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REVIEW ARTICLE

New insights into the epidemiology of childhood atopic dermatitis

C. Flohr[1] & J. Mann[2]

[1]Departments of Paediatric Dermatology & Children's Allergies, St John's Institute of Dermatology, Guy's and St Thomas' Hospitals NHS Foundation Trust and King's College, London; [2]Department of Dermatology, Medway NHS Foundation Trust, Medway Maritime Hospital, Gillingham, Kent, UK

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Correspondence
Dr. Carsten Flohr, MD, MSc, PhD, Departments of Paediatric Dermatology & Children's Allergies, St John's Institute of Dermatology, St Thomas' Hospital and King's College London, London SE1 7EH, UK.
Tel.: +44 (0)20 7188 7188, ext 51601
Fax: +44 (0)20 7188 9782
E-mail: carsten.flohr@kcl.ac.uk

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Abstract

There is a growing desire to explain the worldwide rise in the prevalence of atopic dermatitis (AD). Trend data on the burden of AD suggest that the picture in the developing world may soon resemble that of wealthier nations, where AD affects over 20% of children. This, combined with significant variations in prevalence within countries, emphasizes the importance of environmental factors. Many hypotheses have been explored, from the modulation of immune priming by hygiene, gut microbiota diversity, and exposure to endotoxins through farm animals to the effects of pollution, climate, and diet. The discovery of the filaggrin skin barrier gene and its importance in AD development and severity has brought the focus on gene–environment interactions and the identification of environmental factors that impact on skin barrier function. This article reviews our current understanding of the epidemiology of AD, with an emphasis on the findings reported in the international literature over the last 5 years.

Atopic dermatitis (AD, syn. 'atopic eczema' and 'eczema') is the commonest inflammatory skin disease in children and poses a significant burden on healthcare resources (1–4) and patients' quality of life (1, 5–11). As a consequence, there has been a heightened interest in the identification of environmental risk and protective factors, reflected in a steady increase in the number of publications related to AD epidemiology (Fig. 1). This narrative review appraises our latest insights into the epidemiology of AD and highlights potential areas for future research. Papers were identified, using a systematic MEDLINE search from inception until the end of April 2013, using the Cochrane Collaboration Skin Group search terms for AD in combination with exploded terms for incidence, prognosis, cohort, cross-sectional, and longitudinal studies. A formal systematic review was not possible due to the breadth of the topic and heterogeneity in study methodology. This article is one of two commissioned articles, one focusing on the epidemiology and the other on the prevention of AD.

Is AD still on the increase?

Some of the most valuable AD prevalence and trend data has come from the International Study of Asthma and Allergies in Childhood (ISAAC) (5, 12–14). With close to two million children from 106 countries, ISAAC is the biggest and only allergy study that has taken a truly global approach. ISAAC's strength is the use of a uniform validated methodology, including physical examination for flexural dermatitis (Phase Two only), allowing direct comparison of results between pediatric populations and providing invaluable data on the worldwide burden of allergic disease. ISAAC Phases One and Three were set up to examine time trends and showed that where AD among 13- and 14-year-olds was common in Phase One (mainly in high income settings), prevalences did not significantly increase further or even decreased, whereas AD burden continued to rise in most developing country settings (Fig. 2) (15). As for 6- to 7-year-olds, the majority of centers showed an increase in AD

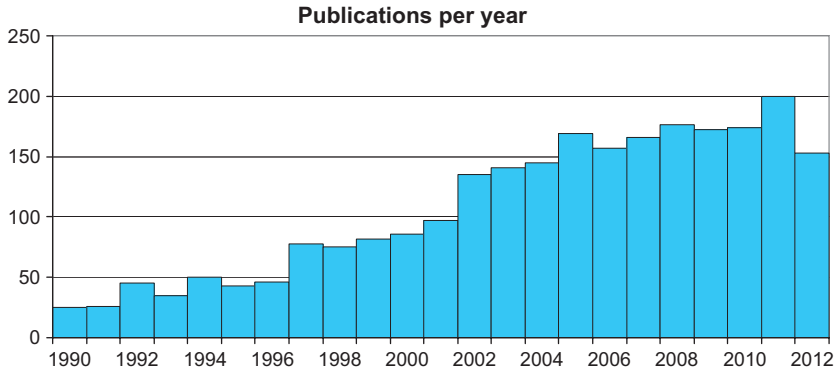

Figure 1 Number of papers retrieved in MEDLINE using search terms for 'atopic dermatitis' and 'epidemiological research' from 1990 until the end of 2012.

symptoms regardless of national *per capita* income. In addition, a recent systematic review of 69 cross-sectional and cohort studies has confirmed that AD is now a worldwide phenomenon with lifetime AD prevalences of well over 20% in many affluent country settings (16). There is also good evidence for an increase in prevalence in low-income countries, in particular in Africa and East Asia.

What can we learn from prevalence surveys?

Although the vast majority of studies only used questionnaire-derived data, even population-based surveys that employed skin examination clearly show significant differences in AD prevalence not only between but also *within* countries, suggesting environmental rather than genetic factors as the main drivers of changes in disease burden (17). Significant changes in the burden of disease over short periods of time, such as observed before and after German reunification, offer opportunities to detect environmental risk factors. While the incidence of AD was stable among preschool children in West Germany after the country's reunification, East Germany saw a rise in the number of newly diagnosed AD cases in children up to the age of 6 years from 16.0% in 1991 to 23.4% in 1997 (18). Similar observations can be made in association with urbanization in developing countries and by studying migrant populations, who move from areas of low to regions with high disease prevalence, typically adopting the AD risk of their new environment (19, 20). Such changes in disease risk have been attributed to the adoption of a 'Western' lifestyle (18, 21). However, what exactly are the lifestyle and other environmental ingredients that are responsible?

Environmental risk factors for AD

Climate

One potential explanation for the differences in prevalence between populations is climate; an area that has received little attention with regard to AD. Based on the ISAAC Phase One data set, an ecological analysis was conducted using information on long-term climatic conditions in the different study areas from the *World Weather Guide* (22). Variables that were examined included latitude, altitude, average outdoor temperature, and relative outdoor humidity. The results, which were adjusted for countries' gross national *per capita* income (GNP), suggest that AD symptoms correlate positively with latitude and negatively with annual outdoor temperature, but none of the other factors. These findings have been supported by cross-sectional studies in Spain (23) and Taiwan (24) and could be due to direct climatic influences, especially UV light exposure, as also suggested by a recent ecological analysis in a US cohort (25). UV light has a well-established immunosuppressive effect (26), partly because it facilitates the conversion of the skin barrier filaggrin (*FLG*) breakdown product trans-urocanic acid into the immunosuppressive cis-urocanic acid isoform (27).

Work that has looked at flare factors in established AD supports this notion, as lower outdoor temperatures, especially in combination with skin irritants, can contribute to disease worsening, whereas indoor climate seems less important (28). However, the relationship between outdoor climate and disease flares is complex with some children reporting worsening in summer and others in winter, as shown in a small longitudinal study among German children (29). The effects of outdoor temperature, UV light, and humidity as well as seasonal changes in pollen counts are likely to interact, and further studies, which also take skin barrier function and hydration status as well as bacterial skin colonization into account, are required.

Urban *vs* rural living

Another important place for epidemiological investigations is areas where people of a similar ethnic makeup and genetic background show significant differences in prevalence within close geographical proximity (30). A systematic review of 26 studies suggested that there was good evidence of higher disease burden in cities compared with the countryside, and this was particularly the case in less affluent settings (31). Where an attempt has been made to identify responsible environmental risk factors linked to urbanization, differences in hygiene-related exposures (parasitic, bacterial, and viral

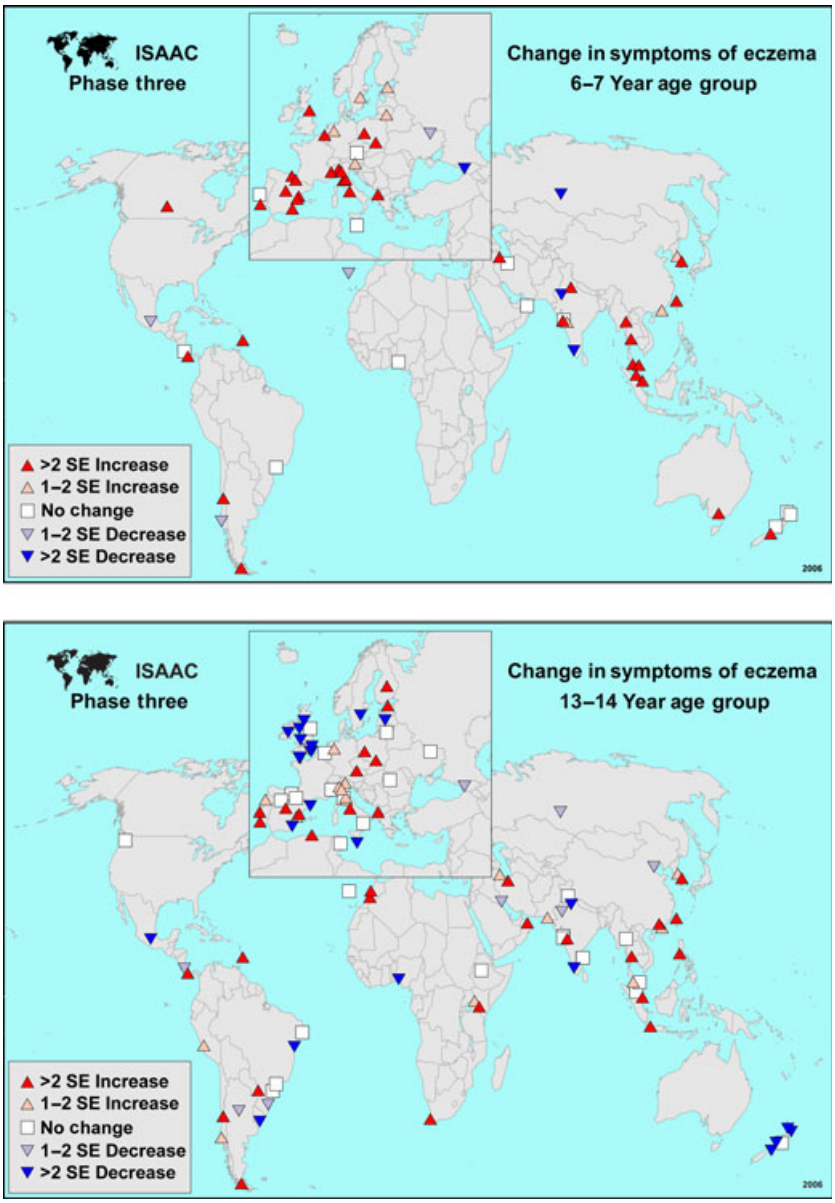

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Figure 2 Worldwide change in AD symptom prevalence between ISAAC Phases One and Three.

infections; vaccination, antibiotics, and farm environment), environmental pollution, including smoking, allergen exposure, and sensitization; diet; and infant feeding practices have received particular attention (20, 31–35).

Diet

Given how uncommon AD and other allergies still are in most developing nations, an important question is whether consumption of a 'Western' affluent diet (i.e., high intake of refined grains, cured and red meats, as well as saturated and unsaturated fatty acids) leads to an increase in AD risk. This was explored in ISAAC Phase Three, and a consistent protective effect was found between frequent consumption of fresh fruits (1–2×/week) and AD risk (adjusted OR = 0.81, 0.67–0.97), whereas the opposite was true for fast-food consumption (≥3×/week, adjusted OR = 1.70, 1.48–1.95) (36). An ecological analysis based on the ISAAC data set came to similar conclusions, showing a consistent inverse association between AD prevalence and *per capita* consumption of vegetables, protein from cereal and nuts, as well as all fresh and frozen fish, even after adjustment for GNP (37).

The latter finding is supported by a number of longitudinal studies that suggested that a high fish intake during

pregnancy lowers AD risk in the offspring up to 5 years of age by 25–43% (38–40). Similar risk reductions have been described in children with a high fish intake during late infancy (41, 42). These results have been attributed to fish's rich content in anti-inflammatory n-3 polyunsaturated fatty acids (n-3 PUFA). Western diets have become low in n-3 PUFAs over the past decades with a corresponding increase in pro-inflammatory n-6 PUFA, such as linoleic acid (43). Consistent with this theory is also that maternal intake in n-6 PUFA during pregnancy is associated with an increased AD risk in Japanese children at 2 years of age, and the finding that children who predominantly consume margarine rather than butter show an increased risk of AD development (36, 43, 44). In addition, case–control studies have demonstrated that AD sufferers have higher levels of linoleic acid in blood (n-6 PUFA precursor) and lower levels of *n*-3 PUFAs (45, 46). However, carefully conducted birth cohort studies failed to show a significant protective effect of higher maternal and cord blood n-3 PUFA, n-3 PUFA : n-6 PUFA ratio, and AD risk (45–47). Equally, the literature on fatty acid profiles in breast milk as a risk factor for allergies has been rather conflicting, with some studies even reporting an increased AD risk in association with n-3 PUFA (48, 49).

Breastfeeding and delayed weaning

Many advocate breastfeeding as a way of preventing allergies, including AD. For instance, the World Health Organization (WHO) recommends that babies are exclusively breastfed for 6 months (50), and most European ministries of health advocate at least 4 months of exclusive breastfeeding to aid allergy prevention (51). It is therefore conceivable that differences in the length of breastfeeding and the age infants are weaned onto solids could explain part of the differences in AD prevalence between study populations. However, data from cross-sectional studies in developed and developing countries, including 51 119 schoolchildren in ISAAC Phase Two, offer little support for this notion (51, 52). Furthermore, a meta-analysis of 27 prospective cohort study populations failed to show a statistically significant benefit with exclusive breastfeeding (pooled OR = 0.89, 0.76–1.04) (53).

Obesity and physical exercise

Increasing numbers of children in affluent settings are overweight. Three studies, including a UK cohort study and a substantial worldwide series of cross-sectional surveys based on the ISAAC Phase Three data set, found an association with obesity, while no association was detected in a number of other cross-sectional studies (54–60). The ISAAC analysis also examined the effect of TV viewing (≥5 h), which showed a positive relationship with AD risk, and this was stronger in obese *vs* overweight *vs* normal/underweight children in a dose–response fashion (61). It remains unclear whether the positive associations seen are causal, for instance due to inflammation mediated by adipokines such as leptin, or related to dietary factors, which could facilitate AD through oxidative stress pathways, as diets excluding antioxidant food, such as fruits and vegetables, are related to increased obesity and AD.

Pollution and tobacco smoke

Questionnaire-based studies on the association between outdoor pollution and AD from Sweden and East Germany found that AD risk increased with living close to heavy traffic (62, 63). However, similar studies in West Germany, Malta, Russia, and Japan did not confirm these findings (64–67). A more recent population-based cross-sectional survey among more than 300 000 Taiwanese schoolchildren with more sophisticated, objective measurement of traffic-related air pollutants, including nitrogen oxides (NO_2) and carbon monoxide (CO), suggested that air pollution may contribute to AD risk, but this association, albeit statistically significant, was weak (OR = 1.12, 1.04–1.22) (24). Similarly, a cohort study among 3000 schoolchildren in West Germany with repeat objective pollutant measurements reported that NO_2 exposure was positively associated with physician-diagnosed AD at age 6 (OR = 1.18, 1.00–1.39) (68). Furthermore, a French cross-sectional survey among more than 5000 schoolchildren in six cities showed a stronger positive relationship with fine-particle pollution (OR = 2.51, 2.06–3.06) (69). Another more recent work has shown similar positive associations with measures of outdoor pollution in a rural setting (70). There is less evidence that AD risk in the offspring increases in association with maternal smoking during pregnancy or environmental tobacco exposure postnatally (71–75).

However, as studies have also demonstrated that allergic sensitization is enhanced in the presence of fine-particle pollution and cigarette smoke (69), it is conceivable that skin barrier impairment and skin inflammation are enhanced in the presence of certain outdoor pollutants. It will be interesting to see whether future studies can explain part of these seemingly contradicting results by determining AD endophenotypes related to skin barrier function.

Skin barrier dysfunction and allergic sensitization

The recent discovery of the common loss-of-function variants in the *FLG* gene, encoding the epidermal barrier protein filaggrin, and the strong association with atopic disease have led to a heightened interest in the role of skin barrier impairment in the development of AD, allergic sensitization, and also food and respiratory allergies (76, 77). The current hypothesis is that in individuals without a skin barrier defect, there is full integrity of the epidermis, marked by minimal transepidermal water loss (TEWL) and adequate protection against microbes and environmental allergens. Carriers of skin barrier gene mutations, such as a loss-of-function mutation in the *FLG* gene, have increased TEWL (Fig. 3). Environmental influences on skin barrier integrity, such as frequent use of detergents (78) and water hardness (79), are associated with an increase in AD risk, probably through reduction in natural moisturizing factor, increase in skin pH, and a subsequent upregulation in protease activity (80). Animal work suggests that antigen-presenting cells in the superficial epidermis can make contact with

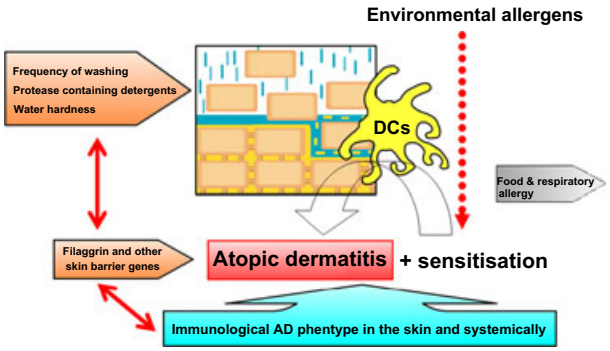

Figure 3 The interplay between skin barrier-related environmental and genetic as well as immunological factors in the development of AD.

not only environmental allergens, such as house dust mites, but also food protein, leading to sensitization, which can trigger AD flares and may also be an important precursor of food and respiratory allergies (81, 82). *FLG* loss-of-function mutations are consistently associated with AD in the context of allergic sensitization to both aeroallergens and foods (83–87). A case–control study in humans also demonstrated a positive association between *FLG* mutation inheritance, AD, and challenge-proven peanut allergy in schoolchildren. The association between AD and peanut allergy remained significant even after adjustment for *FLG* status (88). Similar observations have recently been made in babies as young as 3 months of age, in relation to not only peanut but also other foods (89). Furthermore, the same study found a strong correlation with AD severity in addition to skin barrier impairment (raised TEWL), further supporting the concept that the skin barrier can act as a mediator of allergic sensitization. In this paradigm, allergic sensitization is mainly a secondary phenomenon in AD and an important trigger of disease flares and driver of disease chronicity. This concept is underpinned by the finding that a significant proportion of AD sufferers never become sensitized to environmental allergens and that allergen avoidance both during pregnancy and postnatally has been disappointing as a measure of disease prevention (17, 90–92).

Microbial exposure

The notion that microbial exposure might influence the development of AD originally stemmed from the observation that disease risk is inversely related to sibship size, an effect that has been observed in many different settings, since the original description in a large UK birth cohort in the late 1980s (73, 93–97). There have been two systematic reviews on microbial exposure and AD risk (98, 99). Individual risk factors, including pets and farm animals because of their potential link with endotoxin exposure, are discussed below.

Basic hygiene

One large birth cohort study (n > 10 000), the Avon Longitudinal Study of Parents and Children (ALSPAC), has examined the question whether general hygiene measures at the age of 15 months, such as frequency of washing and use of household cleaners and wet wipes, are associated with AD between 2.5 and 3.5 years of age, and a proportional increase in disease risk was found per increase in hygiene score (adjusted OR = 1.04, 95% CI 1.01–1.07) (78). However, a Japanese cohort with 865 mother–infant pairs found an inverse relationship between a daily bath or shower *vs* washing less frequently (adjusted OR = 0.26, 0.10–0.77) (100). None of these studies took potential gene–environment interactions between hygiene practices, skin barrier gene mutation inheritance, and skin barrier (dys)function into account, and microbial exposures were not measured objectively.

Day care

There is consistent evidence that day care attendance is associated with increased microbial exposure, in particular respiratory tract infections, and there are some cohort studies that have reported a reduction in AD risk in children attending day care facilities during the first year of life (101–103). However, others have found the opposite effect (21, 75, 104, 105), and day care attendance in the first 2 years of life has been identified as the main risk factor to explain the AD prevalence gradient between East and West Germany (21, 105). In addition, a randomized controlled hygiene intervention, with more frequent hand washing and use of antiseptics, did not increase clinical allergy among the intervention group children at the age of 12 years. However, the frequency of parentally reported infections was not reduced to home care levels (106).

Farm environment and animals

The influence of farm environments and animals has also been extensively studied, but no convincing protective effect of living on a farm has been found *per se* (102, 107–116). Interestingly, consumption of unpasteurized farm milk during the first 2 years of life is an independent protective factor against AD development (111, 113), even in nonfarming families (117). This inverse relationship is independent of a family history of allergic disease. Once the raw cow's milk is boiled, the protective effect is lost. The mechanism for these properties of unpasteurized farm milk remains uncertain and could be related to either microbial contamination or other constituents of unprocessed cow's milk (117–119). In addition, direct contact with farm animals reduces AD risk in early life in some settings (116), especially where mothers have regular contact with farm animals during pregnancy, and this protective effect appears even stronger in those who are exposed both pre- and postnatally (116, 120), suggesting that perinatal priming of the immune system may be of particular importance.

Pets

Like farm animals, pets have been implicated as potentially protective against AD (35, 102, 103, 121–136). A meta-analysis of studies revealed an almost uniform protective effect of dog exposure (pooled OR = 0.61 (0.50–0.74), especially where this

occurred in early life (137). The picture is less clear for cats. Although the same meta-analysis showed a protective effect (pooled OR = 0.83, 0.74–0.95), study heterogeneity was significant. It is interesting to note that where *FLG* skin barrier mutation inheritance was taken into account, there was a significantly higher risk of AD in those with *FLG* mutations compared with wild-type children, suggesting that cat sensitization can be facilitated by an impaired skin barrier, which then contributes to AD risk (134, 135, 138).

Endotoxin exposure

Some have argued that the risk reduction seen with farm animal and pet exposure, in particular during pregnancy, is due to endotoxins, a group of lipopolysaccharides found on the cell surface of Gram-negative bacteria, not least because endotoxins are known to be inducers of IL-10 and INF-gamma (139). Birth cohort studies have suggested an up to 50% reduction in AD risk associated with endotoxin exposure (115, 126, 140–144). However, this effect tended to be confined to high endotoxin exposure levels (126, 140) and/or the first year of life (141, 142).

Helminth parasites

Helminth parasites, such as hookworm and *Ascaris lumbricoides*, are potential candidates to explain prevalence gradients between rural and urban areas of tropical developing countries, where such infections remain endemic in the countryside, but become rare, once the lifecycle of the parasite is interrupted due to improved hygiene. Indeed, there is some support for this from cross-sectional studies, but the relationship between helminth parasites and the effect on the immune system of their human hosts is rather complex and depends on the type and burden of the parasite (host-invasive helminths and a higher parasite burden have a stronger immunomodulatory effect) as well as the timing of infection (especially if this occurs in early life or during pregnancy) (145). The strongest evidence for a protective effect of helminth infections on the risk of AD comes from a double-blind randomized controlled trial with deworming therapy conducted among >2500 pregnant mothers in a helminth-endemic area in Uganda during the last trimester of pregnancy, which found an around two times increased AD risk up to 1 year of age in the intervention groups (146). Interestingly, loss of helminth exposure does not appear to affect AD risk later on in life (145, 147), further supporting the notion that perinatal priming of the immune system can provide protection against AD (148).

Childhood infections and vaccinations

What holds true for parasitic infections does not apply to childhood vaccinations, including the BCG vaccine, or common viral and bacterial infections, and the common infection-related exposures in affluent settings (99). As for antenatal infections, a British historical cohort study, using a general practitioner research database, examined the effect of infections during pregnancy on AD in the offspring and found a small increase in AD risk associated with two or more antenatal infections (adjusted HR = 1.16, 95% CI 1.07–1.26) (149). However, a more recent analysis based on historical data on acute viral respiratory infection notifications in former East Germany suggested the opposite: a reduction in AD risk associated with exposure to prenatal viral respiratory infections. This effect was particularly strong for exposures during the last trimester (adjusted HR = 0.70, 0.52–0.95) and extended into the postnatal period up to 7 months of age (150), but this finding has not been replicated in a number of more recent cohorts from New Zealand, the Netherlands, and Germany, which found either positive or no association between infections in early life and subsequent AD development (95, 151, 152).

Where specific viral and bacterial childhood infections, such as chickenpox, mumps, whooping cough, and measles, have been examined, the majority of studies have shown either positive or no associations (102, 153–164), although a US case–control study suggested a 50% risk reduction with parent-reported chickenpox infection that occurred between 0 and 8 years of age (adjusted OR = 0.57, 0.34–0.96), and this effect was particularly strong for children with moderate to severe AD and also associated with a reduced risk of allergic sensitization (165, 166). However, these studies typically rely on parent-reported exposures, rarely take vaccination history into account and also tend to ignore concomitant antibiotic prescribing as an important confounding factor.

Antibiotics

Schmitt et al. (167) examined the complex relationship between respiratory, gastrointestinal, and ear infections, as well as antibiotic prescribing and AD risk and found that it was the antibiotics that seemed to be causally linked with an increased risk of developing AD rather than the infections themselves. Our own recent systematic search identified 17 studies on the association between postnatal antibiotic exposure and the development of AD in the offspring and found an overall risk increase of 41% in those who received at least one course of antibiotics in early life (pooled OR = 1.41, 1.30–1.53) (168). This association remained significant when only longitudinal studies (n = 10) were taken into account (pooled OR = 1.40, 1.19–1.64; Fig. 4). There was also a significant dose–response association, suggesting a 7% risk increase in AD risk with each additional antibiotic course (pooled OR = 1.07 [1.02–1.11]), an effect that was particularly strong for broad-spectrum antibiotics *vs* penicillin (149, 154, 158). It is possible that the risk increase associated with antibiotics is due to changes in the host microbiota, leading to an altered development of the infant's immune system or enhanced immune responses to environmental allergens.

The microbiome of the gut and skin

There is some evidence using conventional culture-based techniques that the early gut microflora of children who later develop AD has more *Staphylococcus aureus* and coliforms

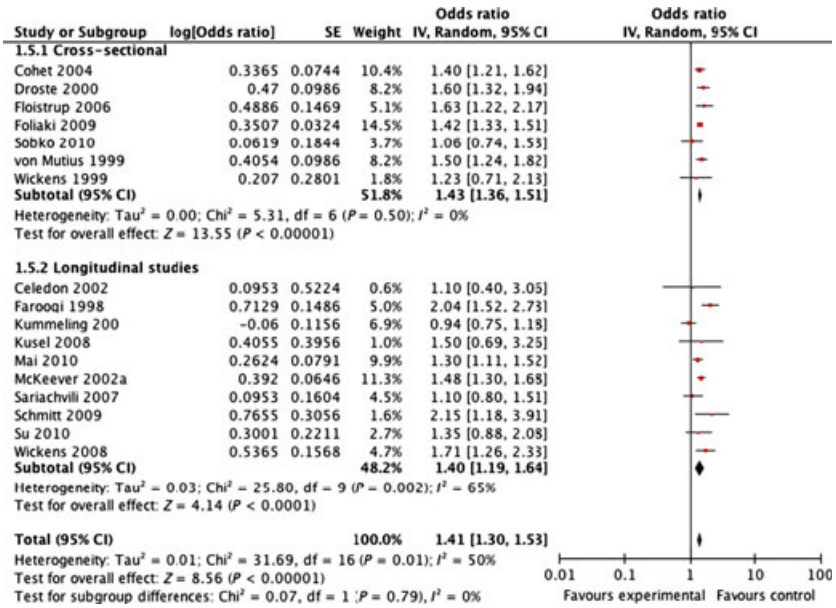

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Figure 4 Postnatal antibiotic exposure and AD risk. Forest plot showing individual and pooled odds ratios for both cross-sectional and longitudinal studies.

and less lactobacilli and bifidobacteria (169–172). However, culture-based methods miss around 80% of human bacteria compared with culture-independent approaches (e.g., next-generation pyrosequencing) that study bacterial DNA directly, and these new technologies promise a deeper understanding of the interactions between the host microbiome of the gut, the skin, the respiratory tract, and the immune system.

Having been sterile *in utero*, the infant's skin, the gut, and respiratory tract quickly become colonized with a broad range of bacterial species postnatally. It is not surprising that environmental factors, such as mode of delivery and feeding practices (breastfeeding *vs* formula milk and time of weaning), influence the host microbiota in the immediate postnatal period (173). In addition, exposure to antibiotics alters the natural balance of the host bacterial communities and encourages the emergence of 'nosocomial' species, such as certain types of staphylococci. It is well established that *S. aureus* is a major cause of skin infection, disease exacerbation, and chronicity in AD (174). There is also evidence from animal models to support the role of the skin microbiota in the (dys)regulation of the cutaneous immune system (175). At the gut interface, the use of new-generation pyrosequencing technology has already shown an association between low diversity of the infant gut microbiota in early life and an increase in AD risk during infancy, especially in high-risk children (176). We are now awaiting studies that utilize this new sequencing technology in the context of population-based studies to shed further light on how the host microbiota influences genetically predisposed skin barrier impairment and environmental factors on the path to AD development. (See Fig. 5 and Box 1 for a summary of significant risk and protective environmental factors.)

Box 1: AD epidemiology – summary of main findings

- Over 20% of children in most developed countries are affected by AD, posing a significant burden on healthcare resources and quality of life.
- AD continues to increase in prevalence, in particular in young children and low-income countries, such as in Africa and East Asia, where there is also often an urban–rural gradient of disease, pointing toward an environmental etiology.
- Main disease risk factors are a 'Western' diet, broad-spectrum antibiotic exposure, and reduced diversity in the bacterial gut flora. Positive associations with traffic-related air pollution (NO_2 and CO), obesity, and lack of exercise have also been identified in some studies.
- Main protective factors are UV light, maternal contact with farm animals during pregnancy and consumption of unprocessed milk, helminth infection during pregnancy, dog, and high-level endotoxin exposure in early life.
- There is no consistent evidence that prolonged exclusive breastfeeding, routine childhood vaccinations and other viral/bacterial pathogens influence AD risk.

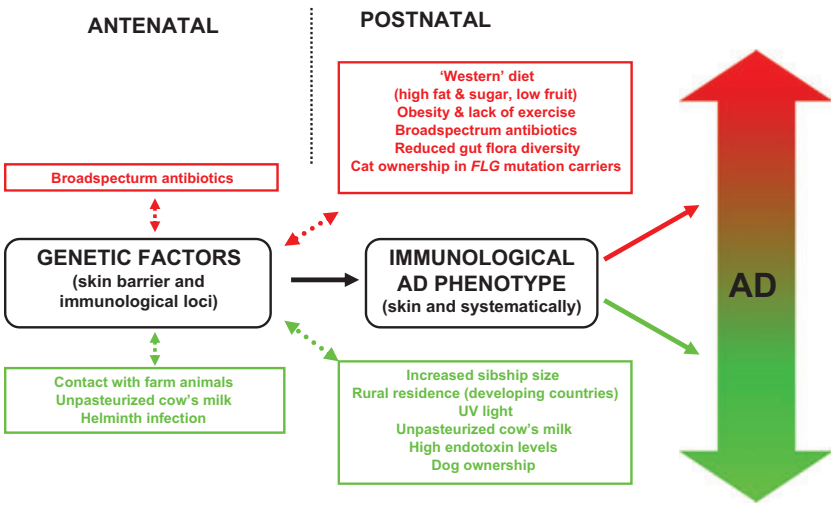

Figure 5 Summary of main environmental risk and protective factors that operate in the antenatal and postnatal period. Risk factors marked in red, protective factors marked in green. Double arrows indicate likely gene-environment interactions.

Interactions between environment, genetic factors, and the immune system

Similar to the new horizons that have recently opened up in relation to the human microbiome, there is further scope to explore the interplay between environmental, genetic, and immunological factors with advancements in technology and an improved understanding of the pathophysiology of AD. The strong risk increase seen in children with *FLG* mutations, who were exposed to a cat during the first year of life, has already been discussed (134, 135). Two German cohort studies also found that the number of older siblings interacted positively with *FLG* skin barrier gene mutation carriage on AD risk, but this needs replication and further investigation, as there is currently no convincing explanation for this finding (96). In addition to *FLG* inheritance patterns, other genetic factors may be involved, as more than 50% of AD sufferers do not carry a *FLG* mutation. Another example of gene–environment interaction is that endotoxin exposure only reduced AD and sensitization risk in those carrying a specific genotype of the CD14 lipopolysaccharide receptor complex encoded on chromosome 5q31.1 in a UK cohort (143). Along the same lines, the Allergy and Endotoxin (ALEX) and the European Prevention of Allergy Risk Factors for Sensitization in Children Related to Farming and Anthroposophic Life Style (PARSIFAL) studies, which have both assessed the impact of exposure to farming environments early in life, have demonstrated a sustained innate immune response through upregulation of the expression of CD14, TLR2, TLR4, TLR5, and TLR9 receptors not only in peripheral blood cells but also in cord blood leukocytes, with a dose–response effect seen with exposure to a higher number of farm animal species and consumption of unpasteurized farm milk (117, 120, 177). Although the exact biological meaning of these findings still needs to be elucidated, these results are additionally supported by the observation that maternal consumption of unprocessed cow's milk modulates cytokine production patterns in young infants (119).

As for the protective effect of helminth parasites on AD development, studies suggest that parasites induce a systemic immunomodulatory network, including gut dendritic cells via TLRs, regulatory T and B cells as well as dendritic cells and anti-inflammatory cytokines (e.g. IL-10 and TGF-beta), which might play a key role in the protection against the allergic phenotype, but this evidence comes primarily from animal work, and further research in human populations is required (148, 178).

What have we achieved so far and where do we go from here?

The epidemiology of AD has travelled a considerable journey from its tender beginnings. Prevalence surveys have been carried out on a global scale, while study designs are becoming increasingly sophisticated, combining well-established questionnaire tools with standardized physical examination and the analysis of biological samples for genetic, immunological, and environmental exposure data. Next-generation pyrosequencing of bacterial DNA now promises to uncover a new world of microorganisms, which might, for example, allow us to understand the protective effect of unprocessed cow's milk and could also shed light on whether the increased AD risk associated with broad-spectrum antibiotics is due to changes in microbial exposure at the gut and/or skin levels. The closer we look, the more complex AD becomes, and we might well be dealing with several distinct entities that clinically manifest in a similar way rather than one disease. Here our improved understanding of skin barrier function and genetic and immunological (bio)markers will help to delineate AD endophenotypes. It is important that population-based study designs incorporate these, as they might explain discrepancies in past study results and are likely to influence the effect of

environmental risk factors on disease development, AD severity, and natural history (179).

From an epidemiological point of view, main areas of interest for future research are the protective effect observed in children who consume unprocessed cow's milk and the reduced risk seen in those infected with helminth parasites (Fig. 5). Given how commonly antibiotics are prescribed, the positive association with AD also requires further study. Such work needs close collaboration between basic scientists, clinical researchers, trialists, and epidemiologists and ultimately could, for instance, bear fruit through the development of a preventative cow's milk product that still preserves its protective properties but does not carry potentially harmful organisms. The evolving helminth story is another example. So far, attempts to treat established allergic disease through voluntary helminth infection in asthmatics and hay fever sufferers have been disappointing (148). Although no such trials exist in patients with AD yet, rather than infecting ourselves with potentially harmful pathogens, success is more likely if we can find creative ways of mimicking what occurs in developing country settings through the development of parasite-derived drugs or vaccines. Many hurdles must be overcome to reach these aims, however, and collaboration with the pharmaceutical industry is needed (178).

In view of all this, is there still a place for 'classical' epidemiology research? The answer is 'yes'. There is, for instance, little data on the epidemiology of AD in North and South America and Eastern Europe. Despite the identification of important environmental risk and protective factors, we also still do not understand well what is responsible for the AD prevalence gradients *within* and *between* countries, with many studies showing significant residual (unaccounted) confounding (21, 35). No doubt, epidemiological AD research will continue, but increasingly make use of tools from microbiology, immunology, and genetics.

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Author contributions

CF wrote the manuscript. JM performed the systematic literature search and provided significant input on drafts of the manuscript as well as the figures.

Conflict of interest

None declared.

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