What’s new in atopic eczema? An analysis of systematic reviews published in 2019. Part 1: Risk factors and prevention

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Conflicts of interest: The authors declare that they have no conflicts of interest

Funding: This article presents independent research funded by the National Institute for Health Research Programme Grants for Applied Research (project number RP-PG-0216-20007). The views and opinions expressed in this article are those of the authors and do not necessarily reflect those of the NIHR, the National Health Service or the Department of Health.

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1111/CED.14788

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**Acknowledgements**: This work was carried out as part of the UK Dermatology Clinical Trials Network (UK DCTN) Fellowship scheme. EE is a UK DCTN SpR Fellow (2019–2022), and ZT is a UK DCTN SAS Fellow (2018–2020).
Summary

This review is part of an annual evidence update on atopic eczema (AE), providing a summary of key findings from 18 systematic reviews published in 2019 on AE risk factors and prevention.

Parental atopy, particularly AE, is a risk factor for offspring AE, and this risk is augmented by the number of parental atopic diseases present and the number of affected parents. Low quality evidence suggests autumn or winter birth increases childhood AE risk compared with birth in spring. There is some evidence to support filaggrin gene-environment interactions, however this is limited by small underpowered studies. There is no evidence to suggest that polymorphisms in the -1082, -592, -819 loci of the interleukin-10 gene increase susceptibility to AE. There is no robust evidence to support a relationship between childhood AE development and yoghurt consumption in the first year of life, gut microbiota variants, prenatal or infantile paracetamol exposure, maternal antibiotic exposure or air pollution. Three systematic reviews investigated the effect of probiotics given during pregnancy or infancy; though low-quality evidence suggests benefits of combined probiotics, these studies are limited by significant heterogeneity. No relationship between the age at which complementary food and beverages are introduced and the risk of developing AE in infancy was identified. Consistent evidence showed no relationship between human milk feeding and infant AE development, aside from limited evidence suggesting a protective role those with atopic heredity. This summary of recent evidence related to AE risk factors and prevention highlights the complex aetiology of AE.
Background
The aim of this first of a two-part annual evidence update is to present key findings from systematic reviews (SRs) published or indexed in 2019 on risk factors for, and the prevention of, atopic eczema (AE). We identified publications using our standard search strategy for used for publishing this series of evidence updates.\textsuperscript{1} SR characteristics (Table S1) and meta-analyses (Table S2) were extracted in duplicate using standardised forms. The quality of each SR was appraised using the AMSTAR2 tool (Table S1).\textsuperscript{2}

Risk Factors

Parental atopy
A meta-analysis of 119 observational studies (241,651 participants) demonstrated a significant association between parental history of atopy and offspring AE (OR 1.81; 95% CI 1.65-1.99); in subgroup analyses of all the atopic diseases, parental history of AE showed the strongest association (OR 3.30; 95% CI 2.46-4.42).\textsuperscript{3} Relative effect sizes were similar for maternal and paternal atopy. The risk of offspring AE development was increased in association with the number of parental atopic diseases present and the number of affected parents. This SR scored highly using AMSTAR2, indicating robust methodological quality of the review.

Season of birth
Meta-analyses of 9 quantitative studies (726,378 participants) demonstrated a weakly positive association between the development of childhood AE and birth in autumn and winter when compared to spring.\textsuperscript{4} However, no clear evidence of an association in the qualitative analysis was found (676,867 participants). Potential concerns about this study include recall bias and AE misclassification because AE was diagnosed from questionnaires. Furthermore, there may be a risk of confounding, as only northern hemisphere countries were included.

Gene-environment interaction
A SR assessed gene-environment interaction (GEI) in the filaggrin (\textit{FLG}) loss-of-function mutation\textsuperscript{5}, which represents the strongest genetic association with AE.\textsuperscript{6} There was limited evidence for GEI between \textit{FLG} genotype and breastfeeding duration, older siblings, phthalate exposure in household dust, urine phthalate metabolite levels, early-life exposure to cat and water
hardness. All GEI increased the risk of AE development, apart from prolonged breastfeeding, which decreased the risk. The authors highlighted that small participant numbers and underpowered studies are the reason for lack of replication, reverse causality was possible due the timepoint of AE diagnosis and that adjusting for confounders was inconsistent, therefore, cautioning the interpretation of these results.

**Interleukin-10 gene polymorphisms**
Two SRs and meta-analyses investigated the association between genetic polymorphisms within the interleukin-10 (IL-10) gene and susceptibility to AE (Qi, Zhao).\(^7,8\) Both SRs investigate the same IL-10 gene loci, and 13 overlapping case-control studies were identified. Both SRs had small samples sizes and neither study defined the AE outcome investigated.

Zhao et al.\(^8\) concluded that the overall no significant association was detected in three single nucleotide polymorphisms (SNPs) (IL-10-1082 G/A, IL-10-592 A/C, IL-10-819 G/A), apart from in the IL-10-819 recessive model. Subgroup meta-analyses revealed ethnicity-specific effects. Qi et al.\(^7\) similarly found no strong evidence to support a relationship between 3 SNPs (IL-10-1082 A/G, IL-10-592 A/C, IL-10–819 T/C) and susceptibility to AE.

**MicroRNA**
A SR investigated whether a link exists between microRNA (miRNA, non-coding RNA that controls gene expression) autism spectrum disorders and AE.\(^9\) Using seven case-control studies (321 participants), authors concluded that miRNA-146 and miRNA-155 are dysregulated in both conditions. However, statistical analyses were not conducted and most of the AMSTAR2 quality criteria was unmet.

**Air pollution**
A SR of 57 observational studies (2,693,223 participants) assessing air pollution and the risk of AE development, concluded that small-scale exposure, such as truck traffic emissions, increases AE prevalence, whilst large-scale exposure to larger particles has no effect.\(^10\) However the quality of evidence was low.
Maternal antibiotic exposure
A SR of seven observational studies investigated the effect of maternal antibiotic exposure on infant AE.\textsuperscript{11} Meta-analyses found that maternal antibiotic exposure was significantly associated with AE by one year of age (1,490 participants) but was not significant after 1 year of age (88,601 participants) or when antibiotic exposure occurred during the third trimester (62,971 participants). The inclusion of few studies, with a low proportion exposed to antibiotics (10-30%), potentially affects the robustness of these results.

Paracetamol exposure
A meta-analysis of 15 studies (901,875 participants) demonstrated that combined (prenatal or infant) paracetamol exposure increased the risk of childhood AE (OR 1.41; 95\% CI 1.23-1.62).\textsuperscript{12} There was, however, no assessment for publication bias and significant heterogeneity between included studies that did not adjust for confounders was identified.

Prenatal and postnatal prevention
Probiotics
Three SRs assessed the effect of probiotics on the development of AE, with overlap in included studies identified.\textsuperscript{13-15} A small SR (1,805 participants) reported that probiotic supplementation in the pregnant mother was associated with a reduced risk of infant AE development\textsuperscript{14}. Two SRs assessed probiotic supplementation in both mother and infant, concluding that probiotic supplementation in the pregnant mother, breastfeeding mother or infant demonstrated risk reduction in childhood AE.\textsuperscript{13,15} On subgroup analysis this relationship was insignificant with infantile supplementation alone. All three SRs conducted meta-analyses for different strains and concluded that mixture probiotics were superior to single strain probiotics,\textsuperscript{13-15} however these results are limited by study heterogeneity.

Gut microbiota
A SR assessed 44 observational and interventional studies (7,059 participants) and concluded that the role of the gut microbiome in the onset and severity of pre-existing AE remains unclear.\textsuperscript{16} Few included studies adjusted for confounders, and multiple critical domains of the AMSTAR2 checklist were unmet.
**Yogurt and fermented milk**
A SR investigated the effects of yogurt and fermented milk products on childhood AE\(^7\) evaluated two prospective cohort studies (2,591 participants). The authors concluded that yogurt consumption in the first year of life is associated with a lower risk of developing AE. Methodological weaknesses related to the literature search strategy and authors’ conflicts of interest were identified.

**Complementary feeding**
A SR undertaken by the United States Department of Agriculture (USDA) as part of the ‘Pregnancy and Birth to 24 months’ project, including 20 observational studies (46,988 participants), found no relationship between the age at which complementary foods and beverages were introduced and the risk of developing childhood AE\(^8\). Furthermore, no relationship was identified between the age of introduction of peanuts, tree nuts, sesame seeds, egg, cow-milk products, fruit, vegetables and meat and the development of AE. Across 15 studies (30,146 participants), there was limited evidence to suggest that introducing fish within a year may reduce the risk of AE. This review scored highly using the AMSTAR2 tool.

**Human milk**
A SR from the USDA ‘Pregnancy and Birth to 24 months’ project found, using mostly observational evidence from Europe (30,052 participants), inconclusive evidence on “never” versus “ever” human milk feeding and “shorter” versus “longer” durations of any human milk feeding with developing AE\(^9\). In childhood (10,185 participants), most associations between the duration of any human milk feeding and AE development were non-significant.

A second SR assessed 27 prospective cohort studies (177,445 participants) from Europe, Asia and Australia, finding no association between AE and total breastfeeding\(^10\). Subgroup meta-analyses demonstrated some evidence for a protective role of “total” and “exclusive” breastfeeding in a cohort with atopic heredity. However, these findings should be interpreted with caution because heterogeneity was evident.
In a SR of 15 studies (2,609 participants) investigating the effect of transforming growth factor beta (TGF-β) in human milk, no consistent association was found with the development of AE.\textsuperscript{21} The methodological quality of this review was considered to be thorough and robust.

**Conclusion**

AE is a complex, multifactorial condition and deconvoluting the risk factors and strategies for prevention is challenging. There is clearly a strong genetic component, but exact mechanisms and the role of environmental factors in AE aetiology requires further elucidation with well conducted, appropriately powered studies.

**Learning Points**

1. Parental atopy, in particular AE, is a risk factor for offspring AE, which is further augmented by the number of parental atopic diseases present and the number of affected parents.

2. There is limited evidence in support of filaggrin gene-environment interactions, including an effect of breastfeeding duration, older siblings, phthalate exposure in household dust and urine phthalate metabolite levels, early-life exposure to cat and water hardness.

3. Studies on probiotic supplementation in pregnancy and infancy have provided limited evidence of benefit in reducing the risk of AE development, however, these reviews are limited by study heterogeneity.

4. There is no robust evidence to support a relationship between the development of childhood AE and yoghurt consumption in the first year of life, gut microbiota variants, prenatal or infantile paracetamol exposure or maternal exposure to antibiotics.

5. Moderate evidence suggests no relationship between the age at which complementary food and beverages are introduced and the risk of developing AE.

6. There is consistent evidence to support no relationship between human milk feeding, or human milk transforming growth factor β, and infant AE.
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