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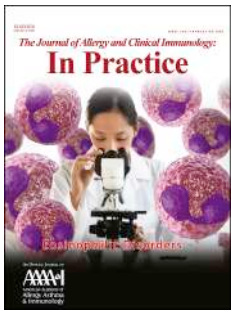

How to prevent Atopic Dermatitis (Eczema) in 2024: theory and evidence

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Title

How to prevent Atopic Dermatitis (Eczema) in 2024: theory and evidence

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Clinical Commentary

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Abstract

Atopic dermatitis (AD) or eczema is a chronic inflammatory skin disease characterized by dry, itchy, and inflamed skin. We review emerging concepts and clinical evidence addressing the pathogenesis and prevention of atopic dermatitis. We review several interventions ranging from skin barrier enhancement strategies; probiotics, prebiotics, and synbiotics, and conversely, antimicrobial exposure; vitamin D and omega fatty acid supplementation; breastfeeding and hydrolyzed formula; house dust mite avoidance and immunotherapy. We appraise the available evidence base within the context of the GRADE approach. We also contextualize our findings in relation to concepts relating atopic dermatitis and individual-patient allergic life trajectories versus a linear concept of the atopic march and provide insights into future knowledge gaps and clinical trial design considerations that must be addressed in future research. Finally, we provide implementation considerations to detect population-level differences in AD risk. Major international efforts are required to provide definitive evidence regarding what works, and what does not, for preventing AD.

Introduction

Atopic dermatitis (AD), commonly referred to as eczema or atopic eczema, is characterized by itch and skin inflammation that impairs multiple aspects of patient and family quality of life[1]. Representing the most common chronic inflammatory skin disease, AD affects an estimated 13% of children and 5% of adults worldwide[1]. In the United States alone, AD incurs an estimated annual cost of over $5 billion[2].

AD typically presents within the first six months of life and persists into adulthood in 25%. Preventing even a modest proportion of cases of AD could therefore yield major individual-patient, health system, and socioeconomic benefits[3-5]. Clinical guidance addressing AD, however, predominantly focuses on treatment[1, 6, 7] rather than prevention[8]. Thus, this review updates the evidence regarding how to prevent AD. We focus on actionable interventions rather than genetics or other non-modifiable factors.

Traditionally, the early onset of AD, compared to other allergic diseases such as allergic rhinitis and asthma, led to the hypothesis that AD progresses to allergic rhinitis and then to asthma in a linear progression sequence[9, 10]. While the average onset of disease among populations may generally follow this pattern, it is now evident that many individuals do not follow this pattern. Longitudinal clustering analyses of patients with AD show diverse life-course trajectories, including AD occurring in isolation, AD with rapid resolution, persistent AD, and various combinations involving AD with rhinitis, asthma, or food allergy (**Figure 1**). These data suggest that the pathogenesis of allergies may not always follow a traditional sequential progression model[11-14]. Thus, whether preventing AD definitively prevents the development of other allergic diseases remains a hypothesis with strong biologic plausibility, but, as of yet, insufficient

supporting clinical outcome data. This review therefore focuses on prevention of AD, rather than prevention of the progression from AD to developing other allergic diseases. Additional reviews in this issue address prevention of other allergic diseases[15.] We also discuss the relevance of considering the degree of risk in the population being targeted for prevention, and whether the intervention is more likely to prevent mild AD, or moderate-to-severe AD to help provide a framework for considering the presented summaries of the evidence addressing the different prevention strategies.

Theories of pathogenesis of AD

The pathophysiology of AD is complex and multifactorial, but the incipient early events causing new disease remain uncertain. Efforts to prevent AD concentrate on enhancing the skin barrier, addressing immune dysregulation, and controlling allergen exposure. In this context, we discuss the relevant mechanistic data and theories associated with these strategies.

Impaired skin barrier

Impaired skin barrier, a hallmark of established AD, may also have a role in the etiology of AD. Skin barrier function is primarily determined by corneocytes and associated stratum corneum intercellular lipid matrix[16]. The cytoskeleton of the corneocytes, formed by keratin-filaggrin bundles, provides mechanical resistance to the skin barrier against environmental stressors[16]. The intercellular lipid matrix, consisting of equal molars of ceramides, free fatty acids and

cholesterol[17], prevent water loss (evaporation/dehydration) and penetration of allergens and irritants into the skin[18]. Consequently, genetic defects in the epidermal barrier (e.g., loss of function of the gene encoding filaggrin [FLG][19]) are associated with developing AD[20]. Prospective birth cohort studies observed that impaired skin barrier function, as determined by higher levels of transepidermal water loss[21], precede overt clinical signs and symptoms of AD[22]. A small number of studies also observed that abnormal early-life lipid profiles precede the development of AD[23-25]. Together, genetic, mechanical (e.g. scratching), chemical, allergen, or irritant epidermal barrier disruption may trigger keratinocytes in the deeper layer of the skin to release IL-33, IL-25, and TSLP, among other signals, leading to subsequent inflammation and sensitization to allergens[26-28].

Immune dysregulation and microbial interactions

Characterized by increased T_H2 responses and over-expression of type 2 inflammatory cytokines (e.g. IL-4, IL-13), an alternative hypothesis proposes AD to be an immune dysregulation disorder[27]. For example, early life changes in skin cytokines such as IL-13 are associated with developing AD[24, 29]. Further, inborn errors of immunity, although rare, illustrate that single gene defects affecting either innate or adaptive immunity can promote eczema[30, 31]. Most individuals that develop AD, however, will not have inborn errors of immunity.

One hypothesis suggests that altered early life microbial exposure may cause dysregulated immune responses[32]. Originally observed as an inverse association between the number of older siblings and risk of developing allergic rhinitis at age 11 or eczema in the first year of life among

17414 infants born in the UK in 1958 and followed for 23 years[32], the hygiene hypothesis has expanded to suggest that microbial interactions with the immune system influence the developmental origins of disease, including AD and allergy. Consistent with this, the timing and composition of microbial colonization is critical to T regulatory cell development[33] and homeostatic immune responses[34]. Further, in patients with AD, normal T regulatory cell immunosuppressive activities are subverted by exposure to Staphylococcal enterotoxin B superantigen[35]. The precise microbes and mechanisms that cause AD, and how to manipulate them therapeutically[36], remain, however, an area of intense investigation.

Interventions to prevent AD – Clinical Evidence

To address the highest clinical evidence for prevention of AD beyond our work as clinicians, researchers, guideline developers, and clinical trialists, we searched MEDLINE, EMBASE and CENTRAL for randomized clinical trials (RCTs) addressing primary prevention of AD using "eczema" OR "dermatitis" OR "atopic dermatitis" AND "primary prevention" "randomized control trial" "clinical trial". We supplemented the search with Epistemonikos and by checking the reference list of reviews addressing AD prevention[8, 37, 38]. **Table 1** summarizes the available clinical evidence for interventions to prevent new AD across different study populations of "high-risk infants" (infants with a family history of allergic disease/AD), and "general population" (infants from the general population with no specific risk of allergic disease/AD).

Skin barrier enhancement

Initial small studies supported emollient use as a means to prevent AD[39-42], while more recent and larger trials, and systematic reviews, mostly among high-risk infants concluded this not to be effective[43-45]. This may be related to the effort required by parents for such skin care routines, or lack of evidence that the interventions used can adequately maintain the infant skin barrier. Further, the PreventADALL trial that employed a skin intervention strategy as emollients with frequent bathing (4 to 7 days per week) showed it may increase AD [multiple imputation RR 1.66 (95%CI 1.20 to 2.30)][46]. Small trials of emollients, among high-risk infants, that are specifically formulated to improve the skin barrier, particularly those that include ceramides, and that commence within the first days of life, have shown more promising results[41, 47, 48]. Thus, potential optimizing the skin barrier to prevent AD requires further investigation. Other strategies that may require less direct parent effort to enhance the infant skin barrier function include the use of water softeners for bathing in hard water settings, with trials ongoing[49].

Probiotics, prebiotics, symbiotics

Probiotics are live microorganisms, typically ingested, that can confer health benefits. Prebiotics are indigestible fibers that promote health benefits by nourishing (gastrointestinal) commensal microorganisms. Synbiotics are a combination of probiotics and prebiotics[50].

Probiotics: Over 35 RCTs including more than 6000 participants (pregnant mothers, infants, or mother-infant pairs) address probiotic supplementation, yet few trustworthy guidelines address primary prevention of atopic dermatitis using probiotics [51-53]. The challenge of interpreting

154 individual trials to inform clinical practice are (1) the volume of information, (2) the mixture of
155 placebo-controlled trials and relatively fewer active-comparator trials, (3) tracking differences
156 between studies such as whether the mother, infant, or both received the probiotic.
157 In 2015, the World Allergy Organization (WAO)-McMaster University GLAD-P: Probiotics
158 guideline, based on systematic review of the available evidence at that time[54], concluded that
159 probiotics prevented AD (typically the last trimester) with single strains (typically *Lactobacillus*
160 [*paracasei* or *rhamnosus*] or *Bifidobacteria* [longum, animalis, or lactis]) when administered to
161 mothers prenatally[55]. The panel graded the overall GRADE certainty of the evidence for modest
162 benefits to be moderate (due to serious risk of bias), and for unlikely harms, low or very low (due
163 to the risk of bias, indirectness and imprecision). The consequent conditional recommendation,
164 based on overall very low certainty, suggested using probiotics directly for infants at risk of
165 developing AD in addition to supplementing probiotics to both pregnant women and
166 breastfeeding mothers of high-risk infants.
167 Many subsequent systematic reviews failed to address the totality of the evidence[54, 56, 57], follow
168 established credible systematic review standards[58-61], or be free from influence by industry (e.g. a
169 recent meta-analysis published by two authors: an executive of a probiotic company along with
170 their paid consultant[62]). While between-trial comparisons suggest consistency in the preventative
171 effects of probiotics among infants either at high or low risk of developing AD, it remains
172 uncertain to whom the intervention is optimal to give to (mothers, infants, or both[57],), which
173 precise strain(s) confer the greatest benefit[56, 63], and whether the preventative effects of
174 probiotics are sustained over several years (e.g. first 6 years of life or even later at 13 years of
175 age)[64, 65]. Major international efforts are required to provide clarity regarding what could be a
176 low-cost, easily implementable, and generally safe public health intervention (**Table 2**).

Prebiotics: The 2015 WAO-McMaster GLAD-P panel identified no credible systematic reviews, individual randomized trials or observational studies addressing prebiotic use in pregnancy or breastfeeding women among the general population. Based on 6 imprecise, indirect population, and high risk of bias RCTs[66] using prebiotic-containing formula among already formula-fed infants, the authors reported GRADE low certainty (RR 0.68, 95% CI 0.40-1.15) for possible AD prevention among infants from both high-risk and general population. In line with the concern about formula creep and inappropriate industry influence overpromoting formula use[67, 68], the GLAD-P panel conditionally recommended for prebiotic formulas among not-exclusively breastfed infants, and conditionally recommended against them among exclusively breastfed infants[66, 69].

Synbiotic: Compared to the greater number of trials addressing probiotics, direct RCT evidence addressing the combination of probiotics and prebiotics for preventing AD is uncertain. A systematic review published in 2016 identified two small (total 1006 participants) and high risk of bias RCTs conducted among high-risk infants and pregnant women, yielding very uncertain estimates ranging from large reductions (RR 0.11) to increases (RR 1.83) in AD risk[70]. A subsequent small and unblinded 2x2 factorial RCT addressing synbiotics, enhanced skin care, both, or neither, conducted in the general population (459 infants)[71] found no difference between the synbiotic-treated and control groups (RR 0.98, 95%CI 0.75-1.29). Thus, there remains uncertainty whether synbiotics provide an important, or little to no, effect. Given the likely modest effects of probiotics, and the likely overestimate, if any effect, of existing estimates of prebiotics in preventing AD, future trials addressing probiotics, prebiotics, or synbiotics must be powered to definitively detect modest effects to provide clarity regarding their relative merits in preventing AD (**Table 2**)

Vitamin D evidence

The 2016 World Allergy Organization-McMaster University Guidelines concluded that vitamin D supplementation, whether during pregnancy, breastfeeding, or in early infancy, did not have clear evidence for preventing AD (very low certainty)[72]. A more recent systematic review of 4 RCTs addressing maternal vitamin D supplementation during pregnancy (between 800 IU to 4000 IU per day) showed modest effects (OR 0.85, 95% CI 0.67-1.08) in preventing AD among infants from mixed populations (high-risk and general population). Of the 4 RCTs, 3 intentionally contaminated the control group by supplementing control mothers with smaller doses (400 IU) of vitamin D[73]. The one study that did not supplement the control group found a larger reduction of AD in the first year of life (OR 0.55, 95% CI 0.32-0.97)[74], although this protective effect waned over time (OR 0.76, 95% CI: 0.47-1.23 at 24 months; OR 0.75, 95% CI: 0.37-1.52 at 48 months). In terms of neonatal or infant supplementation, 3 small trials with some risk of bias conducted among high-risk infants provided very low certainty findings[73, 75, 76]. Thus, vitamin D supplementation during pregnancy may prevent AD, but whether neonatal and infant supplementation prevents AD is uncertain, highlighting the need for further research in this area[72].

Nutrition and other interventions

Breastfeeding and maternal diet: Multiple studies address breastfeeding's potential preventative effect on AD, with systematic reviews of observational studies including both high-risk and

general populations showing a possible protective effect of exclusive breastfeeding for more than 3 months (pooled OR 0.74; 95% CI: 0.57-0.97), at least on early life AD[77]**.** The low certainty evidence is based on observational data as it is not logistically or ethically feasible to randomize individual children having breastfed or not.

We found one RCT addressing more versus less breastfeeding and the development of AD among healthy breastfed infants. PROBIT[78, 79], a 15-cluster RCTs in Belarus randomized, between 1995 to 1996 using simple randomization, maternity hospitals and their paired affiliated polyclinics to a WHO and UNCIEF-based 10-step breastfeeding promotion intervention (baby-friendly hospital initiative) or standard care for that region at that time and produced about a 10% absolute difference in any breastfeeding between groups (73% vs 60% at infant age of 3 months; 50% vs 36% at 6 months; 20% vs 11% at 12 months). At 12 months, compared to the control group, the intervention reduced the incidence of all rashes (cluster- and family atopic history-adjusted OR 0.54 [95%CI 0.31-0.95]), regardless of being defined as atopic eczema (3.3% vs 6.3%), non-eczematous rash, or non-eczematous and non-infectious rash, but not at 6.5 years (cluster adjusted OR 1.0 [95% CI 0.5-1.8])[80]. Only 1% of participants, however, reported having any ISAAC questionnaire-defined eczema, suggesting a very low risk group of developing AD may have been studied. The authors also reported that the initial eczema outcome data at 12 months was not audited. Thus, breastfeeding's long-term effects on AD remain uncertain. These findings further support the need for long-term follow-up of RCTs addressing AD prevention.

Two studies from the late 1980s involving 523 mothers of high-risk infants showed that avoiding allergenic foods during breastfeeding may have no important effect on reducing the risk of AD in children up to 18 months old (RR 1.01, 95% CI: 0.57-1.79)[81].

Hydrolyzed formulas: Systematic reviews and meta-analyses of RCTs addressing partially (12 RCTs) and extensively hydrolyzed formula (7 RCTs) among high-risk infants, showed no clear reduction in AD compared to human breast milk or cow's milk formula[82].

Multi-component breastfeeding and skin intervention: An unblinded RCT among 318 mother-infant pairs in Japan reported that combining routine pediatric care with teleconsultation (consulting about children's health and parenting for 10 minutes) and email newsletters (information about infant skin care with application of daily moisturizer, breastfeeding, and maternal self-care) up to 4-months of age may prevent AD (RR 0.61, 95% CI 0.52-0.97)[83].

Prenatal fatty acid supplementation: RCTs addressing prenatal supplementation with fish oil derived omega-3 polyunsaturated fatty acids suggest that they may not prevent AD among high-risk infants (RR 1.09 [95%CI 0.82-1.46), but the imprecise estimates, ranging from a 5% reduction in absolute risk to a 14% increase in absolute risk, did not definitively rule out the potential for a protective or harmful effect[84]. An earlier small RCT of prenatal blackcurrant seed oil (rich in both omega-3 and omega-6 polyunsaturated fatty acids) versus olive oil supplementation among 319 pregnant women suggested a possible preventative effect at 12 months of age[85].

Childhood vaccination: A systematic review[86] identified 2 RCTs (total 4383 participants, mixed population of high-risk infants and general population) comparing newborn Bacillus Calmette-Guerin (BCG) vs placebo or no BCG vaccination. They suggested early life vaccination may reduce the risk of AD (RR 0.88 [95%CI 0.79-0.98]) during infancy.

Timing of food introduction: Evidence from systematic reviews of 20 studies (mostly cohort studies) indicates that timing for introduction of complementary feeding may not impact the risk of developing atopic disease including AD[87]. Two trials addressing early introduction of egg

(from 4-10 months (RR 0.87; 95% CI: 0.68-1.12)[88, 89] and 14 trials addressing early introduction of cow's milk (<4 years old: RR 1.14 (0.87-1.49); 5-14 years old: RR 1.05 (0.9-1.23)[89] with mixed study populations (high-risk and general population) showed no clear reduction in AD[88].

Dust mite allergen avoidance and immunotherapy: A systematic review and meta-analysis of 7 RCTs (3040 participants) addressing house dust mite (HDM) allergen avoidance strategies suggested they might not prevent AD in high-risk infants [RR 1.09 (95% CI 0.78-1.49)]. While the lack of a clear preventative effect might be explained by either insufficient reduction of dust mite or a lack of a critical causative role for HDM driving incident AD, confidence in drawing strong inferences regarding no effect are limited by risk of bias and imprecision[90]. An additional RCT in early 1990s comparing reducing HDM exposure using acaricides along with maternal and infant avoidance of common food allergens, versus not, among high-risk infants yielded similar findings[91].

While sublingual and subcutaneous dust mite immunotherapy are effective treatments for AD[92], a trial of 111 high-risk infants aged 5-9 months without HDM sensitization randomized to oral HDM or placebo provided uncertainty in AD prevention (17 events per group at 12 months, RR 0.96 [95%CI 0.55-1.67])[93] and also no difference in AD incidence between the two groups at age three[94].

Albendazole treatment: Albendazole, a microtubule inhibitor best known for its clinical use in treating helminth and protozoal infections, promoted the development of AD in the first 5 years of life [HR 1.58 (95% CI 1.15–2.17)] in a 2515-participant RCT in Uganda (70% hookworm or Schistosoma mansoni infection at baseline) comparing maternal treatment during pregnancy with albendazole and prazinquantel versus to placebo[95]. Suggesting a drug-specific, rather than antihelminth effect, the increased incidence of AD occured regardless of whether mothers were

infected with hookworms or not. Further, prazinquantel, a Schisitome-specific voltage-gated calcium channel inhibitor, did not appreciably increase AD [HR 1.15 (95% CI 0.83-1.58)][95]. In contrast, several small trials comparing albendazole treatment to placebo among older children or adults at general population risk for AD suggested no difference in the incidence of AD[96, 97]. Together, these data suggest that perinatal antimicrobial exposure, potentially by disrupting potentially important commensal protozoal microbes[98], may increase the development of AD. Though not completely consistent with the available data, an alternative hypothesis suggests that hookworm immunomodulatory effects that promote worm survival are disrupted by helminth elimination and therefore promote AD [99, 100] . Further mechanistic and clinical research is required to verify and better understand the applicability of this body of evidence.

Antibiotic treatment: Recent systematic review of 5 observational studies suggests antibiotic exposure during pregnancy or delivery, compared to no antibiotic exposure, may increase the risk of developing AD among children (OR 1.28; 95% CI: 1.06–1.53)[101] consistent with the increased risk of AD from previous meta-analyses[101, 102]. The effect of antimicrobial stewardship interventions, to optimize appropriate antimicrobial use in pregnancy, on AD outcomes remain untested.

What can patients and clinicians do today?

Although many possible interventions, and potential risk factors (not reviewed here), have been studied, what can clinicians and patients do now? The science of translating evidence to recommendations for individual patients and populations now follows defined standards[1, 51, 52, 103]. Optimally addressing prevention of allergy requires considering the balance of benefits,

harms, values and preferences, certainty of evidence, and contextual factors (e.g. acceptability, feasibility, resource implications such as cost and time, equity, and practical considerations). Of the interventions summarized in **Table 1**, probiotic and vitamin D supplementation among pregnant mothers and/or infants, and avoiding unnecessary antibiotic exposure, may modestly reduce the risk of childhood AD. The uncertain effects combined with concerns about feasibility, burdens (practical and financial), however, might leave the decision to use supplements preference sensitive. Newborn BCG vaccination's uncertain small preventative effects for AD have additional uncertain applicability, accessibility, and acceptability among non-tuberculosis endemic areas. Patients concerned about the development of AD should also be reassured that should it occur, there are now robust AD treatment guidelines addressing multiple safe and effective therapies[1, 6, 7] that align with patient values and preferences[104]

Future Directions - How could an effective AD prevention strategy be implemented: a population health perspective

When effective AD prevention strategies are definitively identified, it will be important to consider how they could be implemented, and their effectiveness measured at the population level. Lessons from the recent implementation of food allergy prevention guidelines provide insights. Following RCTs, systematic reviews, and meta-analyses showing a reduction in peanut and egg allergy with earlier introduction of these allergens into the infant diet[89], guidelines

around the world began to recommend early allergen introduction as a food allergy prevention strategy[105]. Australian studies subsequently showed a significant shift towards earlier introduction of egg and peanut[106] and that population-level changes in behavior are achievable. However, despite clear evidence of efficacy in clinical trials, there was surprisingly little reduction in the population prevalence of peanut allergy[107.] Reasons for this are still under investigation, but these findings highlight potential difficulties in translating findings from clinical trials to the general population, as well as the importance of monitoring effectiveness of intervention strategies at the population level.

An important factor to consider is whether allergy prevention strategies and guidelines should target only high-risk populations, such as infants with first-degree relatives with AD or other allergic diseases, or the whole population. The advantage of targeting high-risk populations is that it reduces the trial sample size required to detect a difference between groups (**Table 2**) and may also recruit families motivated to adhere with the intervention, particularly if the intervention requires significant effort. However, if the selected population is too narrow, the intervention may have limited overall population impact[37, 108] (**Table 2**). Interventions may offer larger benefits to the community if applied to the whole population. Compliance, however, among families who perceive that their child is not at risk of developing AD may be low depending on the intensity and acceptability of the intervention. The absence of trial data in lower risk populations also means that the benefits for these populations are often unclear.

Currently the strongest predictors of AD risk are based on genome-wide association studies[109], which are not available outside research settings. In the absence of AD risk prediction tools,

studies typically base their inclusion criteria simply on family history of allergic disease. Valid, accurate and accessible risk prediction tools would help families make informed decisions about their child's AD risk, and identify those who may benefit most from preventive interventions.

Finally, it is important to consider the optimal way to measure atopic dermatitis in clinical trials and population-based studies. Measurement of AD outcomes can be difficult because of the multiple definitions of AD[110] and measures of AD severity[111, 112]. Ideally, interventions should prevent the most severe and persistent forms of AD, while the benefits of preventing mild or self-limiting disease are less clear. It is also important that studies measure outcome effects after completion of the intervention to clearly distinguish between true prevention of disease versus delay in detection of AD (treatment of existing AD rather than preventing it). We have provided several examples of potential early preventative effects that were lost after follow-up. Other reviews in this theme issue address prevention of other allergic diseases.

Conclusion

In summary, AD emerges as a substantial global health concern with multifaceted origins, impacting millions and necessitating clarity regarding preventive measures. This review addressed diverse interventions, ranging from early skin interventions, probiotics and prebiotics to nutritional strategies and childhood vaccinations like BCG. Noteworthy findings highlight the complexity of factors influencing AD development, including skin barrier dysfunction, immune dysregulation, the microbiome, and the intricate relationship with the atopic march concept. They also highlight key methodologic limitations, especially a multitude of underpowered trials,

376 comprising the existing evidence base. This review could serve as a resource for patients,

377 clinicians, and researchers, to understand and refine preventive approaches for AD.

Figure 1: Onset of eczema over the age in years

Longitudinal trajectories of eczema subclasses from birth to 12 years of age identified in the secondary analysis of an Australian randomized trial of infants[113] as a birth cohort study[114] (620 participants). From (Lopez DJ, Lodge CJ, Bui DS, et al. Establishing subclasses of childhood eczema, their risk factors and prognosis. Clin Exp Allergy. 2022; 52: 1079–1090. doi:10.1111/cea.14139).

384 **Table 1. Summary of findings for intervention to prevent developing AD in early life**

Intervention	Effect size, RR (95% CI)	No. of participants (studies)	Population studied	Follow-up age	Certainty (quality) of Evidence (GRADE) as reported by authors
Skin intervention (emollients/moisturizer) among infants					
Emollient or moisturizer[45]	1.03 (0.81-1.31)	3075 (7 RCTs)	High-risk infants	6-36 mo	Moderate (inconsistency)
Probiotics, prebiotics, or synbiotics (combination probiotics with prebiotics)					
Probiotics in mothers only [57]	0.69 (0.38-1.26)	2159 (7 RCTs)	Mixed population	1-6 yr	GRADE assessment not done by study authors
Probiotics in infants only[57]	0.85 (0.62-1.17)	1884 (11 RCTs)	Mixed population	1 mo-9 yr	GRADE assessment not done by study authors
Probiotics in infants and mothers[57]	0.65 (0.49-0.86)	4,739(12 RCTs)	Mixed population	18 mo-11 yr	GRADE assessment not done by study authors
Prebiotics in infants[66]	0.68 (0.40-1.15)	2030 (6 RCTs)	Mixed population	3-24 mo	Low (bias and inconsistency)
Synbiotics in infants[70]	0.44 (0.11-1.83)	1320 (2 RCTs)	High-risk infants	6 mo	GRADE assessment not done by study authors
Vitamin D supplementation					
For pregnant women[73]	0.85 (0.67-1.08)	2074 (4 RCTs)	Mixed population	6-36 mo	Moderate (imprecision)
For infants [75]	0.84 (0.64-1.11)	942 (2 RCTs)	Mixed population	12-30 mo	GRADE assessment not done by study authors
Hydrolyzed formula among infants					
Partially hydrolyzed formula[82]	OR 0.84 (0.67 to 1.07)	5372 (12 RCTs)	High-risk infants	0-14 yo	Moderate (risk of bias)
Extensively hydrolyzed formula[82]	Casein eHF OR 0.55(0.28-1.09) whey eHF OR 1.12 (0.88-1.42)	3374 (7 RCTs)	High-risk infants	0-14 yo	Very low (risk of bias, inconsistency, imprecision)
Allergenic food introduction among infants					
Egg introduction[88] at 4-10 months	0.87 (0.68-1.12)	1368 (2 RCTs)	Mixed population	12 mo	GRADE assessment not done by study authors
Cow's milk introduction[89]	<4 yo: 1.14 (0.87-1.49); 5-14 yo: 1.05 (0.9-1.23)	6,798 (12 RCTs, 1 qRCT, 4 CCT)	Mixed population	5 years	Low (imprecision and indirectness)
Maternal diet					
Prenatal Omega-3 polyunsaturated Fatty Acid supplementation[84]	RR 1.09 (0.82 -1.46)	1926 (6 RCTs)	High-risk	6 mo to 6yr	GRADE assessment not done by study authors
or Prenatal blackcurrant seed oil (BCSO) supplementation [85]	RR 0.70 (0.51-0.96)	313 (1 RCT)-BSCO	Mixed population		
Dust mite avoidance among infants					
HDM allergen avoidance[90]	RR 1.08 (0.78–1.49)	3040 (7 RCTs)	High-risk infants	1 to 8 yr	GRADE assessment not done by study authors
Vaccination among infants					
Bacillus Calmette-Guerin (BCG)[86]	RR 0.88 (0.79-0.98)	4383 (2 RCTs)	Mixed population	13 to 18mo	GRADE assessment not done by study authors
Prenatal antimicrobials					
Prenatal albendazole or praziquantel[95]	Albendazole: HR 1.58 (1.15-2.17) Praziquantel: HR 1.15 (0.83-1.58)	2507 (1 RCT)	General population	5 yr	GRADE assessment not done by study authors
Prenatal antibiotic[115]	RR 1.28 (1.06–1.53)	2098 (5 NRS)	General population	6 mo to 4 yrs	Low (inconsistency, publication bias)

385 "Mixed population" indicated population from both high-risk of allergy and general population.
386 Abbreviation: AD: atopic dermatitis; CI: confidence interval; OR: odds ratio, RCT: randomized clinical trial; RR: Risk
387 Ratio; HR: Hazard Ratio;; NRS, non-randomized studies

Alpha	Power	N total	N per group	Study population control group risk		Intervention group risk	Risk ratio	Risk difference	NNT to prevent 1 case of AD
0.05	80%	734	367	high	30%	21%	0.70	-9%	12
0.05	95%	1,214	607						
0.05	80%	1,080	540			22.5%	0.75	-7.5%	14
0.05	95%	1,784	892						
0.05	80%	1,718	859			24%	0.80	-6%	17
0.05	95%	2,840	1,420						
0.05	80%	3,108	1,554			25.5%	0.85	-4.5%	23
0.05	95%	5,142	2,571						
0.05	80%	7,108	3,554			27%	0.90	-3%	34
0.05	95%	11,764	5,882						
0.05	80%	1,230	615	medium	20%	14%	0.70	-6%	17
0.05	95%	2,032	1,016						
0.05	80%	1,812	906			15%	0.75	-5%	20
0.05	95%	2,996	1,498						
0.05	80%	2,894	1,447			16%	0.80	-4%	25
0.05	95%	4,790	2,395						
0.05	80%	5,258	2,629			17%	0.85	-3%	34
0.05	95%	8,702	4,351						
0.05	80%	12,078	6,039			18%	0.90	-2%	50
0.05	95%	19,994	9,997						
0.05	80%	2,712	1,356	low or "general population"	10%	7%	0.70	-3%	34
0.05	95%	4,486	2,243						
0.05	80%	4,010	2,005			7.5%	0.75	-2.5%	40
0.05	95%	6,636	3,318						
0.05	80%	6,426	3,213			8%	0.80	-2%	50
0.05	95%	10,638	5,319						
0.05	80%	11,712	5,856			8.5%	0.85	-1.5%	67
0.05	95%	19,388	9,694						
0.05	80%	26,990	13,495			9%	0.90	-1%	100
0.05	95%	44,684	22,342						

Table 2. Example sample size calculations ordered from top to bottom from most optimistic to pessimistic for a hypothetical future prevention trial addressing atopic dermatitis, assuming various scenarios for the desired power of the trial to detect a difference, if one exists, the risk of the population studied to develop AD, and the assumed size of the effect. Other assumptions: 1:1 allocation ratio, no loss to follow-up, contamination, or non-compliance. For comparison, the available probiotic randomized trials, like many existing RCTs addressing various interventions for AD, range from a total sample size of 81 to 606[56]. Much larger RCTs are required to deliver definitive evidence for whether interventions are effective, or not, for preventing AD. NNT, number needed to treat.

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