard skin care	Risk with Moisturizing skin care				
AD by 6 months to 2 years – *High-risk populations* assessed with: cumulative incidence of AD follow-up: range 6 months to 2 years CRITICAL	310 per 1,000	**223 per 1,000** (183 to 275)	**RR 0.72** (0.59 to 0.89)	3537 (12 RCTs)[1-12]	⨁⨁⨁⨁ High	Regular use of moisturizing skin care may reduce the incidence of AD in the first 2 years of life in high-risk infants.
AD by 1 year- *General populations* assessed with: cumulative incidence of AD follow-up: 1 years CRITICAL	102 per 1,000	**108 per 1,000** (66 to 177)	**RR 1.06** (0.65 to 1.74)	1937 (3 RCTs)[12-14]	⨁⨁⨁◯ Moderate[h]	Regular moisturizing skin care likely does not reduce the incidence of AD in general infant populations.
Skin infections assessed with: Infants with a skin infection follow-up: range 6 months to 2 years IMPORTANT	95 per 1,000	**103 per 1,000** (86 to 124)	**RR 1.09** (0.91 to 1.31)	4038 (8 RCTs)[1, 2, 4-6, 8, 12]	⨁⨁⨁◯ Moderate[a,b]	Regular use of moisturizing skin care likely results in little to no difference in skin infections.
Skin reactions assessed with: rash, stinging, or burning follow-up: range 2 months to 2 years IMPORTANT	143 per 1,000	**137 per 1,000** (106 to 177)	**RR 0.96** (0.74 to 1.24)	1402 (3 RCTs)[5, 6, 12]	⨁⨁⨁◯ Moderate[a,c]	Overall rates of skin reactions were moderate in both arms but regular use of moisturizing skin care may slightly reduce risk. Chaoimh 2023 reported one rash with moisturizer use (n=161) leading to withdrawal from treatment. Skjerven 2020 reported skin symptoms and signs, including itching, oedema, exanthema, dry skin, and urticaria were no more frequent in the skin intervention group (n=544) than in the no-intervention group n=596).
Slippages assessed with: slips follow-up: range 6 months to 12 months IMPORTANT	9 per 1,000	**13 per 1,000** (6 to 28)	**RR 1.48** (0.71 to 3.06)	2413 (3 RCTs)[1, 5, 14]	⨁⨁⨁◯ Moderate[a,d]	Slippage accidents were rare across both arms.
Serious adverse events follow-up: range 6 months to 1 years IMPORTANT	75 per 1,000	**109 per 1,000** (23 to 533)	**RR 1.45** (0.30 to 7.06)	1252 (2 RCTs)[5, 14]	⨁⨁◯◯ Low[a,d,e]	SAEs documented in these studies include seizure, bronchiolitis, croup, influenza, surgery, pneumonia, flu, injury, UTI, allergic reaction, and respiratory distress.
Adverse events with moisturizing skin care assessed with: AEs or side effect with use of emollient skin care follow-up: range 6 months to 1 years IMPORTANT	Five studies[3, 8, 10, 11, 13] (n= 275) report no AEs or side effects with use of regular emollient skin care. Kottner 2022 reported no differences in AEs between emollient skin care and standard care. Ng 2021 reported 1 case of contact dermatitis with use of emollient (n=66), while Techasatian 2021 reported rates of cutaneous AEs of 2.78% and 4.65% with skin care (n=72) and standard care, (n=43) respectively.			850 (7 RCTs)	⨁⨁◯◯ Low[f,g]	AEs with regular moisturizing skin care appear rare and may be equitable with standard care.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** confidence interval; **RR:** risk ratio

Explanations

a. Some concerns with risk of bias across all included studies due to unmasked outcome assessment and minimal outcome measurement information for some studies. Not downgraded for this borderline risk of bias.

b. Downgraded by one level for imprecision due to wide confidence interval including both a potentially harmful effect and no effect.
c. Downgraded one level for imprecision due to CI consistent with benefit and harm
d. Downgraded one level for imprecision due to the small number of events, with a wide CI including both harmful effect and beneficial effect.
e. Downgraded one level for inconsistency. The study in a high risk population suggests increased risk of SAEs, while the study in the general population suggests decreased risk.
f. Downgraded one level for risk of bias as AEs were primarily assessed by unmasked caregivers and specific measurement of AEs was not detailed. Outcome reporting was also limited.
g. Downgraded one level for imprecisions as the individual studies were underpowered and the event rates low.
h. Downgraded one level for imprecision driven by inconsistency: two studies suggest no protective effect, while a third study suggests a protective effect; leading to a CI consistent with potentially meaningful benefit and harm.

Table. Included study characteristics

Study	Population (n)	Age at intervention (days)	Duration of intervention (months)	Age at AD assessment (months)	Intervention	Comparator
Chalmers 2021	High risk (1394)	0-21	12	24	Emollient ≥ qd & after every bath	Standard skin care
Chaoimh 2023	High risk (321)	0-4	2	12	Emollient bid	Standard skin care
Dissanayake 2019	General (549)	0	6	12	Emollient bid or tid	Standard skin care
Harder 2023	High risk (50)	1-21	12	24	Emollient qd	Standard skin care
Horimukai 2014	High risk (118)	0-7	8	8	Emollient qd	Standard skin care with petroleum jelly as desired
Kottner 2022	High risk (160)	0-14	12	24	Emollient qd	Standard care
Lowe 2018	High risk (80)	0-21	6	12	Emollient bid	Standard care
McClanahan 2019	High risk (100)	0-21	24	24	Emollient qd	Standard care (asked not to apply moisturizer daily)
Ng 2021	High risk (200)	0-14	12	12	Emollient bid & moisturizing wash for bathing	Standard care
Simpson 2014	High risk (124)	0-21	6	6	Emollient qd	Standard care without emollient use
Simpson 2025	General (629) High Risk (599)	0-63	24	24	Emollient qd	No emollient use
Skjerven 2020	General (1172)	14	8	12	Emollient bath additive & face cream 4x per week	Standard care
Techasatian 2022	High risk (154)	0-21	6	6	Emollient qd	Standard care without emollient use
Thitthiwong 2019	High risk (53)	0-70	9	9	Emollient qd after bathing	Standard care without emollient use

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Table 2. Allergen Avoidance

Allergen avoidance compared to standard care for primary prevention of AD

Patient or population: healthy, full-term infants aged 12 months or younger at high risk of atopy
Setting: primary prevention
Intervention: Allergen avoidance (special mite-impermeable mattress encasings plus a booklet explaining allergy and giving advice on allergy prevention [Horak 2004] or house dust mite avoidance measures [Mihrshahi 2003])
Comparison: Standard care

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard care	**Risk with allergen avoidance**				
AD by 2 years- *High risk population* assessed with: cumulative incidence of AD follow-up: 2 years CRITICAL	110 per 1,000	**109 per 1,000** (67 to 176)	**RR 0.99** (0.61 to 1.60)	538 (1 RCT)[1]	⨁◯◯◯ Very Low[a,b]	Allergen avoidance may result in little to no difference in AD by 2 years old in high risk populations but the evidence is uncertain.
AD at 18 months- *High risk population* Assessed with: prevalence of AD follow-up: 18 months IMPORTANT	137 per 1,000	**194 per 1,000** (133 to 284)	**RR 1.42** (0.97 to 2.08)	554 (1 RCT)[2]	⨁⨁◯◯ Low[c,d]	Allergen avoidance may result in increased risk of AD at 18 months in high risk populations but the evidence is uncertain.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** confidence interval; **RR:** risk ratio

Explanations
a. Downgraded once for RoB as unmasked with non-standardized outcome assessment.
b. Downgraded twice for imprecision due to small number of events and very wide CI consistent with moderate risk reduction and increase.
c. Downgraded once for RoB due to missing outcome data.
d. Downgraded once for imprecision as CI consistent with an important increase in risk and no difference.

References

1. 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.
2. 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.

Table 3. Water-Softening

Soft water compared to hard water for primary prevention of AD

Patient or population: healthy, full-term infants aged 12 months or younger at high risk for AD
Setting: primary prevention
Intervention: water softener installed in the family home
Comparison: untreated hard water

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with hard water	**Risk with soft water**				
AD by 6 months - *High risk population* assessed with: prevalence of AD follow-up: 6 months CRITICAL	484 per 1,000	**334 per 1,000** (184 to 600)	**RR 0.69** (0.38 to 1.24)	67 (1 RCT)[1]	⨁⨁◯◯ Low[a]	The impact of water softening on the incidence of AD is uncertain due to the underpowered sample.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** confidence interval; **RR:** risk ratio

Explanations
a. Downgraded two levels for imprecision due to a very small number of events, with wide CI consistent with beneficial and harmful effects.

References

1. 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.

Table 4. Early Complementary Feeding

Early complementary feeding compared to standard feeding for primary prevention of AD

Patient or population: Healthy, full-term infants aged 12 months or younger
Setting: primary prevention of AD
Intervention: early complementary feeding of eggs (Palmer 2017) or eggs, peanuts, wheat, and milk (Skjerven 2020)
Comparison: standard feeding without early introduction of eggs, peanuts, milk, or wheat

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard feeding	**Risk with early complementary feeding**				
AD by 12 months-*High risk population* assessed with: cumulative incidence of AD follow-up: 12 months CRITICAL	53 per 1,000	**27 per 1,000** (13 to 56)	**RR 0.51** (0.24 to 1.07)	751 (1 RCT)[1]	⨁◯◯◯ Very low[a,b]	The evidence is very uncertain about the effect of early egg introduction on AD by 12 months in high risk infants.
AD by 12 months-*General population* assessed with: cumulative incidence of AD follow-up: 12 months CRITICAL	81 per 1,000	**90 per 1,000** (63 to 130)	**RR 1.12** (0.78 to 1.62)	1238 (1 RCT)[2]	⨁⨁◯◯ Low[c,d]	Early complementary feeding may result in little to no difference in AD by 12 months in the general population.

Early complementary feeding compared to standard feeding for primary prevention of AD

Patient or population: Healthy, full-term infants aged 12 months or younger
Setting: primary prevention of AD
Intervention: early complementary feeding of eggs (Palmer 2017) or eggs, peanuts, wheat, and milk (Skjerven 2020)
Comparison: standard feeding without early introduction of eggs, peanuts, milk, or wheat

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard feeding	**Risk with early complementary feeding**				
Allergic reactions assessed with: infants with allergic reactions follow-up: 6 months IMPORTANT	One study of early egg introduction reported 3 incidences of anaphylaxis in 820 infants. One study of early introduction of peanut, milk, wheat, and egg reported 17 confirmed allergies in 642 infants.			2058 (2 RCTs)[1, 2]	⨁⨁◯◯ Low[a]	Allergic reactions were rare in both studies.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** confidence interval; **RR:** risk ratio

Explanations
a. Downgrade twice for risk of bias due to concerns about missing outcome data and deviations from assigned interventions.
b. Downgraded twice for imprecision as low event rates led to very with CI consistent with very large risk reduction and no important risk difference.
c. Downgraded once for risk of bias due to concerns with deviations from the assigned intervention.
d. Downgraded once for imprecisions as CI consistent with no meaningful risk difference and possibly meaningful risk reduction.

References

1. 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.
2. 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.

Table 5. Human Milk Consumption

Adapted from: Güngör D, Nadaud P, LaPergola CC, Dreibelbis C, Wong YP, Terry N, Abrams SA, Beker L, Jacobovits T, Järvinen KM, Nommsen-Rivers LA, O'Brien KO, Oken E, Pérez-Escamilla R, Ziegler EE, Spahn JM. Infant milk-feeding practices and food allergies, allergic rhinitis, atopic dermatitis, and asthma throughout the life span: a systematic review. Am J Clin Nutr. 2019 Mar 1;109(Suppl_7):772S-799S. doi: 10.1093/ajcn/nqy283. Erratum in: Am J Clin Nutr. 2019 Oct 1;110(4):1041. PMID: 30982870; PMCID: PMC6500928.[1]

Human milk ever compared to no human milk for primary prevention of AD

Patient or population: Infants aged birth to 24 months
Setting: primary prevention of AD
Intervention: human milk ever
Comparison: No human milk ever

Outcomes	Impact	№ of participants (studies)	Certainty of the evidence (GRADE)
AD by 2 years- *High risk & general populations* assessed with: incidence of AD follow-up: 24 months CRITICAL	Sixteen articles presented inconclusive evidence on never versus ever being fed human milk and AD by 24 months. Three studies reported significant associations but the direction of the point estimates were inconsistent. In 11 studies reporting nonsignificant associations, estimates of effect were also inconsistent in direction, with no discernible trend in the direction of the point estimates.	34891 (16 observational studies)	⊕◯◯◯ Very low[a,b,c]

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** confidence interval

Explanations
a. Downgraded once for RoB due to concerns with the assessment of AD.
b. Downgraded once for inconsistency as the magnitude and direction of the estimates of effect varied across the included studies.
c. Downgraded once for indirectness as a systematic review of non-randomized studies was included.

References

1. 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.

Table 6. Probiotic Supplementation

Probiotic supplementation compared to no probiotics for primary prevention of AD

Patient or population: healthy, full-term infants aged 12 months or younger
Setting: primary prevention
Intervention: probiotic supplementation
Comparison: no probiotics

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Included studies with no poolable data	Comments
	Risk with no probiotics	**Risk with probiotics**					
AD by 1 to 3 years - *High risk populations* assessed with: cumulative AD follow-up: range 1 year to 3 years CRITICAL	348 per 1,000	**271 per 1,000** (205 to 351)	**RR 0.78** (0.59 to 1.01)	1858 (7 RCTs)[1-7]	⨁⨁⨁◯ Moderate[a]	Cabana 2017: At 2yo the cumulative incidence of AD was 30.9% (21.4%, 40.4%) with probiotic use vs 28.7% (19.4%, 38.0%) for an **aHR of 0.95 (0.59, 1.53)**.[8]	Probiotic supplementation likely results in little to no difference in AD by 6mos to 3 years old in high-risk populations.
AD by 1 year - *General population* assessed with: cumulative incidence of AD follow-up: 1 year CRITICAL	200 per 1,000	**126 per 1,000** (42 to 378)	**RR 0.63** (0.21 to 1.89)	72 (1 RCT)[9]	⨁⨁◯◯ Low[b]		The impact of probiotic supplementation on the general population is uncertain due to limited evidence. Combing general population data with high-risk population data: RR 0.82 (0.63, 1.07).
Adverse events assessed with: Infants with AEs follow-up: range 1 year to 2 years IMPORTANT	Three studies reported no adverse events with (n= 239) or without (n=406) probiotic use; Lau 2012 reported similar numbers of AEs in the probiotic (n=303) and placebo groups (n=303) 2951 versus 2925, respectively.			1251 (4 RCTs)[1, 3, 7, 8]	⨁⨁⨁⨁ High		All studies suggest similar rates of AEs between probiotic supplementation and controls, with 3 studies suggesting AEs are rare in general.
Gastrointestinal issues assessed with: Infants with GI issues follow-up: range 6 months to 1 year IMPORTANT	Berni 2017 reported no formula tolerance issues with (n=98) or without =95) probiotic supplementation. Lau 2012 reported abdominal pain (0.8% in both treatment groups), diarrhea (7.5% with probiotics, n=303 and 7.4% with placebo, n=303), and flatulence (0.1% in both treatment groups) but no severe GI issues; Bellomo 2024 reported no significant difference in GI adverse events between the probiotic and no probiotic groups, with all events mild and transient.			1067 (3 RCTs)[1, 3, 7]	⨁⨁⨁⨁ High		Overall rates of GI issues were low and equitable.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** confidence interval; **RR:** risk ratio

Explanations
a. Downgraded one level for imprecision for the small number of events, and CI consistent with meaningful decrease and minimal to no risk difference.
b. Downgraded two levels for imprecision due to very small sample & number of events and wide CI consistent with important reduction and increase in risk.

Table. Included study characteristics

Study	Population (n)	Age at intervention (days)	Duration of intervention (months)	Age at AD assessment (months)	Intervention	Comparator
Bellomo 2024	High risk (268)	0	6	12	Bifidobacterium bifidum in water qd	No probiotic supplementation
Berni 2017	High risk (220)	30-60	12	12	Lactobacillus rhamnosus GG in extensively hydrolyzed casein formula	Extensively hydrolyzed casein formula
Cabana 2017	High risk (184)	0-4	6	24	Lactobacillus rhamnosus GG supplement qd	Inulin placebo 325mg qd
He 2023	High risk (264)	0-14	10 days	36	Clostridium butyricum supplements bid with breast milk	Breast milk

Lau 2012	High risk (606)	28-25	6	36	Oral bacterial lysate containing heat-killed nonpathogenic gram-negative E coli Symbio DSM 17252 and nonpathogenic gram-positive E faecalis Symbio DSM 16440 (1.5-4.5 3 107 bacteria/mL) with a daily dosage of 3 x 0.7 mL.	Placebo
Prescott 2008	High risk (153)	0-2	6	30	Lactobacillus acidophilus in maltodextrin supplement	Maltodextrin placebo
Rautava 2006	General (81)	2-65	12	12	Lactobacillus GG and Bifidobacterium lactis Bb-12 in formula	Placebo in formula
Soh 2009	High risk (253)	0	6	12	Bifidobacterium longum & Lactobacillus rhamnosus in cow's milk formula 60mL qd	Cow's milk formula
West 2009	General (179	120	9	13	Lactobacillus F19 in cereal qd	Cereal

References

1. 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.
2. 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.
3. 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.
4. 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.
5. 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.
6. West CE, Hammarström ML , Hernell O. Probiotics during weaning reduce the incidence of eczema. Pediatr Allergy Immunol 2009;20:430-7.
7. 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.
8. 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.
9. Rautava S, Arvilommi H , Isolauri E. Specific probiotics in enhancing maturation of IgA responses in formula-fed infants. Pediatr Res 2006;60:221-4.

Table 7. Vitamin D Supplementation

Vit D compared to placebo for primary prevention of AD

Patient or population: Healthy, full-term infants aged 12 months or younger at high risk for atopy
Setting: primary prevention of AD
Intervention: vitamin D supplementation (400 IU/d) until 6 months of age
Comparison: placebo until 6 months of age

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with vit D				
AD by 6 months- *High risk population* assessed with: cumulative incidence of AD follow-up: 6 months	193 per 1,000	**218 per 1,000** (121 to 395)	**RR 1.13** (0.63 to 2.05)	170 (1 RCT)[1]	⨁⨁◯◯ Low[a]	Vit D supplementation may result in little to no difference in AD by 6 months in high risk populations.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** confidence interval; **RR:** risk ratio

Explanations

a. Downgraded twice for imprecision due to very wide CI consistent with meaningful risk reduction and large increased risk.

References

1. 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.

Table 8. Prebiotic Supplementation

Prebiotic supplementation compared to no prebiotics for primary prevention of AD

Patient or population: healthy, full-term infants aged 12 months or younger
Setting: primary prevention
Intervention: prebiotic supplementation
Comparison: no prebiotics

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no prebiotics	Risk with prebiotics				
AD by 1 to 2 years - *High-risk populations* assessed with: cumulative incidence of AD follow-up: range 1 year to 2 years *CRITICAL*	364 per 1,000	**309 per 1,000** (247 to 393)	**RR 0.85** (0.68 to 1.08)	961 (3 RCTs)[1-3]	⊕⊕⊕⊕ High	Prebiotic supplementation results in little to no difference in AD by 6mo to 2 years old in high-risk populations.
AD by 1 year - *General population* assessed with: cumulative incidence of AD follow-up: 1 year *CRITICAL*	96 per 1,000	**55 per 1,000** (32 to 93)	**HR 0.56** (0.32 to 0.97)	830 (1 RCT)[4]	⊕⊕⊕◯ Moderate[a]	The rate of AD at 1 year is significantly lower in infants with a low risk of atopy taking a prebiotic supplement.
Adverse events assessed with: infants with AEs follow-up: 18 months *IMPORTANT*	942 per 1,000	**923 per 1,000** (895 to 961)	**RR 0.98** (0.95 to 1.02)	863 (1 RCT)[2]	⊕⊕⊕⊕ High	Prebiotic supplementation results in little to no difference in adverse events.
Infections assessed with: infants with physician-diagnosed or caregiver-reported infections follow-up: range 18 months to 24 months *IMPORTANT*	Arslanoglu 2008 reported 4.1±3.1 episodes of infection with prebiotics supplementation (n=66) vs 5.9±4.1 episodes with placebo (n=68).[1] Boyle 2016 reported 18/432 (4.2%) infants taking prebiotic supplements with infection vs 20/431 (4.6%) controls: RR 0.90 (0.48, 1.67).[2]			997 (2 RCTs)	⊕⊕⊕⊕ High	Overall rates of infection were low but prebiotic supplementation may slightly reduce risk.
Gastrointestinal issues assessed with: infants with gastrointestinal issues follow-up: range 18 months to 24 months *IMPORTANT*	Boyle 2016 reported GI issues related to formula in 69/432 (16%) taking prebiotics vs 65/431 (15%) controls: RR 1.06 (0.78, 1.45).[2] Ranucci 2018 reported acute diarrhea in 50/118 (42%) infants taking prebiotics vs 50/104 (48%) controls: RR 0.88 (0.66, 1.18).[3]			1085 (2 RCTs)	⊕⊕⊕⊕ High	Overall rates of GI issues were moderate but may be slightly higher with prebiotic supplementation.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** confidence interval; **HR:** hazard Ratio; **RR:** risk ratio

Explanations

a. Downgraded one level for imprecision due to wide CI consistent with meaningful risk reduction and trivial effect.

Table. Included study characteristics

Study	Population (n)	Age at intervention (days)	Duration of intervention (months)	Age at AD assessment (months)	Intervention	Comparator
Arslanoglu 2008	High risk (152)	0-14	6	24	8 g/L of neutral short-chain galactooligosaccharides and long-chain fructooligosaccharides in hypoallergenic formula	Placebo supplement in hypoallergenic formula

Boyle 2016	High risk (758)	0-28	6	18	8g/L oligosaccharides in partially hydrolyzed whey formula	Partially hydrolyzed whey formula
Gruber 2010	Low risk (830)	0-56	6	12	8g/L oligosaccharides in cow's milk formula	Cow's milk formula
Ranucci 2018	High risk (400)	0-2	12	24	galacto-oligosaccharide/polydextrose formula	Standard formula

References

1. 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.
2. 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.
3. 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.
4. 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.

Table 9. Synbiotic Supplementation

Synbiotic supplementation compared to no synbiotics for primary prevention of AD

Patient or population: healthy, full-term infants aged 12 months or younger
Setting: primary prevention
Intervention: Lactobacillus rhamnosus LCS-742, Bifidobacterium longum subsp infantis M63, galacto-oligosaccharides and short-chain fructo-oligosaccharides supplemented formula for 6 mos
Comparison: Standard formula for 6 mos

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no synbiotics	Risk with synbiotics				
AD by 6 mos- *General population* assessed with: cumulative incidence of AD follow-up: 6 months	178 per 1,000	**26 per 1,000** (3 to 196)	**RR 0.144** (0.019 to 1.100)	84 (1 RCT)[1]	⨁⨁◯◯ Low[a]	Synbiotic supplementation may result in a reduction in AD at 6 mos in the general population but the evidence is limited.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** confidence interval; **RR:** risk ratio

Explanations
a. Downgraded 2 levels for imprecision due to very small sample and number of events with wide CI consistent with important reduction in risk and little risk difference.

References

1. 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.

Table 10. Fatty Acid Supplementation

Fatty acid supplementation compared to no supplementation for primary prevention of AD

Patient or population: healthy, full-term infants aged 12 months or younger
Setting: primary prevention
Intervention: Fatty acid supplementation
Comparison: no acid supplementation

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with no supplementation	**Risk with Fatty acid supplementation**				
AD by 3 years-*General population* assessed with: cumulative incidence of AD follow-up: 3 years CRITICAL	333 per 1,000	**183 per 1,000** (87 to 400)	**RR 0.55** (0.26 to 1.20)	89 (1 RCT)[1]	⊕◯◯◯ Very low[a,b]	The evidence is very uncertain about the effect of fatty acid supplementation on AD by 3 years old in the general population.
AD at 12 or 18 months- *High risk populations* assessed with: prevalence of AD follow-up: range 12 months to 18 months IMPORTANT	228 per 1,000	**203 per 1,000** (153 to 267)	**RR 0.89** (0.67 to 1.17)	672 (2 RCTs)[2, 3]	⊕⊕⊕◯ Moderate[c]	Fatty acid supplementation likely results in little to no difference in the prevalence of AD at 12 or 18 months in high risk infants.
AD at 9 months- *General population* assessed with: prevalence of AD follow-up: 9 months IMPORTANT	One study reports adjusted odds of AD at 9 mos of 1.2(0.7, 2.1) for infants receiving fatty acid supplemented formula for 6 mos compared to infants not receiving the supplement.			241 (1 RCT)[4]	⊕⊕◯◯ Low[d,e]	The evidence is uncertain about the effect of fatty acid supplementation on AD at 9 months in the general population .
Gastrointestinal issues assessed with: number of events follow-up: range 6 months to 9 months CRITICAL	Two studies report similar rates of GI events in infants receiving a fatty acid supplement compared to infants on the control diet: 15 events in 186 infants vs 19 events in 173 infants, respectively.			359 (2 RCTs)[3, 4]	⊕⊕◯◯ Low[f,g]	Fatty acid supplementation may result in little to no difference in gastrointestinal issues.
Adverse events assessed with: rate of events follow-up: range 9 months to 3 years CRITICAL	Two studies report no significant differences in the rates of nonallergic respiratory illnesses, infections, cognitive development or growth between fatty acid supplementation and no supplementation.			330 (2 RCTs)[1, 4]	⊕◯◯◯ Very low[a,h]	The evidence is very uncertain about the effect of fatty acid supplementation on adverse events.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** confidence interval; **RR:** risk ratio

Explanations

a. Downgraded twice for risk of bias due to incomplete methods reporting and missing outcome data.
b. Downgraded once for imprecision due to wide CI consistent with meaningful reduction and increased risk.
c. Downgraded once for imprecision due to small event rate leading to a wide CI consistent with meaningful reduction and little to no risk difference.
d. Downgraded once for risk of bias due to missing outcome data.
e. Downgraded once for imprecision due to wide CI consistent with no risk difference and large increase in risk.
f. Downgraded once for risk of bias due to missing outcome data and minimal outcome reporting.
g. Downgraded once for small event rate.
h. Downgraded once for imprecision due to small sample.

Table. Included study characteristics

Study	Population (n)	Age at intervention (days)	Duration of intervention (months)	Age at AD assessment (months)	Intervention	Comparator
Birch 2010	General (179)	1-5	12	36	Long-chain polyunsaturated fatty acid supplemented standard formula	Standard formula
Lucas 1999	General (309)	1-7	6	9	Long-chain polyunsaturated fatty acid supplemented standard formula	Standard formula
Mihrshahi 2003	High risk (556)	1	6	12	Long-chain polyunsaturated fatty acid supplement 500mg daily + standard diet	Standard diet
Van Gool 2003	High risk (121)	1-14	6	12	Long-chain polyunsaturated fatty acid supplement (135mg) with vitamin C & E 1g daily	Placebo

References

1. 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.
2. 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.
3. 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.
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Table 11. Enriched Formula

Enriched formula compared to standard formula for primary prevention of AD

Patient or population: healthy, full-term infants aged 12 months or younger
Setting: primary prevention
Intervention: bovine milk fat globule membrane and lactoferrin enriched formula for 12 months
Comparison: standard formula for 12 months

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard formula	Risk with enriched formula				
AD by 18 months assessed with: cumulative incidence of AD follow-up: 18 months CRITICAL	39 per 1,000	**31 per 1,000** (12 to 118)	**RR 0.795** (0.301 to 2.980)	451 (1 RCT)[1]	⨁⨁◯◯ Low[a,b]	Enriched formula may result in little to no difference in AD by 18 months.
Gastrointestinal issues Assessed with: infants with a reported GI AE follow-up: 18 months CRITICAL	689 per 1,000	**585 per 1,000** (510 to 675)	**RR 0.85** (0.74 to 0.98)	451 (1 RCT)[1]	⨁⨁⨁◯ Moderate[a]	GI issues were common across both groups but enriched formula probably reduces gastrointestinal AEs slightly.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** confidence interval; **RR:** risk ratio

Explanations
a. Downgraded once for risk of bias due to unclear methods reporting and concerns with missing outcome data.
b. Downgraded once for imprecision as wide CI consistent with meaningful reduction and increase in risk.

References

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Table 12. PHWFs

PHWFs compared to standard formula for primary prevention of AD

Patient or population: healthy, full-term infants aged 12 months or younger
Setting: primary prevention
Intervention: partially hydrolyzed whey formula (pHWF)
Comparison: standard formula

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard formula	Risk with pHWFs				
AD by 36 months- *High risk populations* assessed with: cumulative incidence of AD follow-up: range 6 months to 36 months CRITICAL	282 per 1,000	**175 per 1,000** (119 to 257)	**RR 0.62** (0.42 to 0.91)	1698 (8 RCTs)[1-8]	⊕⊕◯◯ Low[a,b]	PHWFs may reduce AD by 36 months in high risk populations.
AD by 24 months- *General population* assessed with: cumulative incidence of AD follow-up: 24 months CRITICAL	77 per 1,000	**12 per 1,000** (1 to 217)	**RR 0.15** (0.01 to 2.82)	76 (1 RCT)[9]	⊕◯◯◯ Very low[c,d]	The evidence is very uncertain about the effect of pHWFs on AD by 24 months in the general population.
Adverse events assessed with: infants experiencing AEs follow-up: range 4 months to 6 months CRITICAL	Two studies narratively report no general or digestive reactions, feeding problems, or infections in infants fed pHWF or standard formula.			174 (2 RCTs)[4, 8]	⊕◯◯◯ Very low[e,f]	The evidence is very uncertain about the adverse effects of pHWFs compared to standard formula.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** confidence interval; **RR:** risk ratio

Explanations
a. Downgraded once for risk of bias as the majority of studies were of a high risk due to missing outcome data, concerns with outcome reporting, and/or unmasked outcome assessment.
b. Downgraded once for imprecision as CI consistent with meaningful risk reduction and minimal risk difference.
c. Downgraded once for risk of bias due to minimal methods reporting and randomization based on birth month.
d. Downgraded twice for imprecision due to a very low event rate leading to a very wide CI consistent with a very large reduction or increase in risk.
e. Downgraded twice for risk of bias as the outcome was not systematically assessed or reported.
f. Downgraded once for imprecision as the total sample and event rate in very low.

Table. Included study characteristics

Study	Population (n)	Age at intervention (days)	Duration of intervention (months)	Age at AD assessment (months)	Intervention	Comparator
Chan 2002	High risk (153)	1	4	24	partially hydrolyzed whey formula	conventional cow's milk formula
Chandra 1991	High risk (72)	1	6	18	partially hydrolyzed whey formula	conventional cow's milk formula
Chirico 1997	High risk (35)	1	6	6	partially hydrolyzed whey formula	conventional cow's milk formula
Juvonen 1996	General (144)	1	3 days	24	partially hydrolyzed whey formula	conventional cow's milk formula
Lowe 2011	High risk (620)	1-180	Up to 24	24	partially hydrolyzed whey formula	conventional cow's milk formula

Mallet 1992	High risk (177)	1	4	24	partially hydrolyzed whey formula	adapted cow's milk formula
Nicolaou 2022	High risk (331)	1-70	Up to 6	6	partially hydrolyzed whey formula	conventional cow's milk formula
Vanderplas 1995	High risk (58)	1-5	6	12-36	partially hydrolyzed whey formula	conventional cow's milk formula
Von Berg 2003	High risk (2252)	1	6	12	partially hydrolyzed whey formula	conventional cow's milk formula

References

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Table 13. Soy Formula

Soy formula compared to standard formula for primary prevention of AD

Patient or population: Healthy, full-term infants aged 12 months or younger at high risk for atopy
Setting: primary prevention
Intervention: soy-based formula
Comparison: conventional cow's milk formula

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard formula	**Risk with soy formula**				
AD by 24 months- *High risk populations* assessed with: cumulative incidence of AD follow-up: range 18 months to 24 months CRITICAL	423 per 1,000	**448 per 1,000** (368 to 545)	**RR 1.06** (0.87 to 1.29)	528 (2 RCTs)[1, 2]	⨁⨁◯◯ Low[a,b]	Soy formula may result in little to no difference in AD by 2 years old in high risk infants.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** confidence interval; **RR:** risk ratio

Explanations
a. Downgraded once for risk of bias due to concerns about adherence to study interventions and selective outcome reporting.
b. Downgraded once for imprecision due to a small event rate leading to a wide CI consistent with meaningful risk reduction and increase.

References

1. 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.
2. 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.

Table 14. Goat Milk Formula

Goat milk formula compared to cow milk formula for primary prevention of AD

Patient or population: Healthy, full-term infants aged 12 months or younger
Setting: primary prevention
Intervention: goat milk formula
Comparison: cow milk formula

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with cow milk formula	Risk with goat milk formula				
AD by 1 year- *General populations* assessed with: cumulative incidence of AD follow-up: range 6 months to 12 months CRITICAL	159 per 1,000	**103 per 1,000** (56 to 194)	**RR 0.65** (0.35 to 1.22)	256 (2 RCTs)[1, 2]	⨁◯◯◯ Very low[a,b,c]	The evidence is very uncertain about the effect of goat milk formula on AD by 12 months old in the general population.
Gastrointestinal issues assessed with: infants with GI issues follow-up: 12 months CRITICAL	GI issues including vomiting, and loose or blood-stained stool occurred at equitable rates in the goat and cow milk formula groups.			200 (1 RCT)[1]	⨁⨁⨁◯ Low[d]	The rate of gastrointestinal issues with goat's milk formula may be similar to the rate with cow's milk formula.
Nutritional adequacy assessed with: weight, length, biomarker follow-up: 12 months IMPORTANT	Two studies (n=200) found no differences in weight, length, or biomarkers of nutritional status at 4 to 6 months.[1, 2]			200 (1 RCT)[1]	⨁⨁⨁◯ Low[d]	The nutritional adequacy of goat's milk formula may be similar to that of cow's milk.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** confidence interval; **RR:** risk ratio

Explanations
a. Downgraded once for risk of bias as both studies report AD as an adverse event with limited information of the assessments of the outcome.
b. Downgraded once for inconsistency as one study suggests a protective effect and the other suggests (with extreme imprecision) increased risk.
c. Downgraded twice for imprecision as very small number of events led to a wide CI consistent with meaningful risk reduction and little to no risk difference.
d. Downgraded twice for imprecision due to small samples.

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Table 15. Short-term Early Hydrolyzed Formula

Short-term early hydrolyzed formula feeding compared to breast milk for primary prevention of AD

Patient or population: Healthy, full-term infants aged 12 months or younger
Setting: primary prevention of AD
Intervention: casein hydrolyzed formula for 3 days after birth, then breastfeeding
Comparison: breast milk from birth

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with breast milk	**Risk with short term early hydrolyzed formula feeding**				
AD by 2 years- *General population* assessed with: cumulative incidence of AD follow-up: 24 months CRITICAL	57 per 1,000	**27 per 1,000** (3 to 250)	**RR 0.48** (0.05 to 4.41)	90 (1 RCT)[1]	⨁◯◯◯ Very low[a,b]	The evidence is very uncertain about the effect of short term early hydrolyzed formula feeding on AD by 24 months in the general population.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** confidence interval; **RR:** risk ratio

Explanations
a. Downgraded twice for risk of bias due to quasi-randomized design, potential baseline imbalances, and attrition bias.
b. Downgraded twice for imprecision due to very small number of events leading to very wide CI consistent with very large risk reduction and increase.

References

1. 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.

Table 16. Allergic conjunctivitis

Question: Is allergic conjunctivitis associated with pediatric AD?

№ of studies	Certainty assessment						Impact Effect estimates presented as odds ratios (OR) with (95%CI)	Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Prevalence of allergic conjunctivitis in AD (follow-up: Cross-sectional; assessed with: Pooled prevalence of co-occurring allergic conjunctivitis in children with AD)									
3[1-3]	observational studies	not serious	serious[a]	not serious	serious[b]	none	The pooled prevalence of AC in children with AD (n= 41,169) was **10.2% (0, 22.0).**	⨁⨁◯◯ Low	IMPORTANT
Association between allergic conjunctivitis & AD (follow-up: Cross-sectional; assessed with: Odds of having AC in children with AD compared to children without AD)									
1[2]	observational studies	not serious	serious[c]	not serious	not serious	none	One study suggested higher *adjusted* odds of AC in children with AD: **aOR 1.99 (1.59, 2.49).**[2]	⨁⨁⨁◯ Moderate	CRITICAL

AD: Atopic dermatitis; **AC:** Allergic conjunctivitis; **aOR:** Adjusted odds ratio; **CI:** Confidence interval

Explanations

a. Estimates vary widely across the studies.
b. CI consistent with substantially lower rates than expected in the general population and expected rates.
c. One study suggests increased odds and one study suggests a protective effect.

References

1. 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.
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3. 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.

Table 17. Allergic rhinitis

Question: Is allergic rhinitis associated with pediatric AD?

№ of studies	Certainty assessment						Impact Effect estimates presented as odds ratios (OR) and (95%CIs)	Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Prevalence of comorbid allergic rhinitis & AD (follow-up: Cross-sectional; assessed with: Pooled prevalence of co-occurring allergic rhinitis in children with AD, and vice versa)									

№ of studies	Certainty assessment						Impact Effect estimates presented as odds ratios (OR) and (95%CIs)	Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
18[1-18]	observational studies	serious[a]	serious[b]	not serious	not serious	none	The pooled prevalence of AR in children with AD (n= 693488) is **30.0% (23.7, 36.2).**[1-11, 15-18] The pooled prevalence of AD in children with AR (n= 1585) is **44.1% (28.0, 60.3).**[12-14] <u>Prevalence by severity</u> One study examined AR prevalence by AD severity based on treatment in 404,111 pediatric AD cases and found prevalences of **6.27%, 12.79%,** and **9.79%** in mild, moderate, and severe cases of AD, respectively.[15]	⊕⊕◯◯ Low	IMPORTANT
Association between allergic rhinitis & AD (follow-up: Cross-sectional; assessed with: Odds of having AR in children with AD compared to children without AD, and vice versa)									
9[3, 4, 7, 11, 12, 19-22]	observational studies	serious[c]	not serious	not serious	not serious	none	In the pooled analysis of 5 studies[4, 7, 11, 12, 19], children with AD had higher *adjusted* odds of AR: **aOR 3.59 (2.19, 5.88).** Similarly, one study suggested children with AD have higher *unadjusted* odds of AR: **OR 1.90 (1.57, 2.30).**[20] One study suggests higher *adjusted* odds of AD in children with AR: **aOR 6.21 (5.93, 6.50).**[21] <u>Association by severity</u> One study suggests the *unadjusted* odds of AD in patients with mild AR vs moderate and severe AR^ were **1.69 (1.09-2.62)** and **1.79 (1.13, 2.84),** respectively.[22] Another study suggests that among children with AD, those with AR were **3.4 (1.7, 6.6)** times as likely to report severe AD* compared to children without AR.[3]	⊕⊕⊕◯ Moderate	CRITICAL
Occurrence of allergic rhinitis in AD (follow-up: 3 to approximately 18 years; assessed with: Odds or risk of subsequent AR in children with prior AD compared to children without AD)									
10[5, 9, 14, 23-29]	observational studies	serious[d]	not serious	not serious	not serious	none	In the pooled analysis of 8 studies children with AD had higher odds of subsequent diagnosis of AR: **aOR 2.20 (1.88, 2.59).** One study suggests an increased risk of subsequent AR in children with AD**: aHR 1.40 (1.38, 1.42).**[28] One study suggests an increased risk of AR in children with early on-set AD (dx <1 yo) compared to children without early on-set AD^^: **aHR 2.01 (1.94, 2.09)**[29]	⊕⊕⊕◯ Moderate	CRITICAL

AD: Atopic dermatitis; **AR:** Allergic Rhinitis; **aOR:** Adjusted odds ratio; **CI:** Confidence interval

^Severity based on a modified ARIA classification
*Severity assessed via POEM

Explanations
a. Ten of the 17 studies included in the prevalence data were rated high for risk of bias.
b. Prevalence estimates varied widely.
c. Four of the nine studies relied on unvalidated exposure and/or outcome assessment and were of a high risk of bias.
d. Four of the ten studies relied on unvalidated exposure and/or outcome assessment were rated high for risk of bias.

References

1. 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.
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Table 18: Eosinophilic esophagitis

Question: Is eosinophilic esophagitis associated with pediatric AD?

№ of studies	Certainty assessment						Impact Effect estimates presented as odds ratios (OR) and (95%CIs)	Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Prevalence of AD in EoE (follow-up: Cross-sectional; assessed with: Pooled prevalence of AD in children with EoE)									
6[1-6]	observational studies	serious[a]	not serious	not serious	not serious	none	The pooled prevalence of AD in children with EoE (n= 3020) is **21.8% (7.8%-35.8%).**	⊕⊕⊕◯ Moderate	IMPORTANT
Association between EoE and AD (assessed with: Odds of having EoE in children with AD compared to children without AD)									
1[7]	observational studies	not serious	not serious	not serious	not serious	none	One study suggested higher odds of EoE in children with AD: **aOR 5.22 (4.12-6.61).**	⊕⊕⊕⊕ High	CRITICAL
Occurrence of EoE in AD (follow-up: Up to 17 years; assessed with: Risk of subsequent EoE in children with a prior AD diagnosis compared to children without AD)									
3[5, 8, 9]	observational studies	not serious	not serious	not serious	not serious	none	The pooled risk of EoE in children with AD is: **aHR 4.57 (2.23-9.39).**[8, 9] One other study suggeste higher odds of subsequent EoE in children with AD: **aOR 1.97 (1.64–2.36)**.[5]	⊕⊕⊕⊕ High	CRITICAL

AD: Atopic dermatitis; **EoE:** Eosinophilic Esophagitis **aOR:** Adjusted odds ratio; **HR:** Hazard ratio**; CI:** Confidence interval

Explanations
a. Four of six of the studies included were rated as having high risk of bias.

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Table 19: Food Allergies

Question: Are food allergies associated with pediatric AD?

№ of studies	Certainty assessment						Impact Effect estimates presented as odds ratios (OR) with (95%CI)	Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Prevalence of comorbid AD & FA (follow-up: Cross-Sectional; assessed with: Prevalence of FA in children with AD, and vice versa)									
33[1-33]	observational studies	serious[a]	serious[b]	not serious	not serious	dose response gradient[c]	The pooled prevalence of FA in children with AD (n= 682736) is **23.6% (21.7, 25.4)**.[2, 3, 5, 9-11, 14-16, 21, 24, 26-31, 33] One study of peanut allergy in children with AD (n=195) found a prevalence of **18%.**[12] <u>Prevalence by severity</u> Five studies report increasing FA prevalence with increasing AD severity[5, 10, 11, 23, 34]: *SCORAD 15-40* **30%** vs *SCORAD >40* **50%** *SCORAD<25* **21.6%-23.1% vs** *SOCRAD <u>></u>25* **36.9%-90.7% vs** *SCORAD >50* **44.2%** *Mild-to-moderate AD** **14.1% vs** *Severe AD* **27.0%**	⊕⊕◯◯ Low	IMPORTANT

№ of studies	Certainty assessment						Impact Effect estimates presented as odds ratios (OR) with (95%CI)	Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
							Two studies[9, 30] did not report an increasing prevalence of FA with increasing AD severity[†]: **SCORAD 0-16 6.2%** **SCORAD 16-30 8.2%** **SCORAD 31-40 6.5%** **SCORAD 41-60 21.4%** and **SCORAD >60 31.7%** <u>AD in children with FA</u> The pooled prevalence of AD in children with FA (n= 5,368) was **60.1% (25.3%-95.0%)**.[1, 17-20, 25] The pooled prevalence of AD in children with peanut allergy (n= 1,253,153) was **57.8% (43.9%-71.8%)**.[4, 7, 8, 13] The prevalence of AD in children with an egg allergy (n=315) was **91%** and **75%** in children with a shrimp allergy (n=67) AD.[6, 22, 32]		
Association between food allergies & AD (follow-up: Cross- Sectional; assessed with: Odds of having food allergies in children with AD compared to children without AD, and vice versa)									
16[3, 4, 12, 14, 19-21, 35-43]	observational studies	serious[d]	not serious[e]	not serious	not serious	none	In the pooled analysis of 6 studies, children with AD had higher *adjusted* odds of FA: **aOR 6.53 (3.89, 10.96).**[3, 20, 37-39, 43] Similarly, in the pooled analysis of 3 studies, children with AD had higher *unadjusted* odds of FA: **OR 3.70 (3.06, 4.47).**[19, 21, 35] Children with AD had higher *unadjusted* odds of egg allergy in one study but no association with **egg allergy** in another *adjusted* analysis: **OR 4.43 (1.23 to 15.94)**[36] **aOR 1.995 (0.80, 4.98)**[41] Children with AD had higher odds of **cow milk allergy**: **aOR 4.73 (1.07-20.79).**[41] Children with AD by 18 months had higher odds of **peanut or egg allergy**: **aOR 4.08 (1.10, 15.19).**[42] Children with AD had higher odds of FA at ages 1-3 but not 4-5: **aORs 3.6 (1.8-7.1), 2.7(1.3-5.7), 2.6(1.1-6.3), 1.5(0.5-4.6),** and **1.8(0.6-5.7)** at ages one to five years, respectively.[40]	⊕⊕⊕◯ Moderate	CRITICAL

№ of studies	Certainty assessment						Impact Effect estimates presented as odds ratios (OR) with (95%CI)	Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
							Children with **peanut allergy** had higher odds of AD than did children without peanut allergy: **OR 3.80 (3.56, 4.07).**[4] <u>Association by severity</u> Compared to mild AD, children with moderate and severe AD‡ had increasingly higher odds of FA[14]: *Moderate AD* **aOR 2.4 (1.2-4.8)** *Severe AD* **aOR 7.8 (1.9-31.4).** In children with AD, odds of peanut allergy were higher for each 5-point increase in SCORAD score: **aOR 1.19 (1.06-1.34)**.[12]		
Occurrence of FA in AD (or vice Versa) (follow-up: Up to 15 years; assessed with: Odds/risk of subsequent diagnosis of FA in children previously diagnosed with AD, or vice versa)									
7[35, 44-49]	observational studies	serious[f]	not serious	not serious	not serious	none	In the pooled *adjusted* analysis of 2 studies, children with a prior diagnosis of AD at age 1, had higher odds of a subsequent diagnosis of FA: **aOR 3.14 (2.11, 4.67)**.[35, 44] Similarly, children with AD and 1 or 2 had higher *unadjusted* odds of a subsequent FA diagnosis at 4 than did controls without AD: **OR 2.36 (1.24-4.48)**.[45] Children with a prior diagnosis of AD followed for up to 15 years had a higher risk of a subsequent diagnosis of FA**: aHR 1.40 (1.34, 1.47)**.[48] Children with AD by 1, had higher odds of subsequent **peanut allergy** at 8 than did controls without AD: **aOR 4.43 (1.49-13.2).**[46] Children with AD at 1 that persisted to age 3 had higher odds of subsequent FA diagnosis: **aOR 11.79 (10.72, 12.98).**[47] One study suggests an increased risk of FA in children with early on-set AD (dx <1 yo) compared to children without early on-set AD^: **aHR 4.76 (4.44, 5.10)[49]**	⊕⊕⊕◯ Moderate	CRITICAL

AD: Atopic dermatitis; **FA:** Food allergies; **aOR:** Adjusted odds ratio; **CI:** Confidence interval

***** Severity reported by caregivers in response to the following: "Would you describe (child's) eczema as mild, moderate, or severe?"
† The majority of this data was extracted using the WebPlotDigitizer program.
‡ Severity assessed by SCORAD index, where mild AD<25, moderate was 25-50, and severe was >50.
^1.07% of the AD cohort had a FA diagnosis before their AD diagnosis

Explanations
a. Studies primarily relied on unvalidated and/or self-reported exposure and/or outcome assessment; 19/33 studies were rated as moderate to high risk of bias.

b. Prevalence estimates varied widely across studies in all analyses; I^2 for pooled estimates were 99.84% for AD in FA, 99.67% for AD in peanut allergy, and 99.59% in FA in AD, all indicating significant heterogeneity.
c. Prevalence by AD severity data is suggestive of a dose response gradient but the certainty of the evidence was not upgraded due to downgrading for risk of bias and inconsistency.
d. Studies primarily relied on unvalidated and/or self-reported exposure and/or outcome assessment; Seven of the 16 studies were rated as having high risk of bias.
e. All but one allergy-specific study report ORs consistent with a significant positive association between FAs and AD. The reported magnitudes of associations are also largely consistent.
f. Studies primarily relied on unvalidated and/or self-reported exposure and/or outcome assessment; 6/7 studies were rated as moderate or high risk of bias.

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Table 20. Asthma

Question: Is asthma associated with pediatric AD?

№ of studies	Certainty assessment						Impact Effect estimates presented as odds ratios (OR), risk ratios (RR) or hazard ratios (HR) with (95%CI)	Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Prevalence of comorbid asthma & AD (follow-up: Cross-sectional; assessed with: Pooled prevalence of asthma in children with AD, and vice versa)									
44[1-44]	observational studies	serious[a]	not serious[b]	not serious	not serious[c]	none	The pooled prevalence of asthma in children with AD (n= 955,098) is **21.4% (19.6, 23.1).**[1-26, 36-42, 44] The pooled prevalence of AD in children with asthma (n=117,164) is **30.1% (11.8, 48.5).**[27-34, 43] <u>Prevalence by severity</u> One study reported an increased prevalence of asthma in severe AD compared to mild-to-moderate disease* (36.9% vs 24.3%, respectively.[35] Similarly, another study reported increasing asthma prevalence in children with clear/almost clear, mild, moderate, and severe AD†: 22.9%, 26.5%, 35.7%, and 35.7%, respectively.[3] However, a third study reported the highest prevalence of asthma in children with moderate AD‡ (27.2%) compared to mild (13.0%) and severe (23%) disease.[23]	⊕⊕⊕◯ Moderate	IMPORTANT
Association between asthma & AD (follow-up: Cross-sectional; assessed with: Odds of having asthma in children with AD compared to children without AD, and vice versa)									
20[2, 4, 9-11, 18, 20, 23, 26, 28-31, 33, 34, 45-49]	observational studies	serious[a]	not serious	not serious	not serious	none	In the pooled *adjusted* analysis of 9 studies, children with AD have higher odds of asthma: **aOR 3.03 (2.30, 4.01)**.[4, 9, 18, 26, 45-49] Similarly, in the pooled *unadjusted* analysis of 5 additional studies, children with AD had higher odds of asthma: **OR 2.65 (1.72, 4.08).**[2, 10, 11, 20, 23] In the pooled *adjusted* analysis of 2 studies, children with asthma have higher odds of AD: **aOR 2.60 (2.37, 2.86)**.[29, 30] Similarly, in the pooled *unadjusted* analysis of 4 additional studies, children with asthma had higher odds of asthma: **OR 3.34 (1.71, 6.53).**[28, 31, 33, 34]	⊕⊕⊕◯ Moderate	CRITICAL
Occurrence of asthma in AD (follow-up: up to 18 years; assessed with: Risk of subsequent diagnosis of asthma in children diagnosed with early AD [0-6] or children diagnosed at any age with AD compared to children without AD)									
14[5, 13, 25, 40, 50-59]	observational studies	serious[d]	not serious	not serious	not serious	none	In the pooled analysis of 6 studies, children with a prior diagnosis of AD between the ages of 0-2, have higher odds of a subsequent diagnosis of asthma: **aOR 1.92 (1.66, 2.21)**.[5, 25, 50-52, 56] In the pooled analysis of 2 studies, children with a prior diagnosis of AD between the ages of 0-2, have a higher *adjusted* risk of a	⊕⊕⊕◯ Moderate	CRITICAL

№ of studies	Certainty assessment						Impact Effect estimates presented as odds ratios (OR), risk ratios (RR) or hazard ratios (HR) with (95%CI)	Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
							subsequent diagnosis of asthma: **aRR 1.77 (1.43, 2.21)**.[54, 55] Similarly, children with an AD diagnosis between the ages 0-6 had a higher *unadjusted* risk of asthma at age 7: **RR 1.74 (1.70, 1.78).**[53] One study suggests an increased risk of asthma in children with early on-set AD (dx <1 yo) compared to children without early on-set AD^: **aHR 4.76 (4.44, 5.10)[59]** In the pooled analysis of 4 studies children with an AD diagnosis had a higher risk of a subsequent asthma diagnosis than children without AD: **aHR 1.75 (1.68, 1.83)**.[13, 40, 57, 58]		

AD: Atopic dermatitis; **aOR**: Adjusted odds ratio; **CI**: Confidence interval; **aHR:** Adjusted hazard ratio; **aRR**: Adjusted risk ratio

*Severity reported by caregivers in response to the question "Would you describe (child's) eczema or skin allergy as mild, moderate, or severe?"
† Severity determined via Patient-Oriented Eczema Measure (POEM)
‡ Severity determined by treatment: Mild AD= no treatment with following therapies; Moderate AD=(i) a second potent topical corticosteroid within 1 year, or (ii) a first topical calcineurin inhibitor; Severe AD= (i) systemic immunosuppressant treatment, (ii) phototherapy use or (iii) referral to dermatology (as 96% of AD patients in UK are managed exclusively by GPs)
^2.29% of the AD cohort had an asthma diagnosis before their AD diagnosis

Explanations
a. Studies relied primarily on unvalidated and/or self-reported exposure and/or outcome assessment; NOS scores ranged from 3-8 suggesting a moderate-to-high risk of bias.
b. Prevalence estimates varied widely across the studies, but the evidence was not downgraded due to the expected inherent variability in prevalence due to geographic location, setting, etc.
c. Although the prevalence estimate for co-occurring AD in asthma populations is imprecise, the evidence was not downgraded as the estimate for co-occurring asthma in AD populations is precise and was given greater weight in decision-making given direct alignment with the research question and more robust evidence base.
d. Studies relied primarily on unvalidated and/or self-reported exposure and/or outcome assessment; NOS scores ranged from 6-9 suggesting a low-to-moderate risk of bias.

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Table 21. Alopecia areata

Question: Is alopecia areata associated with pediatric AD?

№ of studies	Certainty assessment						Impact	Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Effect estimates presented as odds ratios (OR) with (95%CI)		
Prevalence of AD in children with AA (follow-up: Cross-sectional; assessed with: Pooled prevalence of co-occurring AD diagnosis in children with AA)									
3[1-3]	observational studies	serious[a]	serious[b]	not serious	not serious	none	The pooled prevalence of AD in children with AA (n=12,603) is **28.6% (23.3, 33.8)**.	⊕⊕◯◯ Low	IMPORTANT
Association between AD & AA (follow-up: Cross-sectional; assessed with: Odds of having AA in children with AD compared to children without AD, and vice versa)									
5[1, 4-7]	observational studies	serious[c]	not serious[d]	not serious	serious[e]	none	In the pooled analysis of 2 studies, children with AD have higher *unadjusted* odds of AA: **OR 3.17 (1.71, 5.86)**.[4, 6] Among hospitalized children, AD was associated with a diagnosis of AA: **aOR 23.58 (7.34, 75.76)**.[7] In the pooled analysis of 2 studies, children with AA have higher *unadjusted* odds of AD: **OR 4.99 (1.32, 18.80)**.[5]	⊕⊕◯◯ Low	CRITICAL
Occurrence of AA in AD (follow-up: Up to 18 years; assessed with: Risk of subsequent diagnosis of FA in children previously diagnosed with AD, or vice versa)									
3[8-10]	observational studies	not serious[f]	serious[g]	not serious	not serious[h]	none	The pooled analysis of 2 studies suggests no association between AD and subsequent diagnosis of AA: **aHR 1.96 (0.72, 5.35).** A second study suggests no association between subsequent diagnosis of AA in children with AD: **OR 1.29 (0.61, 2.72).**	⊕⊕◯◯ Low	CRITICAL

AD: Atopic dermatitis; **AA**: Alopecia areata; **aOR**: Adjusted odds ratio; **CI**: Confidence interval

Explanations

a. Studies relied on unvalidated or self-reported exposure and outcome assessment; NOS scores ranged from 3-5 suggesting a high risk of bias.
b. Prevalence estimates varied across the studies; Statistically significant heterogeneity I^2= 91.8%
c. Studies relied primarily on self-reported or unvalidated exposure and outcome assessment; NOS scores ranged from 4 to7 suggesting a moderate-to-high risk of bias.
d. Inconsistency driven by imprecision in the estimate of the effect of the smallest included study was noted but did not result in downgrading given the overall consistency of the data.
e. CIs for effect estimates in non-hospitalized children are consistent with minimal/weak positive association and strong/very strong positive association.
f. Both studies relied on unvalidated exposure and/or outcome assessment, but the NOS scores of 7-8 suggest a low risk of bias, not downgraded for borderline RoB concerns about validated assessment as downgraded for borderline inconsistency given the varied direction of effect estimates despite more weight given to the aHR.
g. The adjusted HR suggests a positive association, while the unadjusted OR does not.
h. The CI for the aHR is consistent with a positive association and this measure was given more weight than the imprecise unadjusted OR.

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Table 22. Urticaria

Question: Is urticaria associated with pediatric AD?

№ of studies	Certainty assessment						Impact Effects estimates presented as odds ratios with (95% CI)	Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Prevalence of comorbid urticaria & AD (follow-up: Cross-sectional; assessed with: Prevalence of urticaria in children with AD, and vice versa)									
10[1-10]	observational studies	serious[a]	serious[b]	not serious	not serious	none	The pooled prevalence of urticaria in children with AD (n= 54360) is **9.5% (7.2, 11.8).**[1-6] The pooled prevalence of AD in children with urticaria (n= 7080) is **16.7% (5.1%-24.8%).**[7-10]	⊕⊕◯◯ Low	IMPORTANT
Association between urticaria & AD (follow-up: Cross-sectional; assessed with: Odds of urticaria in children with AD compared to children without AD, and vice versa)									
6[1, 2, 5-7, 10, 11]	observational studies	serious[c]	not serious	not serious	not serious	none	The pooled analysis of 3 studies suggests higher *adjusted* odds of urticaria in children with AD: **aOR 2.98 (2.84 -3.14).**[5, 6, 11] Similarly, one study suggested higher *unadjusted* odds of urticaria in children with AD: **OR 2.79 (2.31, 3.36).**[2] Two studies suggested higher *adjusted* and *unadjusted* odds of AD in children with urticaria: **aOR 2.35 (2.03, 2.72)** [10] **OR 6.0 (2.60, 14.12)**[7] One study suggested the *unadjusted* prevalence ratio of urticaria in AD patients was **2.30 (2.15–2.46).**[1]	⊕⊕⊕◯ Moderate	CRITICAL
Occurrence of urticaria in AD (follow-up: up to 18 years; assessed with: Odds/risk of subsequent diagnosis of urticaria in children with AD compared to children without AD or vice versa)									

№ of studies	Certainty assessment						Impact Effects estimates presented as odds ratios with (95% CI)	Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
3[12-14]	observational studies	not serious	not serious	not serious	not serious	none	The pooled analysis of 2 studies suggests an increased risk of subsequent urticaria in children with AD: **aHR of 1.76 (1.42, 2.18).**[12, 14] One study suggested higher odds of subsequent AD in children with chronic urticaria: **aOR 2.92 (1.65, 5.19**).[13]	⊕⊕⊕⊕ High	CRITICAL

AD: Atopic dermatitis; **aOR:** Adjusted odds ratio; **aHR:** Adjusted hazard ratio**; CI:** Confidence interval

Explanations

a. Five of the ten studies included were rated as having high risk of bias.
b. Point estimates varied from 3.9%-26.9% for AD in urticaria and from 3.4% to 17.8% in urticaria in AD.
c. Cross-sectional; Two of the seven studies were rated as having high risk of bias.

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Table 23. Attention Deficit Hyperactivity Disorder

Question: Is ADHD associated with pediatric AD?

№ of studies	Certainty assessment						Impact	Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Effect estimates presented as odds ratios (OR), risk ratios (RR) or hazard ratios (HR) with (95%CI)		
Prevalence of ADHD in children with AD (follow-up: Cross-sectional; assessed with: Pooled prevalence of ADHD diagnosis in children with AD)									
12[1-12]	observational studies	serious[a]	serious[b]	not serious	not serious	none	The pooled prevalence of ADHD in children with AD (n=158,832) is **8.2% (6.4, 10.0).**	⊕⊕◯◯ Low	IMPORTANT
Association between ADHD & AD (follow-up: Cross-sectional; assessed with: Odds of having ADHD in children with AD compared to children without AD, and vice versa)									
13[3-5, 7, 8, 13-20]	observational studies	serious[c]	not serious	not serious	not serious	none	In the pooled analysis of 9 studies, children with AD have higher odds of ADHD: **aOR 1.43 (1.26, 1.63)**.[3-5, 7, 8, 13-16] In the pooled analysis of 4 studies, children with ADHD had higher odds of AD: **aOR 1.76 (1.38, 2.24)**.[17-20]	⊕⊕⊕◯ Moderate	CRITICAL
Occurrence of ADHD in early onset AD (follow-up: up to 18 years; assessed with: Risk of subsequent diagnosis of ADHD in children diagnosed with AD before the age of 4 compared to children without AD)									
4[6, 21-23]	observational studies	not serious[d]	not serious[e]	not serious	serious[f]	none	AD diagnosed between 0-4 years was ***not associated*** with subsequent ADHD diagnosis between the ages of 6 and 11**: aRR 1.27 (0.71, 2.28)**.[21] AD diagnosed between the ages of 1 and 4 was ***not associated*** with subsequent ADHD diagnosis between the ages of 10 and 18: **aOR 1.12 (0.80, 1.56)**.[6] Children with AD diagnosed between the ages of 1 month and 3 years old were more likely to have a subsequent diagnosis of ADHD: **aHR 2.92 (2.48, 3.45).[22]** A second study of the same population suggested children with AD diagnosed before the age of 2 were more likely to have a subsequent diagnosis of ADHD: **aHR 1.15 (1.12, 1.18).[23]**	⊕⊕⊕◯ Moderate	CRITICAL
Occurrence of ADHD in AD (follow-up: up to 18 years; assessed with: Risk of subsequent diagnosis of ADHD in children with a prior AD diagnosis compared to children without AD)									
6[24-29]	observational studies	not serious[d]	not serious	not serious	not serious	none	In the pooled analysis of 3 studies, children with a prior diagnosis of AD have higher odds of a subsequent diagnosis of ADHD: **aOR 1.31 (1.19, 1.45).[24-26]** Children with a previous diagnosis of AD by a hospital physician as either an inpatient or outpatient were more likely to have a subsequent hospital diagnosis of ADHD and moderate-to-severe* and severe AD were associated with greater risk increases[27]: **Overall aHR 1.65 (1.33, 2.05)** Mild AD 1.46 (0.85, 2.49)	⊕⊕⊕⊕ High	CRITICAL

№ of studies	Certainty assessment						Impact	Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Effect estimates presented as odds ratios (OR), risk ratios (RR) or hazard ratios (HR) with (95%CI)		
							Mild-Moderate AD 1.31 (0.88, 1.93) Moderate-Severe AD 1.84 (1.42, 2.38) Severe AD 3.23 (1.77, 5.90) In the pooled analysis of 2 studies, a previous diagnosis of AD (n=476,986) was ***not associated*** with a subsequent diagnosis of ADHD but one study suggests severe AD† was associated with a weak protective effect[28, 29]: **Overall polled aHR 1.12 (0.93, 1.34)** Mild AD aHR 1.02 (0.98, 1.06) Moderate AD aHR 1.05 (0.93, 1.18) Severe AD aHR 0.76 (0.58, 0.98)		

AD: Atopic dermatitis; **ADHD**: Attention deficit hyperactivity disorder; **aOR**: Adjusted odds ratio; **CI**: Confidence interval; **aHR:** Adjusted hazard ratio; **aRR**: Adjusted risk ratio

Footnotes

***** AD severity based on medication use: mild= no prescriptions filled as follows; mild-moderate AD=any filled prescription of moderately potent topical corticosteroid; moderate-severe AD= any filled prescription of potent topical corticosteroids or topical tacrolimus; severe AD= any filled prescription for very potent topical corticosteroid or systemic immunosuppressant.

† AD severity based on medication use: mild AD= no treatment with following therapies; moderate AD=(i) a second potent topical corticosteroid within 1 year, or (ii) a first topical calcineurin inhibitor; severe AD= (i) systemic immunosuppressant treatment, (ii) phototherapy use or (iii) referral to dermatology (as 96% of AD patients in UK are managed exclusively by GPs).

Explanations

a. Studies primarily relied on unvalidated or self-reported exposure and outcome assessment; NOS scores ranged from 4-8 suggesting a high-to- moderate risk of bias.

b. Prevalence rates varied widely across the studies ranging from 1.2% to 1.4% in the largest studies to 23.7% in the smallest study.

c. Studies primarily relied on unvalidated or self-reported exposure and outcome assessment; NOS scores ranged from 5-8 suggesting a low to moderate risk of bias.

d. While the studies relied primarily on unvalidated, medication proxy, or self-reported exposure and outcome assessment the NOS scores ranging from 7-8 suggest an overall low risk of bias.

e. Two estimates of effect are imprecise, suggesting modest decreases in risk to important increases. The third estimate of effect suggests a large magnitude of increased risk, while the final estimate suggests minimal/no important differences in risk. This borderline inconsistency did not lead to downgrading as the evidence was downgraded for borderline imprecision (see imprecision note).

f. Two of the four estimates of effect have CIs consistent with a protective effect and moderate-to-strong positive association.

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Table 24. Autism Spectrum Disorder

Question: Is ASD associated with pediatric AD?

№ of studies	Certainty assessment						Impact	Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Effect estimates presented as odds ratios (OR) or hazard ratios (HR) with (95%CI)		
Prevalence of comorbid ASD & AD (follow-up: Cross-sectional; assessed with: Pooled prevalence of ASD diagnosis in children with AD, and vice versa)									
7[1-7]	observational studies	serious[a]	serious[b]	not serious	serious[c]	none	The pooled prevalence of ASD in children with AD (n= 106,601) is 1**.5% (1.0, 2.1).**[3, 4, 6, 7] The pooled prevalence of AD in children with ASD (n= 10,498) is **10.0% (5.3, 14.6).**[1, 2, 5]	⊕◯◯◯ Very Low	IMPORTANT
Association between ASD & AD (follow-up: Cross-sectional; assessed with: Odds of having ASD in children with AD compared to children without AD, and vice versa)									
6[1, 3-5, 8, 9]	observational studies	serious[a]	not serious	not serious	serious[d]	none	In the pooled analysis of 4 studies, children with AD had higher odds of ASD: **aOR 2.12 (1.35, 3.33)**.[3, 4, 8, 9] In the pooled analysis of 2 studies, ASD in children was ***not associated*** with AD: **aOR 1.27 (0.90, 1.79)**.[1, 5]	⊕⊕◯◯ Low	CRITICAL
Occurrence of ASD in AD (follow-up: up to 13 years; assessed with: Risk of subsequent diagnosis of ASD in children with AD compared to children without AD, or vice versa)									
5[10-14]	observational studies	serious[e]	not serious[f]	not serious	not serious	none	In the pooled analysis of 4 studies, children with a prior diagnosis of AD were more likely to have a subsequent diagnosis of ASD: **aHR 1.33 (1.08, 1.65)**.[11-14] Children with a previous diagnosis of AD had higher odds of subsequent diagnosis of ASD**: aOR 1.10 (1.01, 1.20).**[10] <u>Risk by severity</u>[13] For 409, 431 children with a previous diagnosis of AD and 1,809,029 children without an AD diagnosis followed for an average of 5 years, mild and severe AD^ were ***not associated*** with an increased risk of a subsequent diagnosis of ASD: Mild AD: aHR 1.00 (0.96, 1.05) Moderate AD: aHR 1.25 (1.11, 1.41) Severe AD: aHR 1.04 (0.82, 1.31)	⊕⊕⊕◯ Moderate	CRITICAL

AD: Atopic dermatitis; **ASD**: Autism spectrum disorder; **aOR**: Adjusted odds ratio; **CI**: Confidence interval; **aHR:** Adjusted hazard ratio

^ AD severity was determined by medication use.

Explanations

a. Studies primarily relied on unvalidated or self-reported exposure and/or outcome assessment; NOS scores ranged from 5-9 suggesting a low to moderate risk of bias.

b. Prevalence rates varied widely across the studies in both analyses.

c. CI for the prevalence of ASD in AD is consistent with both lower and greater than expected rates given general global population prevalence estimates (~1%).

d. Both CIs are consistent with no/weak positive association and moderate/strong positive association.

e. Studies relied primarily on unvalidated exposure or outcome assessment; the NOS scores of 8 suggest an overall low risk of bias.
f. Inconsistency in the pooled HR analysis driven by the smallest included study is noted but did not result in downgrading for this borderline inconsistency.

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Table 25. Substance Use

Cigarette Smoking

Question: Is cigarette smoking associated with pediatric AD?

№ of studies	Certainty assessment						Impact Effect estimates presented as odds ratios (95% CI)	Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Association between cigarette smoking & AD (assessed with: Odds of cigarette smoking in children with AD compared to children without AD)									
6[1-6]	observational studies	serious[a]	not serious[b]	not serious[c]	not serious	none	In the pooled *adjusted* analysis of 5 studies, a history of AD is ***not associated*** with a history of/current cigarette smoking: **aOR 1.02 (0.90, 1.15).**[1, 2, 4-6] Similarly, an *unadjusted* analysis found ***no association*** between a history of AD in children and a history of cigarette smoking: **OR 0.98 (0.94, 1.02).**[3]	⨁⨁⨁◯ Moderate	CRITICAL

AD: Atopic dermatitis; **aOR**: Adjusted odds ratio; **CI**: Confidence interval

Explanations
a. All studies relied on self-reported exposure and outcome assessment; NOS scores of 6 suggest moderate risk of bias.
b. The smallest study contributed an effect estimate that is not consistent with the majority of the evidence, but the findings contributed minimally to the analysis.
c. The majority of the evidence is from surveys of Korean adolescents, this may impact the generalizability of the evidence to adolescents in other geographic and cultural contexts.

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Table 26. Drinking Alcohol

Question: Is drinking alcohol associated with pediatric AD?

№ of studies	Certainty assessment						Impact Effect estimates presented as odds ratios with (95% CI)	Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Association between alcohol drinking & AD (follow-up: Cross-sectional; assessed with: Odds of drinking alcohol in children with AD compared to children without AD)									
5[1-5]	observational studies	serious[a]	not serious	not serious[b]	not serious	none	In the pooled adjusted analysis of 4 studies, a history of and/or current AD was ***not associated*** with current drinking, including binge drinking: **aOR 1.03 (0.99, 1.08)**.[1, 3-5] However, compared to children without AD, children with a history of AD had higher *unadjusted* odds of a history of drinking alcohol**: OR 1.10 (1.07, 1.13).**[2]	⨁⨁⨁◯ Moderate	CRITICAL

AD: Atopic dermatitis; **aOR**: Adjusted odds ratio; **CI**: Confidence interval

Explanations
a. All studies relied on self-reported exposure and outcome assessment; NOS scores of 6 suggest a moderate risk of bias.
b. The majority of the evidence is from surveys of Korean adolescents, this may impact the generalizability of the evidence to adolescents in other geographic and cultural contexts.

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1. 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.
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Table 27. Illicit Substance Use

Question: Is illicit substance use associated with pediatric AD?

№ of studies	Certainty assessment						Impact Effect estimates presented as odds ratios with (95% CI)	Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Association between illicit drug use (excluding marijuana) & childhood AD (follow-up: up to 14 years; assessed with: Odds of illicit drug use, excluding marijuana, in the past year by children with AD compared to children without AD)									
1[1]	observational studies	serious[a]	not serious	not serious	not serious	none	A history of AD was ***not associated*** with illicit drug use in the past year: **aOR 1.13 (0.95, 1.33)**	⊕⊕⊕◯ Moderate	CRITICAL
Association between substance use & AD (follow-up: Cross-sectional; assessed with: Odds of substance use (expanded diagnostic clusters code PSY02) in children with AD compared to children without AD)									
1[2]	observational studies	serious[b]	not serious	not serious	not serious	none	AD was ***not associated*** with substance use: **aOR 1.09 (0.76, 1.56).**	⊕⊕⊕◯ Moderate	CRITICAL

AD: Atopic dermatitis; **aOR**: Adjusted odds ratio; **CI**: Confidence interval

Explanations

a. The study relied on self-reported exposure and outcome assessment; a NOS score of 6 suggests a moderate risk of bias.
b. The study relied on unvalidated outcome assessment; a NOS score of 7 suggests a low risk of bias.

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Table 28. Anxiety

Question: Is anxiety associated with pediatric AD?

№ of studies	Certainty assessment						Impact Effect estimates presented as odds ratios or hazard ratios with (95% CI)	Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Prevalence of comorbid anxiety and AD (follow-up: Cross-sectional; assessed with: Pooled rates of anxiety in children with AD and vice versa)									
10[1-10]	observational studies	serious[a]	serious[b]	not serious	not serious	none	The pooled prevalence of anxiety in children with AD across 7 studies (n=22,993,212) is **2.5% (2.2%, 2.9%).**[1, 3-6, 8, 9] One small study suggested the prevalence of AD in children with anxiety (n=188) was **32.4%**.[2] Prevalence by severity One study[6] suggested increasing anxiety prevalence with increasing AD severity as reported by caregivers: **mild AD 5.5%, moderate AD 9.1%, and severe AD 16.3%**. While 2 additional studies[3, 7] do not suggest a correlation between anxiety prevalence and AD severity as assessed via POEM: **clear 4.7%, mild AD 9.6%, moderate AD 8.6%,** and **severe AD 15.4%** or medication proxy **mild AD 0.49%, moderate AD 1.01%,** and **severe AD 0.64%.**	⊕⊕◯◯ Low	IMPORTANT
Association between anxiety & AD (follow-up: Cross-sectional; assessed with: Odds of anxiety in children with AD compared to children without AD, and vice versa)									
5[2, 4-6, 11]	observational studies	serious[a]	not serious	not serious	not serious	none	In the pooled analysis of 4 studies, children with AD have increased odds of anxiety: **aOR 1.33 (1.14, 1.57).**[4-6, 11] One study suggested children with anxiety had increased odds of AD: **aOR 8.80 (3.76, 20.58**).[2] Association by severity One study[6] suggested increasing odds of anxiety with increasing AD severity as reported by caregivers: *Mild AD* **aOR 1.44 (1.01, 2.05)** *Moderate AD* **aOR 2.18 (1.47, 3.23)** *Severe AD* **aOR 2.81 (1.28, 6.17)**	⊕⊕⊕◯ Moderate	CRITICAL
Occurrence of anxiety in AD (follow-up: up to 18 years; assessed with: Risk of subsequent diagnoses of anxiety in children with a prior AD diagnosis compared to children without AD)									
5[7, 8, 12-14]	observational studies	not serious[c]	serious[d]	not serious	not serious	none	A pooled analysis of 5 studies suggests increased risk of subsequent diagnosis of anxiety in children with AD: **aHR 1.45 (1.06, 1.99).** Occurrence by severity One study suggested a slight increase in risk of developing anxiety in mild AD^ (**aHR 1.08 [1.06, 1.10]**) but reduced risk in moderate (**aHR 0.81 [0.77, 0.84**]) and severe AD (**aHR 0.77 [0.70, 0.84**]).[7]	⊕⊕⊕◯ Moderate	CRITICAL

AD: Atopic dermatitis; **aOR**: Adjusted odds ratio; **aHR**: Adjusted hazard ratio; **CI**: Confidence interval

^ All patients with AD were considered to have mild disease by default. They were classified as having moderate AD at the first of receiving: (i) a second potent topical corticosteroid within 1 year, or (ii) a first topical calcineurin inhibitor (which is reserved in the UK for moderate AD). Patients were classified as having severe AD at the first of (i) systemic immunosuppressant treatment, (ii) phototherapy use or (iii) referral to dermatology (as 96% of AD patients are managed exclusively by GPs)

Explanations

a. All studies relied on unvalidated and/or self-reported exposure and/or outcome assessment; NOS scores ranged from 5-8 suggesting a low to moderate risk of bias.
b. Rates varied widely across studies, with 4 studies suggesting high rates and 3 studies suggesting low rates.
c. While the studies relied on unvalidated exposure and/or outcome assessment the NOS scores of 7-8 suggest an overall low risk of bias.
d. 3/5 studies suggest no association, while 2/5 studies suggest a positive association; there is a lack of overlap across some studies.

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Table 29. Depression

Question: Is depression associated with pediatric AD?

№ of studies	Certainty assessment						Impact Effect estimates presented as odds ratios or hazard ratios with (95% CI)	Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Prevalence of comorbid depression & AD (follow-up: Cross-sectional; assessed with: Prevalence of depression in children with AD, and vice versa)									
6[1-6]	observational studies	serious[a]	serious[b]	not serious	not serious[c]	none	The pooled prevalence of depression in children with AD across 5 studies (n=473,343) is **1.9% (1.3, 2.4)**.[1, 2, 4-6] One study suggested the rate of AD in children with depression (n=46) was **30.4%**.[3] <u>Prevalence by severity</u> One study suggested that 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%.**[5] While a second study suggested no correlation between increasing AD severity as determined by medication use and prevalence of depression: **mild AD 0.21%, moderate AD 0.70%, severe AD 0.28%.**[6]	⨁⨁◯◯ Low	IMPORTANT
Association between depression & AD (follow-up: Cross-sectional; assessed with: Odds of co-occurring diagnoses of depression and AD in children with AD compared to controls without AD)									
3[3, 5, 7]	observational studies	serious[d]	not serious	not serious	serious[e]	none	The pooled analysis of 2 studies suggests **no association** between AD and a diagnosis of depression: **aOR 1.45 (0.77, 2.73)**.[5, 7] One study suggested children with depression had higher odds of AD: **aOR 9.92 (2.94, 33.43)**.[3] <u>Association by severity</u> One study[5] suggested increasing self-reported AD severity may be associated with increased odds of depression: **Mild AD aOR 1.64 (1.06, 2.53)** **Moderate AD aOR 2.02 (1.31, 3.14)** **Severe AD aOR 2.12 (1.00, 4.48)**	⨁⨁◯◯ Low	CRITICAL
Occurrence of depression in AD (follow-up: range 12 months to 17 years; assessed with: Risk of subsequent diagnosis of depression in children with a prior diagnosis of AD compared to children without AD, and vice versa)									
6[6, 8-12]	observational studies	serious[f]	serious[g]	not serious	serious[i]	none	One study suggested increased odds of an AD diagnosis within the 12 months prior to a depression diagnosis in children with depression compared to non-depressed children: **aOR 1.50 (1.37, 1.64)**.[9]	⨁◯◯◯ Very low	CRITICAL

№ of studies	Certainty assessment						Impact Effect estimates presented as odds ratios or hazard ratios with (95% CI)	Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
							The pooled analysis of 5 studies suggests **no association** between AD and a subsequent diagnosis of depression: **aHR 1.17 (0.93, 1.46)**.[8, 10-12] <u>Occurrence by severity</u> One study suggested a slight increase in risk of developing anxiety in mild AD^ (**aHR 1.05 [1.03, 1.09]**) but reduced risk in moderate (**aHR 0.68 [0.65, 0.71**]) and severe AD (**aHR 0.64 [0.58, 0.70**]).[6]		

AD: Atopic dermatitis; **aOR**: Adjusted odds ratio; **aHR**: Adjusted hazard ratio; **CI**: Confidence interval

^ All patients with AD were considered to have mild disease by default. They were classified as having moderate AD at the first of receiving: (i) a second potent topical corticosteroid within 1 year, or (ii) a first topical calcineurin inhibitor (which is reserved in the UK for moderate AD). Patients were classified as having severe AD at the first of (i) systemic immunosuppressant treatment, (ii) phototherapy use or (iii) referral to dermatology (as 96% of AD patients are managed exclusively by GPs)

Explanations

a. Studies relied on unvalidated and/or self-reported exposure and/or outcome assessment; NOS scores ranged from 4-8 suggesting a moderate to high risk of bias.
b. The two smallest studies suggest substantially larger rates of depression than the 3 larger studies; there is inconsistent evidence of correlation between AD severity and prevalence of depression.
c. The sample size of the study reporting AD in children with depression is very small, suggesting imprecision; However, more weight was given to the more precise pooled prevalence estimate given alignment with the research question.
d. Studies relied on unvalidated or self-reported exposure and/or outcome assessment; NOS scores of 4-7 suggest a moderate to high risk of bias.
e. CI for pooled odds consistent with both a protective effect and important increase in odds; the small size for the study in children with depression is very small suggesting imprecision; CIs for association by AD severity are largely consistent with no association and increased odds.
f. Studies relied on unvalidated or self-reported exposure and/or outcome assessment; NOS scores ranged from 6-8 suggesting a low to moderate risk of bias
g. For the pooled analysis, one study suggests a slight but statistically significant reduction in risk in AD, two studies suggests no significant association between AD, while a third study suggests a large magnitude of increased risk; The results across the 3 bodies of evidence are also inconsistent suggesting increased odds and no association.
h. Pooled CI consistent with both a protective effect and large magnitude of increased risk.

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Table 30. Suicide

Question: Is suicidal ideation or suicide associated with pediatric AD?

№ of studies	Certainty assessment						Impact Effect estimates presented as odds ratios or hazard ratios with (95%CI)	Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Prevalence of suicidal ideation in children with AD (follow-up: Cross-sectional; assessed with: Prevalence of suicidal ideation in children with AD)									
4[1-4]	observational studies	serious[a]	serious[b]	not serious[c]	serious[d]	none	The pooled prevalence of suicidal ideation in children with AD across 4 studies (n=623,566) is **8.4% (5.7, 11.0)**.	⨁◯◯◯ Very low	IMPORTANT
Prevalence of suicide attempts in children with AD (follow-up: 12 months; assessed with: Prevalence of suicide attempts in the previous 12 months in children with AD)									
1[2]	observational studies	serious[e]	not serious	not serious	not serious	none	One study suggested the rate of suicide attempts in the previous 12 months in children with AD was **4.51%**.	⨁⨁⨁◯ Moderate	IMPORTANT
Prevalence of suicide in AD (assessed with: Prevalence of suicide in children with AD)									
1[4]	observational studies	serious[f]	not serious	not serious	not serious	none	One study suggested the incidence rate of suicide in children with AD is **0.02 (0.02, 0.03) per 1,000 person-years**.	⨁⨁⨁◯ Moderate	IMPORTANT
Association between suicidal ideation & AD (follow-up: Cross-sectional; assessed with: Odds of suicidal ideation in children with AD compared to children without AD)									
5[1-3, 5, 6]	observational studies	serious[a]	not serious	not serious[c]	not serious	none	The pooled analysis of 2 studies suggests children with AD have higher *adjusted* odds of suicidal ideation: **aOR 1.15 (1.02, 1.30)**.[5, 6] Similarly, the pooled analysis of 3 studies suggests children with AD have higher *unadjusted* odds of suicidal ideation: **OR 1.21 (1.16, 1.27)**.[1-3]	⨁⨁⨁◯ Moderate	CRITICAL
Association between suicide attempts & AD (follow-up: 12 months; assessed with: Odds of a suicide attempt in the previous 12 months in children with AD compared to children without AD)									
1[2]	observational studies	serious[e]	not serious	not serious	not serious	none	One study suggested higher odds of a recent suicide attempt in children with AD: **OR 1.18 (1.15, 1.21)**.	⨁⨁⨁◯ Moderate	CRITICAL

№ of studies	Certainty assessment						Impact Effect estimates presented as odds ratios or hazard ratios with (95%CI)	Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Occurrence of suicidal ideation or attempts in AD (follow-up: mean 5-7 years; assessed with: Adjusted risk of subsequent suicidal ideation or attempts in children with AD compared to children without AD)									
1[4]	observational studies	serious[f]	not serious	not serious	not serious	none	One study suggested suicidal ideation/attempts are **not associated** with AD: **aHR 0.98 (0.95, 1.01).** Occurrence by severity Considering AD severity as determined by medication use**- mild AD** is associated with a slight increase in risk **(aHR 1.04 [1.01, 1.08**]) while **moderate (aHR 0.76 [0.70, 0.81]**) and **severe AD (aHR 0.74 [0.63, 0.86])** are associated with reduced risk.	⨁⨁⨁◯ Moderate	CRITICAL
Occurrence of suicide in AD (follow-up: mean 5-7 years; assessed with: Risk of suicide in children with AD compared to children without AD)									
1[4]	observational studies	serious[f]	not serious	not serious	not serious[g]	none	One study suggested suicide was **not associated** with AD: **aHR 0.85 (0.64, 1.14).** Occurrence by severity Considering AD severity as determined by medication use, suicide was **not associated** with AD of any severity^: **mild AD aHR 0.92 (0.67, 1.28**), **moderate AD aHR 0.74 (0.41, 1.34**), **severe AD aHR 0.31 (0.04, 2.24)**.	⨁⨁⨁◯ Moderate	CRITICAL

AD: Atopic dermatitis; **aOR**: Adjusted odds ratio; **HR:** Hazard ratio; **CI**: Confidence interval

^ All patients with AD were considered to have mild disease by default. They were classified as having moderate AD at the first of receiving: (i) a second potent topical corticosteroid within 1 year, or (ii) a first topical calcineurin inhibitor (which is reserved in the UK for moderate AD). Patients were classified as having severe AD at the first of (i) systemic immunosuppressant treatment, (ii) phototherapy use or (iii) referral to dermatology (as 96% of AD patients are managed exclusively by GPs)

Explanations

a. Studies relied on unvalidated and/or self-reported exposure and outcome assessment; NOS scores of 6-8 suggest a moderate risk of bias.
b. Two studies using diagnostic codes suggest a very low rate of suicidal ideation, while 2 studies relying on self-reported outcome assessment suggest substantially higher rates.
c. Data were primarily derived from adolescent populations in Korea, this may impact generalizability to adolescents in other geographic and cultural contexts.
d. CI consistent with lower-than-anticipated and higher-than-anticipated rates of suicidal ideation based on reported global rates in adolescents.
e. Study relied on self-reported exposure and outcome assessment; NOS score of 6 suggests moderate risk of bias.
f. Study relied on unvalidated outcome assessment.
g. Event rate is very low leading to imprecise CIs. However, the sample size is robust.

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Table 31. Obesity

Question: Is obesity associated with pediatric AD?

№ of studies	Certainty assessment						Impact Effect estimates presented as odds ratios with (95% CI)	Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Prevalence of obesity^ in children with AD (follow-up: Cross-sectional; assessed with: Pooled prevalence of obesity in children with AD)									
6[1-6]	observational studies	serious[a]	serious[b]	not serious	not serious	none	The pooled prevalence of obesity in children with AD across 6 studies was **10.7% (7.3, 14.0).**	⨁⨁◯◯ Low	IMPORTANT
Association between obesity^ & AD (follow-up: Cross-sectional; assessed with: Odds of obesity in children with AD compared to children without AD)									
15[1, 3-16]	observational studies	serious[c]	not serious	not serious	not serious	none	In the pooled analysis of 9 studies, children with AD had higher *adjusted* odds of obesity than did controls without AD: **aOR 1.35 (1.15, 1.58).**[3, 4, 6-10, 15, 16] The pooled *unadjusted* analysis of 5 studies also suggests higher odds of obesity in children with AD: **OR 1.19 (1.02, 1.40)**.[1, 11-13] One study suggests obese children had higher odds of AD than non-obese children**: aOR 2.45 (1.06, 5.67).**[5] <u>Association by severity</u> One study suggests odds of obesity are higher in children with moderate-to-severe AD^ compared to children with mild AD**: aOR 2.59 (1.64, 4.10).**[6]	⨁⨁⨁◯ Moderate	CRITICAL

AD: Atopic dermatitis; **aOR**: Adjusted odds ratio; **CI**: Confidence interval

^ Severity defined by response to the following: "Would you describe (child's) eczema or skin allergy as mild, moderate, or severe?".

Explanations
a. Studies primarily relied on self-reported exposure and/or outcome assessment; 4/6 studies were of a high risk of bias.
b. Prevalence rates varied widely across the studies from 3.6% to 17.9%.
c. Studies primarily relied on self-reported exposure and/or outcome assessment; 5/15 studies were of a high risk of bias.

^Table. Study Definitions of Obesity

Study	Definition of Obesity

Augustin 2015	Diagnostic codes (ICD 10)
Gilaberte 2020	Expanded diagnostic cluster code (NUT03)
Huang 2021	Diagnostic codes (ICD 10)
James 2013	BMI ≥ 30kg/m^2
Kim 2019	BMI ≥ 95th percentile
Lei 2016	BMI ≥ 95th percentile
Lim 2017	BMI ≥ 95th percentile
Lin 2015	BMI > 23kg/m^2
Manjunath 2022	BMI ≥ 95th percentile
Reddy 2024	BMI ≥ 90th percentile
Seong 2023	BMI ≥ 95th percentile
Silverberg 2014	BMI ≥ 95th percentile
Silverberg 2015	BMI ≥ 95th percentile
Silverberg 2016	BMI ≥ 95th percentile
Song 2014	BMI > 95th percentile
Sybilski 2015	BMI ≥ 30kg/m^2

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Table 32. Dyslipidemia

Question: Is dyslipidemia associated with pediatric AD?

№ of studies	Certainty assessment						Impact Effect estimates presented as odds ratios (95% CI)	Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Prevalence of dyslipidemia in children with AD (follow-up: Cross-sectional; assessed with: Prevalence of hyperlipidemia and hypercholesterolemia in children with AD)									
2[1, 2]	observational studies	serious[a]	not serious	not serious	not serious	none	One study suggested the prevalence of hyperlipidemia in children with AD (n=30,354) was **0.71%**.[1] One study suggested the prevalence of hypercholesterolemia in children with AD (n=1,603) was **1.8 % (0.8, 2.7**).[2]	⨁⨁⨁◯ Moderate	IMPORTANT
Association between dyslipidemia & AD (follow-up: Cross-sectional; assessed with: Odds of disorders of lipid metabolism, hyperlipidemia, and hypercholesterolemia in children with AD compared to children without AD)									
5[2-5]	observational studies	serious[b]	not serious	not serious	serious[c]	none	Two studies suggest dyslipidemia is ***not associated*** with disorders of lipid metabolism in children with AD: **aOR 1.22 (0.87, 1.72).**[3, 5] Two studies suggested increased *adjusted* and *unadjusted* odds of hyperlipidemia in children with AD: **aOR 1.87 (1.69, 2.06)** **OR 1.30 (1.12, 1.50)**.[1, 4] One study suggested hypercholesterolemia is ***not associated*** with AD: **aOR 1.72 (0.83, 3.56).**[2]	⨁⨁◯◯ Low	CRITICAL

AD: Atopic dermatitis; **aOR**: Adjusted odds ratio; **CI**: Confidence interval

Explanations

a. Studies relied on self-reported or unvalidated exposure and outcome assessment; One study is of a high risk of bias and one study is on a moderate risk of bias.
b. Studies relied on self-reported or unvalidated exposure and outcome assessment; One study is of a high risk of bias.
c. The CIs for both dyslipidemia and hypercholesterolemia are imprecise as they are consistent with both meaningfully increased and decreased odds. The evidence for dyslipidemia is also inconsistent with one study suggesting meaningfully increased odds and another study suggesting trivial difference.

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Table 33. Diabetes

Is diabetes associated with pediatric AD?

№ of studies	Certainty assessment						Impact Effect estimates presented as odds ratios with (95% CI)	Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Prevalence of diabetes^ in children with AD (follow-up: Cross-sectional; assessed with: Prevalence of diabetes in children with AD)									
2[1, 2]	observational studies	serious[a]	not serious	not serious	serious[b]	none	The pooled prevalence of diabetes in children with AD across 2 studies is **0.2% (0.0, 0.5%).**	⨁⨁◯◯ Low	IMPORTANT
Association between diabetes^ & AD (follow-up: Cross-sectional; assessed with: Odds of diabetes in children with AD compared to children without AD)									
4[1-4]	observational studies	serious[a]	not serious	not serious	not serious	none	In the pooled analysis of 3 studies, children with AD have higher *adjusted* odds of diabetes: **aOR 1.27 (1.04, 1.54).**[3-5] Similarly, one study reported higher *unadjusted* odds of diabetes in children with AD: **OR 1.31 (1.06, 1.61).**[1]	⨁⨁⨁◯ Moderate	CRITICAL

AD: Atopic dermatitis; **aOR**: Adjusted odds ratio; **CI**: Confidence interval

Explanations

a. Studies relied on unvalidated or self-reported exposure and outcome assessment; One study is of a high risk of bias.

b. CI consistent with both a rate of diabetes lower and higher than expected based on rates in the general pediatric population.

^Included studies varied in assessment and definition of diabetes and most do not distinguish between type 1 and type 2 diabetes. See below for the per study definition of diabetes:

Study	Definition of Diabetes
Augustin 2015	Diagnostic codes (ICD 10) for “diabetes mellitus”
Gilaberte 2020	Expanded Diagnostic Cluster END06-09 “Diabetes”
Huang 2021	Diagnostic codes (ICD 10) for Diabetes mellitus type 2
Silverberg 2016	Self-reported; “Has a doctor or other health professional ever told you that (child) had diabetes?”

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Table 34. Metabolic Syndrome

Question: Is metabolic syndrome associated with pediatric AD?

№ of studies	Certainty assessment						Impact Effect estimates presented as odds ratios with (95% CI)	Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Association between metabolic syndrome & AD (follow-up: Cross-sectional; assessed with: Odds of metabolic syndrome in children with AD compared to children without AD)									
1[1]	observational studies	serious[a]	not serious	not serious	not serious	none	One study suggested the odds of metabolic syndrome may be increased in children with AD: **aOR 1.61 (1.28, 2.01).**	⊕⊕⊕◯ Moderate	CRITICAL
Prevalence of metabolic syndrome in children with AD (follow-up: Cross-sectional; assessed with: Prevalence of metabolic syndrome in children with AD)									
1[2]	observational studies	Not serious	not serious	not serious	serious[b]	none	The prevalence of metabolic syndrome in children with AD in a single study was 24% (n=50)	⊕⊕⊕◯ Moderate	IMPORTANT

AD: Atopic dermatitis; **aOR**: Adjusted odds ratio; **CI**: Confidence interval

Explanations

a. Study relied on unvalidated exposure and outcome assessment but is otherwise of a low risk of bias.
b. Very small sample is concerning for precision

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Table 35. Cardiovascular Diseases

Question: Are cardiovascular diseases associated with pediatric AD?

№ of studies	Certainty assessment						Impact Effect estimates presented as odds ratios with (95% CI)	Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Association between CVDs & AD (follow-up: Cross-sectional; assessed with: Odds of having CVDs in children with AD compared to children without AD)									
5[1-5]	observational studies	serious[a]	not serious	not serious	not serious	none	<u>*Hypertension*</u> In the pooled analysis of 3 studies, children with AD had higher *adjusted* odds of hypertension: **aOR 1.20 (1.03, 1.39).**[2-4] However, an unadjusted analysis reported ***no association*** between AD and hypertension: **OR 1.02 (0.85, 1.23)**.[1] <u>*Ischemic Heart Disease*</u>	⊕⊕⊕◯ Moderate	CRITICAL

<table>
<tr><th rowspan="2">№ of studies</th><th colspan="6">Certainty assessment</th><th rowspan="2">Impact
Effect estimates presented as odds ratios with (95% CI)</th><th rowspan="2">Certainty</th><th rowspan="2">Importance</th></tr>
<tr><th>Study design</th><th>Risk of bias</th><th>Inconsistency</th><th>Indirectness</th><th>Imprecision</th><th>Other considerations</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>An adjusted analysis reported no association between AD and ischemic heart disease: aOR 0.83 (0.50, 1.39).[2] Conversely, an unadjusted analysis reported higher odds of ischemic heart disease in children with AD: OR 1.59 (1.03, 2.45).[1]

Incidence rates[5]<table><tr><th>With AD (per 100,000 PY)</th><th>Without AD (per 100,000 PY)</th><th>Absolute Effect (95% CI)</th></tr><tr><td>4.0 (2.8 to 5.6)</td><td>3.4 (2.3 to 4.9)</td><td>0.6 more (–0.9 to 2.3) per 100,000 person-years</td></tr></table>
<u>Other CVDs</u>
A comparison of 33,591 children with AD and 182,700 without AD suggests no association between AD and the following CVDs[2]:
Peripheral Vascular Disease aOR 1.44 (0.63, 3.28)
Cardiac Arrhythmia aOR 1.29 (0.99, 1.67)
Congestive Heart Failure aOR 1.56 (1.00, 2.43)
Other Cardiovascular Disorders (expanded diagnostic cluster CAR16) aOR 1.04 (0.81, 1.32)

Higher odds of the following CVDs were reported for children with AD:
Cardiac Valve Disorders aOR 1.57 (1.12, 2.20)
Congenital Heart Disease aOR 1.25 (1.09, 1.43)</td><td></td><td></td></tr>
<tr><td colspan="10">Occurrence of arrhythmia in AD (follow-up: up to 18 years; assessed with: Risk of subsequent diagnosis of arrythmia in children diagnosed with AD compared to children without AD)</td></tr>
<tr><td>1[6]</td><td>observational studies</td><td>not serious</td><td>not serious</td><td>not serious</td><td>serious[b]</td><td>none</td><td>An adjusted analysis reported no association between AD and arrhythmia: aHR: 1.04 (0.85, 1.27)</td><td>⨁⨁⨁◯ Moderate</td><td>CRITICAL</td></tr>
<tr><td colspan="10">Major cardiovascular events (follow-up: up to 7 years; assessed with: Incidence rate per 100,000 person-years of MACE in children diagnosed with AD compared to children without AD)</td></tr>
<tr><td>1[5]</td><td>observational studies</td><td>not serious</td><td>not serious</td><td>not serious</td><td>not serious</td><td>none</td><td><table><tr><th>With AD (per 100,000 PY)</th><th>Without AD (per 100,000 PY)</th><th>Absolute Effect (95% CI)</th></tr><tr><td>9.6 (7.6 to 12.0)</td><td>6.4 (4.8 to 8.4)</td><td>3.2 more (1.2 to 5.6 more) per 100,000 person-years</td></tr></table></td><td>⨁⨁⨁⨁ High</td><td>CRITICAL</td></tr>
</table>

AD: Atopic dermatitis; **CVD:** Cardiovascular disease **aOR**: Adjusted odds ratio; **CI**: Confidence interval

Explanations

a. All studies relied on unvalidated and/or self-reported exposure and/or outcome assessment; NOS scores ranged from 4-7 suggesting a low-to-moderate risk of bias.
b. CI consistent with both a protective effect and important increase in risk.

References

1. 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.
2. 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.
3. Silverberg JI. Atopic disease and cardiovascular risk factors in US children. J Allergy Clin Immunol 2016;137:938-40.e1.
4. 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.
5. 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.
6. 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.

Table 36. Bone Fractures

Question: Are fractures associated with pediatric AD?

№ of studies	Certainty assessment						Impact Effects estimates presented as odds ratios or risk ratios with (95% CI)	Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Association between pathologic fractures & AD (follow-up: Cross-sectional; assessed with: Odds of pathologic fractures in children with AD compared to children without AD)									
1[1]	observational studies	serious[a]	not serious	not serious	serious[b]	none	One study suggested **no association** between pathologic fracture and AD: **aOR 0.63 (0.36, 1.11).**	⨁⨁◯◯ Low	CRITICAL
Occurrence of any bone fracture in AD (follow-up: up to 10 years; assessed with: Risk of subsequent bone fracture in children with AD compared to children without AD)									
3[2-4]	observational studies	serious[c]	not serious	not serious	not serious	none	One study suggested AD is associated with a small increase in the risk of any bone fracture**: aRR 1.08 (1.05, 1.10) p<0.001**. Similarly, a pooled estimate from 2 studies[3, 4] (with potential population overlap) suggests a small increase in the subsequent risk of fracture in children with AD: **aHR 1.09 (1.08, 1.09)** and that the risk of fracture increased with increasing AD severity^: Mild AD**: aHR 1.12 (1.11-1.14)** Moderate-to-severe: **aHR 1.23 (1.20, 1.26)**	⨁⨁⨁◯ Moderate	CRITICAL

AD: Atopic dermatitis; **aOR**: Adjusted odds ratio; **aRR:** Adjusted risk ratio; **CI**: Confidence interval
^AD classified as mild unless treated with immunosuppressants.

Explanations
a. Study relied on unvalidated outcome assessment; NOS score 7.
b. CI consistent with a protective effect and association.
c. Studies relied on unvalidated exposure and/or outcome assessment; NOS scores 7-8.

References

1. 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.
2. 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.
3. 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.
4. 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.

Table 37. Osteoporosis

Is osteoporosis associated with pediatric AD?

№ of studies	Certainty assessment						Impact Effects estimates presented as odds ratio (95% CI)	Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Association between osteoporosis & AD (follow-up: Cross-sectional; assessed with: Odds of osteoporosis in children with AD compared to children without AD)									
1[1]	observational studies	serious[a]	not serious	not serious	serious[b]	none	One study suggested osteoporosis was **not associated** with AD: **aOR 2.15 (0.78, 5.92) p=0.14.**	⨁⨁◯◯ Low	CRITICAL

AD: Atopic dermatitis; **aOR**: Adjusted odds ratio; **CI**: Confidence interval

Explanations

a. Study relied on unvalidated outcome assessment; NOS score 7.
b. CI consistent with a protective effect and strong positive association.

References

1. 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.

Table 38. Any Skin Infections (general)

Question: Are skin infections associated with pediatric AD?

№ of studies	Certainty assessment						Impact Effects estimates presented as odds ratio (95% CI)	Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Prevalence of skin infections in AD (follow-up: Cross-sectional; assessed with: Prevalence of any skin infections in children with AD)									
2[1, 2]	observational studies	serious[a]	not serious	not serious	not serious	none	The pooled prevalence from 2 studies of any skin infection in children with AD (n=4,826,954) is **16.1% (16.1, 16.1).**	⨁⨁⨁◯ Moderate	IMPORTANT
Association between skin infections & AD (follow-up: Cross-sectional; assessed with: Adjusted odds of skin infections in children with AD compared to children without AD)									
2[3, 4]	observational studies	serious[b]	not serious	not serious	not serious	none	One study reported higher odds of skin infections in AD**: aOR 2.23 (2.16, 2.31) p<0.0001**.[4] Similarly, a 2nd study reported in multivariable models controlling for age, race, sex and insurance status, AD **was associated**	⨁⨁⨁◯ Moderate	CRITICAL

№ of studies	Certainty assessment						Impact Effects estimates presented as odds ratio (95% CI)	Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
							with cutaneous infections (e.g. eczema herpeticum, erysipelas, herpes simplex, cellulitis) [no quantitative data provided].[3]		

AD: Atopic dermatitis; **aOR**: Adjusted odds ratio; **CI**: Confidence interval

Explanations

a. Most data are from a study that relied on unvalidated exposure and outcome assessment; NOS scores of 6 and 7 suggest moderate to low risk.
b. One study relied on unvalidated outcome assessment, one study minimally reported the outcome; NOS scores of 6 and 8 suggest moderate to low risk.

References

1. 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.
2. 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.
3. Narla S , Silverberg JI. Association between childhood atopic dermatitis and cutaneous, extracutaneous and systemic infections. Br J Dermatol 2018;178:1467-8.
4. Ren Z , Silverberg JI. Association of Atopic Dermatitis With Bacterial, Fungal, Viral, and Sexually Transmitted Skin Infections. Dermatitis 2020;31:157-64.

Table 39. Bacterial Skin Infections

Question: Are bacterial skin infections associated with pediatric AD?

№ of studies	Certainty assessment						Impact Effects estimates presented as odds ratios or risk ratios with (95% CI)	Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Prevalence of bacterial skin infections in AD (follow-up: Cross-sectional; assessed with: Prevalence of bacterial skin infections in children with AD, and vice versa)									
3[1-3]	observational studies	serious[a]	not serious	not serious	not serious	none	Studies reported **impetigo**[2] in **34.3%** (401/1,169) and **S. aureus skin infection** in **36.0%**[3] (422/ 1,171) of children with AD. One study reported **4.1%** (40/977) of children with S. aureus infection have AD.[1]	⊕⊕⊕◯ Moderate	IMPORTANT
Association between bacterial skin infections & AD (follow-up: Cross-sectional; assessed with: Risk/odds of bacterial skin infections in children with AD compared to children without AD)									
4[3-6]	observational studies	serious[b]	not serious	not serious	not serious	none	The pooled analysis of 3 studies suggests AD is associated with increased odds of **impetigo**: **aOR 2.18 (1.13, 4.23)**.[4-6] One study suggested AD is associated with increased odds of **cellulitis: aOR 2.01 (1.90, 2.12)**.[4] One study suggested AD is associated with an increased risk of **S. aureus** skin infection: **aRR 1.28 (1.16, 1.40)**.[3]	⊕⊕⊕◯ Moderate	CRITICAL

AD: Atopic dermatitis; **aOR**: Adjusted odds ratio; **aRR**: Adjusted risk ratio; **CI**: Confidence interval

Explanations
a. Studies relied on self-reported exposure and/or outcome assessment; NOS scores of 5-6 suggest moderate risk.
b. Most studies relied on self-reported or unvalidated exposure and/or outcome assessment; NOS scores of 6-9 suggest low to moderate risk.
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References

1. 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.
2. 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.
3. 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.
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5. 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.
6. 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.

Table 40. Viral Skin Infections

Question: Are viral skin infections associated with pediatric AD?

№ of studies	Certainty assessment						Impact Effects estimates presented as odds ratios with (95% CI)	Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Prevalence of viral skin infections in AD (follow-up: Cross-sectional; assessed with: Prevalence of viral skin infections in children with AD, and vice versa)									
2[1, 2]	observational studies	serious[a]	not serious	not serious	not serious	none	One study reported **herpes simplex** infection in **16.3%** and **MC** infection in **24.8%** of children with AD (n=1,149).[2] One study reported AD in **46.5%** (79/170) of children with MC infection.[1]	⨁⨁⨁◯ Moderate	IMPORTANT
Association between viral skin infections & AD (follow-up: Cross-sectional; assessed with: Adjusted odds of viral skin infections in children with AD compared to children without AD)									
4[3-6]	observational studies	serious[b]	not serious	not serious	not serious	none	The pooled analysis of 3 studies suggests AD is associated with increased odds of **MC infection**: **aOR 2.91 (2.26, 3.76)**.[3-5] The pooled analysis of 4 studies suggests AD is associated with increased odds of **warts: aOR 1.66 (1.42, 1.94).**[3-6] One study suggested AD is associated with increased odds of **coxsackie viral infection: aOR 1.88 (1.63, 2.18).**[3]	⨁⨁⨁◯ Moderate	CRITICAL

<table>
<tr><th rowspan="2">№ of studies</th><th colspan="6">Certainty assessment</th><th rowspan="2">Impact
Effects estimates presented as odds ratios with (95% CI)</th><th rowspan="2">Certainty</th><th rowspan="2">Importance</th></tr>
<tr><th>Study design</th><th>Risk of bias</th><th>Inconsistency</th><th>Indirectness</th><th>Imprecision</th><th>Other considerations</th></tr>
<tr><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td>One study suggested AD is associated with increased odds of herpes simplex infection: aOR 2.08 (2.04, 2.12).[4]</td><td></td><td></td></tr>
<tr><td colspan="10">Occurrence of viral skin infection in AD (follow-up: up to 10 years; assessed with: Risk of subsequent diagnosis of a viral skin infection in children with AD compared to children without AD)</td></tr>
<tr><td>3[7-9]</td><td>observational studies</td><td>serious[c]</td><td>not serious</td><td>not serious</td><td>not serious[d]</td><td>none</td><td>Two studies suggested increased <i>adjusted</i> and <i>unadjusted</i> odds of a subsequent MC diagnosis in AD:
aOR 1.13 (1.11, 1.16) p<0.005.[8]
OR 2.51 (1.10, 6.01).[7]

Incidence of herpes zoster per 100,000 person-years[9]:<table><tr><th>With AD (per 100,000 PY)</th><th>Without AD (per 100,000 PY)</th><th>Absolute Effect (95% CI)</th></tr><tr><td>349.6 (337.1 to 362.5)</td><td>250.8 (240.2 to 261.7)</td><td>98.8 more (96.9 to 100.8) per 100,000 person-years</td></tr></table></td><td>⨁⨁⨁◯
Moderate</td><td>CRITICAL</td></tr>
</table>

AD: Atopic dermatitis; **MC**: Molluscum contagiosum; **aOR**: Adjusted odds ratio; **aRR**: Adjusted risk ratio; **CI**: Confidence interval

Explanations

a. One study relied on self-reported outcome assessment; NOS scores of 4-5 suggest high risk.
b. Most studies relied on unvalidated or self-reported exposure and/or outcome assessment: NOS scores of 6-9 suggest low to moderate risk.
c. Studies relied on unvalidated exposure and/or outcome assessment; NOS scores 7-8 suggest a low to moderate risk.
d. More weight was given to the precise adjusted effect estimate, so the data was not downgraded for the imprecision of the unadjusted effect estimate.

References

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2. 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.
3. 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.
4. 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.
5. 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.
6. 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.

7. 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.
8. 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.
9. 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.

Table 41. Fungal Skin Infections

Question: Are fungal skin infections associated with pediatric AD?

№ of studies	Certainty assessment						Impact Effects estimates presented as odds ratios (95% CI)	Certainty	Importance
	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations			
Association between fungal skin infections & AD (follow-up: Cross-sectional; assessed with: Adjusted odds of fungal skin infections in children with AD compared to children without AD)									
3[1-3]	observational studies	serious[a]	not serious	not serious	not serious	none	The pooled analysis of 3 studies suggests AD is associated with higher odds of fungal skin infection: **aOR 2.12 (1.72, 2.61).**	⨁⨁⨁◯ Moderate	CRITICAL

AD: Atopic dermatitis; **MC**: Molluscum contagiosum; **aOR**: Adjusted odds ratio; **aRR**: Adjusted risk ratio; **CI**: Confidence interval

Explanations

a. Most studies relied on unvalidated exposure and/or outcome assessment; NOS scores of 7-9 suggest low risk.

References

1. 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.
2. 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.
3. 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.