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The Role of Environmental Exposures in Atopic Dermatitis

Shanthi Narla[1] · Jonathan I. Silverberg[2]

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Abstract

Purpose of Review Although genetic factors clearly play a role in the development of atopic dermatitis (AD), the recent dramatic increase in the prevalence of AD in low- and middle-income countries is not consistent with only a role of genetic factors. These findings strongly suggest that environmental factors may play an important role in the pathogenesis of AD.

Recent Findings We reviewed the role of gene-environment studies; in utero exposures including tobacco smoke, alcohol, maternal stress, various digestive supplements, and gestational diabetes; early-life exposures including diet, gut microbiota, antibiotics, and breastfeeding; climate including temperature, ultraviolet radiation exposure, and air pollution; and household products, indoor allergens, water hardness, pH, and skin microbiota and their effects on AD.

Summary Environmental factors definitely play a role in the pathogenesis of AD. However, identifying definitive factors continues to be difficult in the setting of conflicting evidence and the complex interactions between genotypes and the environment resulting in a multitude of AD phenotypes. All of the different environmental interactions discussed highlight the importance of intervening on multiple levels in a patient's environment to improve or even prevent AD symptoms. Further, the importance of modifying environmental factors early on in a person's life is demonstrated. When possible, all of these environmental factors should be considered in treating a patient with AD and the appropriate modifications should be made at population and individual levels.

Keywords Atopic dermatitis · Environment · Prenatal · Tobacco smoke · Alcohol · Maternal stress · Gene-environment interactions · Fatty acids · Prebiotics · Probiotics · Postbiotics · Gestational diabetes · Antibiotics · Breastfeeding · Climate · Temperature · Ultraviolet radiation · Air pollution · Household products · Indoor allergens · Water hardness · pH · Skin microbiota · Gut microbiota · Cesarean section · Hygiene hypothesis

Abbreviations

AD	Atopic dermatitis
GEI	Gene-environment interactions
UVR	Ultraviolet radiation
FLG	Filaggrin
GDM	Gestational diabetes mellitus
SCFA	Short-chain fatty acids
AD-E	Atopic dermatitis or eczema
ISAAC	International Study of Asthma and Allergies in Childhood
TRAP	Traffic-related air pollution
SNP	Single-nucleotide polymorphisms
MMP	Matrix metalloproteinase
TNF	Tumor necrosis factor
IL	Interleukin
HPs	Household products
NMF	Natural moisturizing factor
SR	Systematic review
PRR	Pattern recognition receptor
AMP	Antimicrobial peptide
RCT	Randomized controlled trial
EPA	Eicosapentaenoic acid
DHA	Docosahexaenoic acid
PUFA	Polyunsaturated fatty acids
scGOS	Short-chain galactofructoside
lcFOS	Long-chain fructo-oligosaccharide
BMI	Body mass index

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✉ Jonathan I. Silverberg
JonathanISilverberg@Gmail.com

[1] Department of Dermatology, St. Luke's University Health Network, Easton, PA 18045, USA

[2] Department of Dermatology, The George Washington University School of Medicine and Health Sciences, Suite 2B-430, 2150 Pennsylvania Avenue, Washington, DC 20037, USA

COCOA	Cohort for Childhood Origin of Asthma and Allergic Diseases
PSKC	Panel Study on Korean Children
ISAAC	International Study of Asthma and Allergies in Childhood Phase III
C-section	Cesarean section
$PM_{2.5}$, PM_{10}	atmospheric particulate matter that have a diameter of less than 2.5 micrometers and 10 micrometers
NO_2	Nitrogen dioxide
SO_2	Sulfur dioxide
AhR	Aryl hydrocarbon receptor
TEWL	Transepidermal water loss
HDM	House dust mites
SE	Staphylococcal enterotoxin
CE	Cornified cell envelope

Introduction

The recent dramatic global increase in the prevalence of atopic dermatitis (AD) [1] suggests that shifting environmental factors play a role in the development of AD [2, 3]. Numerous environmental factors, such as climate and stress, can be triggers of itch in AD [4]. This article is a non-systematic review of the current evidence for environmental risk factors in AD (Table 1). In general, we address systematic reviews and level of evidence where available. Otherwise, we address key individual studies of exposures.

AD Pathogenesis

AD is caused by a complex overlap of genetic, immunologic, and environmental factors.

Parental history of AD is associated with a 2–3-fold increased risk of childhood AD [5]. Monozygotic twins have ~3 times higher concordance rate than dizygotic twins [6]. The strongest genetic risk factor for AD is loss-of-function mutations of the filaggrin (FLG) gene, contributing to skin-barrier dysruption, [7] though many AD patients do not have FLG mutations, and ~40% of individuals with FLG null mutations do not have AD [8]. Another gene implicated is the serine protease inhibitor Kazal-type 5, which is important in skin-barrier homeostasis, including stratum corneum desquamation, lipid barrier construction, and development of the cornified cell envelope (CE) [9].

Keratinocytes produce antimicrobial peptides (AMPs) (e.g., human β-defensin 1) [9], and pattern recognition receptors recognize molecules found on pathogens and activate microbial and pro-inflammatory responses required to eliminate the infectious agents [10]. *S. aureus* colonizes skin of 30–100% of AD patients, but only 20% of healthy people [11]. *S. aureus* colonization may precede AD flares and facilitate inflammation in AD [12]. Consequently, mutations in pattern recognition receptors (e.g., toll-like receptor 2 (TLR2), TLR6, TLR9) and AMPs may play a role in the initiation and exacerbation of AD [9]. However, it is unclear if microbial change is a cause of or effect from barrier dysfunction and cutaneous inflammation [11].

Th2 effector cells producing interleukins (IL)-4, 5, 13, and 31 and Th22 cells producing IL-22 and S100A proteins predominate in the acute and chronic phases of disease, with increased IL-17 production shown in a subset of patients [13, 14]. These mediators are implicated in downregulation of terminal differentiation genes and tight junction products (e.g., claudins), which contribute to barrier defects in AD [13]. Keratinocytes differentiated in the presence of IL-4 and IL-13 exhibited reduced FLG gene expression, even in patients without FLG null mutations, and also downregulated loricrin and involucrin, important proteins that facilitate the terminal differentiation of the epidermis and formation of the CE. While Th2 cells facilitate *Staphylococcus aureus* binding and colonization, IL-4 and IL-13 inhibit skin production of AMPs, predisposing AD skin to staphylococcus infections. IL-31 is implicated in itch and skin-homing of T cells [13, 15]. Chronic AD lesions are also associated with enhanced IL-5 and IL-12 production, and increased Th1 cells and related cytokines (e.g., interferon gamma) [14, 15].

Gene-Environment Interactions

Individual responses to environmental exposures are driven by gene-environment interactions (GEIs). A systematic review (SR) of GEI in AD found that FLG null mutations were most widely replicated across studies and had the strongest effect size. GEIs were demonstrated between FLG genotype and multiple risk factors of AD, such that older siblings, phthalate exposure in household dust and urine phthalate metabolite levels, early-life exposure to cats, and water hardness were associated with increased AD risk. Breastfeeding duration was inversely associated with AD risk. There were no interactions between FLG and day-care attendance, gender, maternal parity, maternal AD, maternal smoking, early-life environmental tobacco smoke exposure, birth year, serum vitamin D levels, or maternal IgE sensitization. Evidence for GEI in AD is relatively limited, with few studies, small sample sizes, and study results not being replicated [16].

Table 1 Summary of effect sizes for various environmental exposures and atopic dermatitis

Type	Environmental exposure	Study	Type of study	Number of studies (*N*)	Effect size [95% CI]	*P* value	Comments	LOE, SORT
Gene (FLG)-environment interactions	Older siblings in patients attending day care	Blakeway et al. [16]	SR	12	OR 3.27 [1.14–9.36]	< 0.05	Only 12 studies included Low number of individuals with AD and FLG loss-of-function mutations Many of the exposures only had 1 study (e.g., older siblings in day care)	2,B
	Older siblings in patients not attending day care				OR 2.41 [1.06–5.48]	< 0.05		
	Cat exposure				HR 11.11 [3.79–32.60]	0.0008		
	Cat exposure				HR 3.82 [1.35–10.81]	0.011		
	Water hardness				HR 2.72 [2.03–3.66]	< 0.05		
	Urine phthalate metabolite levels				MBP: aOR 4.74 [1.45–15.5]; MBzP: aOR 3.46 [1.03–11.58]	0.015; 0.018		
In utero	Smoking	Kantor et al. [17]	SR	23	Overall: OR 1.06 [0.80–1.40]	> 0.05	There was a positive association between AD and maternal smoking during pregnancy in studies from Asia and a NOS score less than 6, but an inverse association seen in studies with a sample size > 5000	2,B
					Studies from Asia: OR 1.59 [1.28–2.03]	< 0.05		2,B
	Smoking	Shinohara and Matsumoto [18]	Cross-sectional	1	aOR 5.21 [1.08–25.15]	0.020	Enrolled 1,177 parent-infant pairs, in which infants >6 months old	2,B
	Alcohol	Halling-Overgaard et al. [22]	SR	4	Pooled OR 1.16 [1.09–1.24]	< 0.0001	3 birth cohorts, 1 cross-sectional study included; originated from 4 different countries: Denmark, Japan, UK, Germany; all four studies reported mixed results	2,B
	Fish oil and omega-3 fatty acids	Furuhjelm et al. [26]	RCT	1	OR 0.22 [0.06–0.81]	< 0.015	Placebo-controlled; 145 women pregnant women were enrolled	2,B
	High maternal fish intake	Group et al. [27]	Prospective birth cohort	1	aOR 0.75 [0.57–0.98]	< 0.05	Data from 2,641 children at 2 years of age was assessed	2,B
	Maternal fish consumption (≥ 1/week)	Willers et al. [28]	Longitudinal birth cohort	1	OR 0.57 [0.35–0.92]	0.008	1,253 children participated at 5 years and maternal food frequency questionnaire available for 1,212	2,B
	Omega-3 fatty acids or fish intake	Best et al. [29]	SR	15	RR 0.53 [0.35–0.81]	0.004	A total of 13 publications from 10 prospective cohort studies, and 7 publications from 5 unique RCTs were included; meta-analysis limited due to heterogeneity of results	2,B
	Prenatal antibiotics	Huang et al. [33]	SR	7	OR 1.93 [1.35–2.76]	< 0.05	7 observational studies	2,B
	Probiotics	Yin et al. [41]	SR	22	Overall: RR 0.81 [0.70–0.93];	< 0.05	22 RCTs, heterogeneity test showed significant heterogeneity so random effects model was used in analyses	2,B

Table 1 (continued)

Type	Environmental exposure	Study	Type of study	Number of studies (*N*)	Effect size [95% CI]	*P* value	Comments	LOE, SORT
					Lactobacillus and *Bifidobacteria*: RR 0.68 [0.52–0.90]			
	Gestational diabetes mellitus	Kumar et al. [44]	Prospective birth cohort	1	OR 7.2 [1.5–34.5]	< 0.05	Included 680 children; mother-child pairs followed to a mean age of 3.2 ± 2.3 years	2,B
	Prenatal maternal distress	Chang et al. [51]	Population-based birth cohort	1	COCOA: Depression: HR 1.31 [1.02–1.69] Anxiety: HR 1.41 [1.06–1.89]; PSKC: Distress: OR 1.85 [1.06–3.25]	< 0.05	2 sets of birth cohorts were analyzed separately: COCOA and PSKC	2,B
	Maternal vitamin D levels in pregnancy	Wei et al. [76]	SR	3	Pooled OR 0.904 [0.831–0.983]	< 0.05	2,172 mother-child pairs; all were prospective cohort studies	2,B
Infants	Prebiotics	Osborn and Sinn [38]	Cochrane Database SR	4	Typical risk ratio 0.68 [0.48–0.97]	0.03	1,218 infants; no significant heterogeneity found between studies	2,B
	Vitamin C in breast milk	Hoppu et al. [54]	Prospective cohort	1	OR 0.30 [0.09–0.94]	0.038	34 mother-infant pairs included; maternal intake of vitamin C in diet but not as supplement was shown to determine the concentration of vitamin C in breast milk	2,B
	Increased birth weight	Panduru et al. [58]	SR	10	OR 1.1 [1.02–1.17]	0.01	Included cross-sectional, case-control, and cohort studies, 110,974 patients	2,B
	Assisted birth	Gerlich et al. [60]	Prospective cohort	1	Flexural eczema (FE): 2.2 [1.2–4.3]; Doctor's diagnosis of AD: 1.9 [1.0–3.4]	< 0.05	Being female increased the risk of presenting with FE in childhood or doctor's diagnosis of AD in adulthood	2,B
	Breastfeeding	Lin et al. [63]	SR	27	Pooled estimates: Total: 1.01 [0.93–1.10] Exclusive: 0.99 [0.88–1.11]	> 0.05	Prospective cohort studies included; heterogeneity was substantial across studies	2,B
					Children with atopic hereditary: Total: RR 0.85 [0.74–0.98] Exclusive: RR 0.83 [0.70–0.97]; Children without atopic hereditary: Total: RR 1.11 [0.94–1.31] Exclusive: RR 1.19	< 0.05		

Table 1 (continued)

Type	Environmental exposure	Study	Type of study	Number of studies (*N*)	Effect size [95% CI]	*P* value	Comments	LOE, SORT
					[1.02–1.40]			
	Breastfeeding >3–4 months	Lodge et al. [65]	SR	42	OR 0.74 [0.57–0.97]	0.023	Estimate principally from 24 cohort studies, 17 cross-sectional studies, 1 case-control; there was a reduced risk of eczema below the age of 2 years from pooling the 6 cohort studies' estimates comparing exclusive breastfeeding greater than 3–4 months with other feeding types	2,B
	House dust mite avoidance	Bremmer and Simpson [105]	SR	7	RR 1.08 [0.79–1.49]	0.66	7 RCTs, largely unblinded, 3 trials utilizing a dust mite avoidance approach but no additional interventions	2,B
Children	Maternal depression	Kim et al. [47]	Retrospective cohort	1	aOR 1.755 [1.183–2.602]	< 0.05	13,782 subjects (8,091 mothers)	2,B
	Maternal depression	Mckenzie and Silverberg [48]	Prospective cohort	1	Postpartum depression: aOR 1.32 [1.06–1.64]; Maternal depression in the last year: At 5 years: aOR 1.54 [1.20–1.99] At 9 years: aOR 1.36 [1.10–1.71] At 15 years: aOR 1.43 [1.13–1.80]	< 0.05	4,898 children born in 20 metropolitan US cites	2,B
	Diet (recently diagnosed AD versus AD diagnosed >12 months ago)	Cho et al. [69]	Cross-sectional	1	Fast food: OR 1.405 [1.150–1.717] Energy drinks: OR 1.457 [1.175–1.807] Convenience food: 1.304 [1.138–1.495]	< 0.001	53,373 subjects (male 26,642; female 26,731); among them, the number of recently diagnosed AD patients was 3,898, and that of the previous-diagnosed AD patients was 9,574. The weighted prevalence of the recently-diagnosed AD and previously-diagnosed AD patients was 7.4% and 18.0%, respectively.	2,B
	Fast food ≥ 3 times/week	Ellwood et al. [70]	Prospective cohort	1	Adolescents (13–14 years): Current eczema: OR 1.21 [1.14–1.34] Severe eczema: OR 1.70 [1.48–1.95] Children (6–7 years): Severe eczema: OR 1.30 [1.05–1.61]	< 0.05	Data from 319,196 adolescents from 107 centers in 51 countries and 181,631 children from 64 center in 31 countries were included in the diet analysis	2,B
	Diet	Wang et al. [71]	SR	2	Fast food: Severe eczema: aOR 1.51 [1.16–1.96] Hamburgers:	< 0.05	2 cross-sectional studies (total of 23,028 participants)	2,B

Table 1 (continued)

Type	Environmental exposure	Study	Type of study	Number of studies (*N*)	Effect size [95% CI]	*P* value	Comments	LOE, SORT
					Severe eczema: aOR: 1.51 [1.16–1.96]			
	Smoking	Kantor et al. [17]	SR	20	Active: OR 2.19 [1.34–3.57]	< 0.05	Active smoking: association remained significant in studies on both adults and children, across all regions, and irrespective of sample size; all studies were cross-sectional and NOS ≥ 6	2,B
				66	Passive: OR 1.15 [1.01–1.30]		Passive smoking: Remained significant in cross-sectional studies but not in cohort studies, South/Central America, Africa, sample sizes < 5000, and NOS < 6	2,B
	Vitamin E	Oh et al. [82]	Case-control, population--based	1	OR 0.33 [0.16–0.67]	< 0.05	Reduced AD risk was found with 1 SD increase of serum a-tocopherol (OR 0.64 [0.41–0.98]); final analysis included 180 AD (mean age 5.3 ± 0.9 years) and 242 non-AD (mean age 5.2 ± 1.0 years) children	2,B
	Climate	Silverberg, Hanifin, and Simpson [87]	Prospective population--based	1	Higher relative humidity: OR 0.80 [0.69–0.93]; Higher UV index: 3rd quartile: OR 0.87 [0.78–0.96], 4th quartile: OR 0.74 [0.65–0.84]; Higher annual mean temperature: 3rd quartile: OR 0.76 [0.65–0.87], 4th quartile: OR 0.85 [0.75–0.98]; Heating degree day: 3rd quartile: OR 1.17 [1.04–1.31]; Higher annual precipitation: 2nd quartile: OR 1.33 [1.11–1.60], 3rd quartile: OR 1.47 [1.22–1.76], 4th quartile: OR 1.39 [1.16–1.66]	0.003; 0.006, < 0.0001; 0.0002, 0.02; 0.01; 0.002, < 0.0001, 0.0003	A merged analysis of the 2007 National Survey of Children's Health from a representative sample of 91,642 children age 0–17 years and the 2006–2007 National Climate Data Center and Weather Service measurements of relative humidity (%), indoor heating degree days (HDD), clear sky UV indices ozone levels, and outdoor air temperature	2,B
	Climate	Sargen, Hoffstad, and Margolis [89]	Prospective cohort study	1	Higher temperature: OR 0.90 [0.87–0.93];	< 0.001, 0.009, 0.04	5,595 US children; higher humidity lost significance in multivariate analyses ($p = 0.44$)	2,B

Table 1 (continued)

Type	Environmental exposure	Study	Type of study	Number of studies (*N*)	Effect size [95% CI]	*P* value	Comments	LOE, SORT
					Increased sun exposure: OR 0.93 [0.89–0.98]; Higher humidity: OR 0.90 [0.812–0.997]			
	Pet dander (early exposure before development of AD)	Pelucchi et al. [99]	SR	21	Dogs: pooled RR 0.72 [0.61–0.85] Pets overall: pooled RR 0.75 [0.67–0.85] Cats: 0.94 [0.76–1.16]	–	26 publications from 21 birth cohort studies; no heterogeneity emerged across the subgroups examined, except for geographic area; dogs = 15 studies, cats = 13 studies, pets overall = 11 studies	2,B
Adults	Alcohol	Silverberg and Greenland [21]	Retrospective cohort study	1	Odds of ever drinking 12 or more alcoholic beverages annually: aOR 1.16 [1.03–1.31], including current intake of moderate amounts: aOR 1.33 [1.09–1.62] and heavier amounts: aOR 1.58 [1.23–2.03]	0.02, 0.005, < 0.001	27,157 and 34,525 adults ages 18 to 85 years from the 2010 and 2012 National Health Interview Survey	2,B
	Alcohol	Halling-Overgaard et al. [22]	SR	13	Pooled OR 1.06 [0.92–1.23]	0.44	Eighteen studies were included in the qualitative analysis (comparing alcohol drinkers to abstainers), and 12 studies were included in the quantitative analysis; adults and adolescents included	2,B
	Smoking	Kantor et al. [17]	SR	20	Active: OR 1.30 [1.06–1.59]	< 0.05	Active smoking: association remained significant in studies on both adults and children, across all regions, and irrespective of sample size; all studies were cross-sectional and NOS ≥ 6	2,B
				66	Passive: OR 3.62 [1.71–7.69]		Passive smoking: Remained significant in cross-sectional studies but not in cohort studies, South/Central America, Africa, sample sizes < 5000, and NOS < 6	2,B
	Air pollutants	Fan et al. [95]	Prospective cohort	1	PM_{10} RR = 1.0052 [1.0014–1.0090]	< 0.05	There were 72,305 eczema outpatient visits in total, making up 21.8% of all outpatients living in Chengdu referred to the dermatology clinics in West China Hospital of Sichuan University from 2011 to 2015, and an average of 40 visits for eczema per day after excluding the outpatients living outside downtown area of Chengdu.	2,B
	Higher usage of household products	Choi, Kim, and Kim [98]	Prospective cohort	1	Lifetime diagnosis of AD: OR 1.77 [1.23–2.54]	< 0.01, < 0.001, < 0.001	1,500 subjects were included in the analysis; online survey so recall bias may be present	2,B

Table 1 (continued)

Type	Environmental exposure	Study	Type of study	Number of studies (*N*)	Effect size [95% CI]	*P* value	Comments	LOE, SORT
					Symptoms of AD in last 12 months: 2.66 [1.92–3.70] Treatment of AD in last 12 months: 2.37 [1.48–3.80]			
	Increased frequency of usage of household products	Choi, Kim, and Kim [98]	Prospective cohort	1	Lifetime diagnosis of AD: OR 1.88 [1.31–2.70] Symptoms of AD in last 12 months: 2.14 [1.54–2.96] Treatment of AD in last 12 months: 2.23 [1.39–3.60]	< 0.01, < 0.001, < 0.01	1,500 subjects were included in the analysis; online survey so recall bias may be present	2,B

OR odds ratio, *aOR* adjusted odds ratio, *HR* hazard ratio, *RR* relative risk, *AD* atopic dermatitis, *MBP* monobutyl phthalate, *MBzP* mono-benzyl phthalate, *SORT* strength of recommendation taxonomy, *SR* systematic review, *LOE* level of evidence, *NOS* Newcastle-Ottawa Scale, *UK* United Kingdom, US United States of America, *RCT* randomized controlled trial, *COCOA* Cohort for Childhood Origin of Asthma and Allergic Diseases, *PSKC* Panel Study on Korean Children, *SD* standard deviation

In Utero Exposures

Smoking

A SR and meta-analysis found that a diagnosis of AD is associated with higher odds of active smoking and exposure to passive smoke in both adults and children. In comparison, no association between AD and maternal smoking during pregnancy overall; however, in sensitivity analyses, childhood AD was associated with maternal smoking during pregnancy in Asian cohort studies, and inversely associated with maternal smoking in studies with a sample size ≥ 5000. No differences were observed between AD prevalence and amount of smoking ($n = 5$) [17]. A Japanese cross-sectional study found that fetal exposure to tobacco smoke after 28 weeks of gestation was associated with higher cumulative incidence of AD. Smoke exposure during the first 6 months of life was not associated with cumulative incidence of AD [18].

The mechanism of maternal smoking increasing risk of childhood AD is unclear. In one study, maternal smoking after 24 weeks of gestation altered DNA methylation of the aryl hydrocarbon receptor (AhR) in newborns with smoking-induced epigenetic changes persisting 18 months post-birth [19]. Polychlorinated biphenyls (PCBs) and 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) are environmental pollutants present in cigarette smoke, whose biological effects are mediated by AhR [20]. However, the association of in utero smoking and childhood AD may be confounded by other AD risk factors, such as race/ethnicity, education, and socioeconomic status that account for this association. The regional differences for the association between childhood AD and maternal smoking during pregnancy may be related to public health policy or cultural differences such as prohibition against smoking indoors versus climate differences (e.g., humidity) [17]. Further large-scale studies are needed to determine the contribution of smoking during pregnancy toward the development of childhood AD while controlling for the various confounding factors mentioned above to elucidate regional differences.

Alcohol

Analysis of 2010–2012 National Health Interview Survey Data found that adult AD was associated with greater odds of ever drinking ≥ 12 alcoholic beverages annually, including current moderate and heavier intake [21]. However, a SR and meta-analysis of 12 studies found mixed results for the association between alcohol consumption and AD. There was an association between alcohol use during pregnancy and development of AD in offspring. However, there was no consistent association between alcohol use and AD in adults and adolescents [22].

Fish Oil and Omega-3 Fatty Acids

Eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) are long-chain omega-3 polyunsaturated fatty acids (n-3 PUFA), found in oily fish, that are thought to inhibit the formation of prostaglandin E2 and leukotriene B4 and might protect against allergic diseases [23]. Conflicting results were found regarding n-3 PUFA supplementation during pregnancy and risk of infantile AD [24]. Three RCTs examined the development of food allergy and eczema after n-3 PUFA supplementation during pregnancy [25]. One study demonstrated a reduction in incidence of IgE-associated eczema in infants with a family history of allergic disease after very high doses of DHA and EPA [26]. In a prospective birth cohort study, high maternal intake of margarine and vegetable oils during the last 4 weeks of pregnancy was associated with AD during the first 2 years of the offspring's life, whereas high maternal fish intake was inversely associated with AD [27]. Similar results were observed in a longitudinal birth cohort study that followed children until age 5 years [28].

Pooled results from a SR and meta-analysis (10 prospective cohort studies, 5 RCTs) showed reduced AD in the first 12 months of life with maternal intake of n-3 PUFAs, albeit with considerable heterogeneity of results [29].

Hygiene Hypothesis

The hygiene hypothesis states that the decreasing incidence of infections in western countries (and more recently developing countries) is leading to increasing incidence of autoimmune and allergic diseases [30]. Conversely, early-life exposures to microbes and their products may help steer the immature immune system away from AD and allergic disease. In several studies, maternal exposure to farm animals in pregnancy was associated with reduced risk of childhood AD, and increased immune responses that may protect against asthma and allergies [31]. Further, early-life exposure to older siblings or children in day-care nurseries may protect against atopy [32]. A SR of seven observational studies showed that prenatal antibiotic use was associated with increased eczema in infancy, and antibiotic exposure in utero was likely associated with eczema even after 1 year of age [33].

Proposed mechanisms for the hygiene hypothesis include decreased antigenic stimulation from fewer childhood infections leading to decreased levels of regulatory cytokines (e.g., IL-10 and TGF-β). A matched case-control study found that incident AD was lower for children who had ≥ 4 infections vs. no infections. Daily contact with dogs was also inversely associated with AD risk [32].

Immune stimulation by endotoxin may also be important for maturation of the immune system [34]. A cross-sectional study of 812 children ages 6–13 years from farming and nonfarming households in rural Europe found that higher endotoxin levels in mattress dust correlated with decreased frequency of hay fever, allergic asthma, and allergic sensitization [35]. However, not all microbial pathogens protect against AD. Respiratory syncytial virus appears to increase the risk of AD [15]. Thus, each pathogen may have distinct effects on AD and allergic risk.

Prebiotics

The effects of prebiotics and probiotics in AD and allergic diseases may be related to the hygiene hypothesis [36]. Prebiotics are non-digestible fibers (e.g., oligosaccharides) that stimulate the growth and/or activity of gut microbiota (probiotics) for beneficial effects [37]. The effect of prebiotic supplementation on the prevention and treatment of AD has been less studied than the effect of probiotic supplementation. A 2013 Cochrane review of RCTs or quasi-RCTs found that prebiotics given to infants reduced AD risk [38]. A double-blind, placebo-controlled RCT fed a prebiotic-supplemented (0.8 g/100 ml short-chain galactofructoside [scGOS]/long-chain fructo-oligosaccharide [lcFOS]) or placebo-supplemented (0.8 g/100 ml maltodextrin) hypoallergenic formula to infants during the first 6 month of life and found lower 5-year cumulative incidence of AD in the scGOS/lcFOS vs. placebo group; persistent AD was numerically less common [39]. Further interventional studies are needed to determine definitive risk reduction.

Probiotics

Probiotics may inhibit Th2 and stimulate Th1 cytokines, e.g., interferon gamma [36]. In murine studies, probiotics reduced AD symptoms, IgE levels, infiltration of lymphocytes and granulocytes, and levels of IL-4, 5, 10, and 13 [40]. A meta-analysis of 22 RCTs showed that probiotic supplementation during pregnancy and/or infancy reduced AD incidence. Intervention with *Lactobacillus* and *Bifidobacterium* had the largest effect. Probiotic supplementation during pregnancy and/or infancy was more effective at preventing AD in children age ≤ 2 vs. > 2 years [41].

Postbiotics

Postbiotics (e.g., microbial cells, cell constituents, and metabolites) are bioactive compounds produced by food-grade microorganisms during fermentation [42]. Little evidence is available regarding the use of postbiotics during the prenatal or postnatal periods for AD prevention. A pilot study found that ingesting fermented rice flour containing *Lactobacillus paracasei* CBA-L74 for 12 weeks was associated with lower SCORAD scores in children ages 6 months to 6 years; all had a SCORAD < 35 and reduced or suspended topical

corticosteroid application [43]. Further large-scale RCTs are needed to draw definitive conclusions.

Gestational Diabetes

A study conducted in 680 children, with mother-child dyads recruited at birth and followed prospectively until age 3.2 ± 2.3 years, showed that gestational diabetes mellitus (GDM) was associated with childhood AD and early allergen sensitization independent of maternal pre-pregnancy BMI and fetal growth. These associations were not observed in preterm births [44]. One study showed that at 6-month post-delivery, 30.8% of offspring from mothers who had GDM developed AD, food allergy, or allergic proctocolitis compared to none from the healthy controls group. At the third trimester of pregnancy, blood samples from the GDM group had a higher proportion of Th2, Th17, and Treg cells compared to the control group. Higher circulating c-reactive protein and total IgE levels were noted in the GDM group [45].

The mechanism by which GDM affects AD and allergen sensitization remains unclear. Placental microbiota may contribute to fetal homeostasis and healthy barrier function. Placentas in women with GDM showed lower amounts of bacteria belonging to the *Pseudomonadales* order and *Acinetobacter* genus compared to healthy controls. Lower levels of *Acinetobacter* were associated with lower placental expression of IL-10, a key anti-inflammatory cytokine, and TIMP3. Hence, GDM may modify the placental microbiome, leading to lower IL-10 levels, pushing toward allergen sensitization and AD development [46].

Maternal Stress

Data from 13,782 pediatric subjects (8,091 mothers) < 18 years in the 2007–2014 Korea National Health and Nutrition Examination Surveys showed that maternal depression was associated with children's AD [47]. Data from the Fragile Families and Child Wellbeing Study found that maternal depression in the past year was associated with higher odds of AD at age 5, 9, and/or 15 years in US children. Postpartum depression was also associated with more persistent AD in children, [48] whereas a Danish study of 8,062 children with AD found no associations between paternal or prenatal maternal psychiatric disease with AD in the offspring [49].

In a SR of 11 studies, maternal stress was associated with eczema risk in their offspring [50]. Stress factors included the following: depression, postpartum depression, prenatal anxiety, maternal stress during pregnancy, prenatal adverse life events, job strain during pregnancy, prenatal distress, and perceived stress. The limited number and heterogeneity of studies precluded determining the time period in pregnancy most impacted by maternal stress [50].

Similar results were found in a study of two general population-based cohorts (Cohort for Childhood Origin of Asthma and Allergic Diseases [COCOA] and the Panel Study on Korean Children [PSKC]). Prenatal maternal distress increased AD risk in offspring in COCOA and PSKC. In COCOA, prenatal maternal depression and anxiety scores were related to the predicted probability of AD. Prenatal distress decreased placental glutathione to glutathione disulfide ratios and 11β-hydroxysteroid dehydrogenase type 2 levels, especially in those who developed AD and increased IgE levels at age 1 year [51].

A recent SR and meta-analysis ($n = 6$ studies) showed the prevalence of parental depression to be higher in children with AD versus without AD or healthy controls [52]. Caring for children with AD may lead to parental stress that may increase the incidence rates of AD in future offspring.

Early-Life Exposures

Maternal Diet

A 2014 Cochrane review of five trials involving 952 participants did not observe a protective effect of maternal dietary antigen avoidance during pregnancy on the incidence of AD in the first 18 months of life, but did note an association with lower mean gestational weight [53]. However, higher concentrations of vitamin C in breast milk were associated with reduced risk of atopy in the infant [54]. Similarly, low vitamin D levels in breastmilk might be a risk factor for infantile AD [55].

Birth Weight

A SR of 42 studies showed that a birth weight increase of 1 kg was associated with a 17% greater risk of AD in children, and a 34% greater risk of ever or current AD in infants up to 2 years of age [56]. A study of Japanese children found that AD occurred at a lower prevalence at age 18 months but not at 3 years among those who had low (< 2500 g) vs. normal (> 2500 g) birthweight [57]. Similarly, a SR and meta-analysis ($n = 10$ studies) found that low birth weight was a protective factor against the occurrence of AD. Moreover, increased birth weight was a risk factor for AD [58].

Vaginal vs. Cesarean Section

In a study examining the relationship between mode of delivery and the structure of the initial microbiota body habitats in newborns, vaginally delivered infants acquired bacterial communities (in all body habitats—skin, oral, nasopharyngeal, and gut) resembling their own mother's vaginal microbiota, dominated by *Lactobacillus*, *Prevotella*, or *Sneathia* spp., and cesarean

section (C-section) infants harbored bacterial communities (in all body habitats—skin, oral, nasopharyngeal, and gut) similar to those found on the skin surface, dominated by *Staphylococcus*, *Corynebacterium*, and *Propionibacterium* species [59]. Children born by C-section, especially those with assisted birth, were at greater risk for developing asthma, flexural eczema, and sensitization [60]. In contrast, a large cohort study found an association between C-section and AD, but this effect was attenuated after adjustment. In stratified analyses, there was some evidence that C-section may increase AD risk among certain subgroups such as firstborns or overweight/obese pre-pregnancy BMI, but the associations were weak [61].

Breastfeeding

Breast milk is rich in PUFAs. As mentioned previously, PUFAs can be categorized as n-3 or n-6 PUFAs; while n-3 PUFAs have anti-inflammatory properties and stabilize T cell membranes, n-6 PUFAs can enhance inflammatory responses [62]. In a recent SR and meta-analysis of 27 prospective cohort studies, the pooled estimate for the effect of exclusive breastfeeding on AD was not significant. Heterogeneity was substantial across studies. There was weak evidence for a protective effect of breastfeeding against AD in cohorts with a history of family atopy. In cohorts without atopic heredity, there was actually an increased risk of AD in exclusively breast-fed infants [63].

An observational study of eighty-seven exclusively breastfed infants with AD found that discontinuation of breastfeeding and shifting to partially hydrolyzed whey formula might actually improve symptoms and shorten AD duration, regardless of sex, age, and parental atopy history [64]. A 2015 SR including 42 studies found low- to very-low-grade quality evidence, from pooling six cohort studies, that exclusive breastfeeding for greater than 3–4 months vs other feeding types was associated with a reduced risk of eczema up to 2 years of age [65]. More well-designed interventional studies are needed to conclusively determine the role of breastfeeding and its effects on AD.

A recent SR and meta-analysis of 45 studies from 20 different countries showed that no associations were observed between early introduction of cow's milk or cow's milk formula and the development of eczema or AD. Little high-quality evidence was available [66]. A meta-analysis of 17 studies showed that timing of solid food introduction was not associated with eczema. One controlled trial provided weak evidence for early introduction of allergenic foods around 4 months with reduced risk of eczema [67].

Childhood and Adolescent Diet

Diet may play a role in the development of AD, especially in children and adolescents [68]. Of note, many studies examined the relationship of different aspects of diet and nutrition on AD. However, each aspect was only assessed in one or two studies, limiting evidence-based conclusions about their role in AD.

A cross-sectional analysis from the 2017 Korean Youth Risk Behavior Web-based survey found that adolescents with a 1-year vs. past history of diagnosed AD were more likely to consume fast foods, energy drinks, or convenience food, especially in high school students [69]. Findings from the International Study of Asthma and Allergies in Childhood Phase III found increased eczema prevalence and severity in children and adolescents who consumed fast food ≥ 3 times per week. In particular, consumption of butter, eggs, margarine, nuts, pasta, potato, rice, and seafood ≥ 3 times per week was associated with increased eczema prevalence [70]. Consumption of hamburgers was associated with eczema severity [71].

A survey of 169 patients found that dietary modification best improved skin in AD when white flour products, gluten, and nightshades were removed, and vegetables, organic foods, and fish oil were added [72].

Short-chain fatty acids (SCFA) exert anti-inflammatory responses and modulate itch through neuroendocrine mechanisms mediated by the gut. A diet rich in fat and low in fiber was shown to alter the gut microbiome by impairing SCFA production and shifting immune homeostasis toward a pathogenic Th2 phenotype [73]. A murine study showed that western diet for 10 months led to increased incidence of dermatitis compared to a control diet. Bile acid receptors, e.g., Takeda G protein receptor 5 and sphinosine-1-phosphate receptor 2, IL-17A, IL-6, TNFα, IL-23, IL-4, and IL-31, were elevated in lesional skin [74]. These may regulate itch, keratinocyte proliferation, metabolism, and/or inflammation.

Future large-scaled prospective and interventional studies are needed to fully confirm the association between AD and diet and the possibility that diet and weight control in childhood may help to mitigate or even prevent AD or symptom development.

Micronutrients

A SR of ten studies found no consistent associations between maternal vitamin D levels in pregnancy or at birth and risk of developing eczema in infants (≤ 1 year old) [75]. Another SR and meta-analysis found that lower maternal vitamin D during pregnancy was associated with increased risk of childhood eczema [76]. A meta-analysis of three vitamin D supplementation trials found clinical meaningful improvements of SCORAD scores, with greatest improvement in trials lasting 3 months. AD patients, especially children, may have decreased vitamin D levels, and benefit from supplementation, though more studies are needed to support definitive recommendations [77].

There is limited and inconsistent evidence to support the relationship between AD and other micronutrient deficiencies, or whether micronutrient supplementation improves AD. A SR including 49 studies examined the relationship between oral micronutrients and AD. One study of 17 young adults (ages 20–42 years) found that AD severity, as judged by SCORAD, increased as plasma vitamin C levels and levels of epidermal ceramides decreased [78]. A prospective follow-up study from birth to 48 months of 159 children with a family history of allergic disease found that increased intake of retinol, calcium, and zinc with perinatal administration of probiotics reduced the risk of AD while an increase in vitamin C intake increased the likelihood of AD [79].

Vitamin E impedes synthesis and release of prostaglandins [80]. In a double-blind, placebo-controlled RCT of 70 patients with mild-to-moderate AD, vitamin E (400 IU/day) treatment for 4 months was associated with improvement in itching, extent of lesion, and SCORAD index [81]. In a food-questionnaire study of 180 children with AD and 242 without AD, dietary vitamin E levels were inversely associated with AD, and reduced AD risk was found with increased serum alpha-tocopherol [82].

Zinc serves as a cofactor in cellular growth, proliferation, and regeneration and is thought to possess anti-inflammatory properties [80]. Serum zinc levels were measured in 65 children with AD and were lower than in healthy controls [83]. An 8-week double-blind placebo-controlled RCT of oral zinc sulfate 185.4 mg per day in 50 children with AD, ages 1–16 years, did not show improvement in disease severity [84]. In contrast, in 58 children with AD (2–14 years of age), low hair zinc levels were found at baseline. After 8 weeks of zinc supplementation, eczema assessment severity index (EASI) scores, TEWL, visual analogue scales for pruritus, and hair zinc levels improved in comparison to children with AD [85]. While individual studies showed some link between AD and micronutrient deficiency or improvement of AD with micronutrient supplementation, the level of evidence to support clinical recommendations is very weak.

Climate

A SR explored the mechanisms for worsening AD in the wintertime and proposed that low humidity and temperatures can lead to an overall decrease in skin-barrier function making it more susceptible to mechanical stress and more reactive toward skin irritants and allergens [86].

A US population-based ecological study of 91,642 children ages 0–17 years showed that the 1-year prevalence of AD was associated with decreased outdoor temperature, low humidity, and low ultraviolet B radiation index, and the use of increased indoor heating [87]. Study data from ISAAC, including children ages 6–7 and adolescents ages 13–14 years, suggests that extremely low or high UVR levels might increase the risk of AD [88]. Another study found that higher temperatures, humidity, and increased sun exposure were associated with poorly controlled eczema. However, higher humidity lost statistical significance in multivariate analysis [89].

A Danish study found that lower monthly temperature was associated with more AD clinic visits and hospitalizations and more topical corticosteroid and calcineurin inhibitor prescriptions [90]. More hours of cloud cover were associated with increased healthcare utilization for AD, while more hours of bright sunlight were inversely associated with healthcare utilization [90]. Denmark has a relatively homogeneous and colder climate, whereas a study of ambulatory visits for AD to all physicians in the USA, which has one of the most diverse climates in the world, did not find increased outpatient healthcare utilization for AD during winter time in any region [91]. The greatest number of visits occurred in May and June, with smaller peaks in January and October [91].

Hospitalizations for AD in the USA were highest in the spring and summer for adults and children. Hospitalization rates for AD were highest in the northeast (colder) and lowest in the south (warmer) during the winter, but highest in the south (warmer) and lowest in the northeast (colder) during the summer [92]. Extreme cold temperature may increase risk of hospitalization for AD in the winter, whereas extreme hot temperature may worsen AD in the spring and summer.

Air Pollution

Multiple studies found associations of air pollution with AD prevalence and AD-related outcomes. In a retrospective study performed in Hubei, China, exposure to high levels of air pollutants during the gestational period and first year of life was associated with increased incidence of AD in preschool children [93]. A time-stratified case-crossover study in Beijing, China, found that short-term increases in small particle air pollution ($PM_{2.5}$, PM_{10}) overall, and nitrogen dioxide (NO_2) and sulfur dioxide (SO_2) in particular, were associated with increased outpatient visits for eczema/dermatitis [94]. Associations of air pollutants with outpatient visits for eczema/dermatitis were stronger in older patients and females, and when high concentrations of air pollution occurred for prolonged consecutive days [94]. The associations of outpatient visits for eczema/dermatitis with $PM_{2.5}$, PM_{10}, and NO_2 were stronger during the warm season (May–October) [94]. Similar outcomes were observed in Chengdu, China, where the frequency of eczema visits to the hospital correlated with air pollutants and barometric pressure in univariate analyses, but negatively correlated with relative humidity [95].

Mechanisms of air pollutants exacerbating AD include penetrating skin through larger pores and hair follicles [96], generating free radicals, inducing inflammatory responses and

disrupting skin barrier, activating AhR that regulates cell proliferation, inflammation, and melanogenesis, and/or altering skin flora [97]. Particulate matter leads to secretion of pro-inflammatory cytokines, e.g., tumor necrosis factor (TNF)-α, IL-1α, IL-8, and upregulation of matrix metalloproteinases 1, 2, and 9 [96].

Household Products

An online survey of 1,500 South Korean households evaluated the relationship between use of 23 different types of household products in the past year and AD in adults [98]. Highest-quartile use of household products was associated with ever being diagnosed with AD, symptoms, and treatment of AD in the past year [98].

Pet Dander

A 2012 meta-analysis of 26 publications from 21 birth cohort studies found that exposure to dogs or pets overall was associated with lower risk of developing AD, suggesting that early-life pet exposure protects against AD [99].

In contrast, a Chilean study of children ages 0–17 years with active AD found no association of tobacco exposure, pet ownership, aerosol use, visible dust, or home carpets/rugs with AD severity. While dust samples from all homes had dog and cat dander, children with AD living in homes with higher concentrations of dust mites and animal dander had more severe AD compared to those who lived in homes with lower concentrations [100]. In the pediatric population, exposure to unfamiliar pets was associated with increased AD severity [101]. Persistent AD lesions occurred more often in patients with sensitization to animal dander, and IgE sensitization to animal dander may increase risk of developing asthma or rhinitis in AD patients [102]. Pet exposures may differentially affect AD, with early-life exposures potentially protecting against AD, and exposures after AD onset potentially worsening disease.

Dust Mites

Homes of patients with AD vs. healthy controls found that patients with moderate-severe eczema had increased concentration of house dust mites (HDM) vs. healthy controls (median 85 vs. 8 mites/0.1 g mattress dust) [103]. Hypersensitivity to HDM was found in up to 90% of atopic patients with AD or allergic bronchial asthma [104]. However, a SR and meta-analysis of 7 RCTs found that HDM avoidance provided no benefit in preventing AD [105]. Further, patch testing to dust mites allergens had no clinical utility in determining the diagnosis or etiology of dermatitis; there was no association observed between "positive" HDM patch testing with a personal history of AD, asthma, or hay fever compared with a nonatopic clinical population of patients with dermatitis [106]. These studies suggest that while HDM may be associated with AD, causation still cannot be established; further, no adequate interventions currently exist to eradicate HDM.

Water Hardness

UK infants exposed to above-average levels of water hardness had increased risk of having visible AD at age 3 months. Hard water may affect skin-barrier integrity via $CaCO_3$, leading to dryness and inflammation, and increase skin pH leading to enhanced protease activity in the stratum corneum, accelerating breakdown of corneodesmosomes, and reducing lipid lamellae synthesis [107]. High $CaCO_3$ levels increased TEWL loss in children with and without FLG mutations [107]. Similar results were observed in other large studies [108, 109]. A study of 46 AD patients with and without FLG mutations and 34 healthy control subjects found that sites washed with hard water had increased sodium lauryl sulfate deposits that increased TEWL and caused irritation, particularly in AD patients carrying FLG mutations [110]. However, in an observer-blind RCT involving 336 children with moderate/severe AD, use of water softeners provided no additional benefit to usual care [111, 112]. There is inadequate evidence to support clinical recommendations regarding use of water softeners.

pH

The acid mantle refers to the slightly acidic pH (4–6) of normal skin that contains amino acids, lactic acid, fatty acids, and other components such as ceramide which play an important role in skin-barrier integrity. An acidic pH is required to synthesize ceramides [113], and inhibit the catalytic activity of kallikrein 5 and 7 skin proteases [114]. Elevated pH can decrease expression of LEKT1, a kallikrein inhibitor, leading to enhanced desquamation in AD-affected skin [115].

Corneodesmosomes function in holding the corneocytes together and contain natural moisturizing factor (NMF). The conversion of filaggrin into NMF can help restore the acidic pH and functions as a buffer in skin. When less filaggrin is present, as in AD, serine proteases are triggered leading to enhanced breakdown of corneodesmosomes and epidermal-barrier dysruption [115–117].

Skin pH is elevated in AD [115]. Frequent bathing and personal care products, e.g., soaps, surfactants, and detergents, can remove NMF and skin lipids and increase skin pH beyond optimal physiologic levels [118–120]. Frequent

washing with alkaline soaps can reduce buffering capacity, which increases risk for irritation and AD flares [114–116, 119, 121, 122]. Vehicles with a slightly acidic pH, milder surfactants, and free of fragrances or other common irritants may improve skin-barrier function in AD. In some studies, cleansing and moisturizing helped maintain skin pH levels by enabling sufficient water retention and improving atopic skin [121–124].

Skin Microbiome

Staphylococcus aureus typically colonizes lesions, and to a lesser extent, non-lesional skin and noses of AD patients. *Staphylococcus* colonization rates and abundance in lesional skin increases with AD severity [12]. AD patients have higher prevalences of IgE against staphylococcal enterotoxin (SE) A and B compared with healthy controls [125]. Moreover, *Staphylococcus* colonization in AD lesional and non-lesional skin is accompanied by diminished microbial diversity, particularly with decreased *Streptococcus*, *Corynebacterium*, and *Prophionibacterium* [126].

It remains unclear whether the increased levels of *Staphylococcus aureus* is a byproduct or cause of AD. Dysbiosis might trigger barrier disruption in AD. SE B can act as a superantigen that activates lymphocytes and macrophages. Phenol-soluble modulin (PSM)-α from *S. aureus* can stimulate the production of IL-36α and IL-1α in keratinocytes, leading to production of IL-17 in γδT cells, innate lymphoid cell type 3, and CD4+ T cells, and enhanced neutrophil recruitment. *S. aureus* also triggers Th2 skewing by initiating production of thymic stromal lymphopoietin and stimulating mast cell degranulation through TLR2-dependent mechanisms. Finally, *S. aureus* can enhance the production of serine proteases by keratinocytes and metalloproteases in dermal fibroblasts which can further disrupt the skin barrier [127]. In contrast, skin colonization by *S. aureus* was attributed to the inadequate induction of cathelicidin and β-defensins, which directly inhibit the growth of bacteria. Relative expression of these AMPs was lower in AD skin than in other skin inflammatory conditions, e.g., psoriasis, rosacea, and wounds, and the amount of AMPs is not enough to suppress the growth of *S. aureus* [127].

Conventional AD treatments, including emollient use, water baths, bleach baths, and topical steroids, may restore bacterial diversity [128, 129].

Conclusion

Myriad environmental exposures may impact AD. These environmental factors should be considered when assessing and treating AD patients. Multi-level interventions are warranted, particularly early in life, to address these environmental factors and potentially prevent and/or improve AD. Currently, the strongest albeit far from complete evidence is available for the associations between probiotic supplementation during pregnancy, active smoking in children and adults, climate, air pollution, pH, and cutaneous *Staphylococcus aureus* and AD. However, a lot more evidence is required in order to make definitive conclusions about the benefits of specific interventions.

Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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