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REVIEW

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# Global differences in atopic dermatitis

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## Abstract

Atopic dermatitis (AD) is a chronic inflammatory skin disorder, with a highly variable prevalence worldwide. Recent evidence, however, has shown an increase in prevalence in the Asia Pacific region. Nevertheless, most of the published literature has focused mainly on Western populations, and only few clinical trials have included subgroups of other ethnic populations. Reasons for the observed ethnic and geographical differences in AD are not well established. This calls into question the need for a better understanding of AD pathogenesis and inter-ethnic differences in clinical and immuno-phenotypes. These differences may reflect inherent variability in disease mechanisms between populations, which in turn may impact upon treatment responses such as biologics that are currently tailored mainly to a specific immuno-phenotype (T-helper type 2 dominant). In this article, we reviewed existing literature on the prevalence of AD globally, highlighting differences, if any, in the clinical and immuno-phenotypes of AD between different ethnicities. We discussed genetic and environmental factors that affect AD in different populations and therapeutic considerations. Our review highlights AD as a disease with ethnic-dependent clinical and immunological heterogeneity and calls for greater inclusion of ethnic diversity in future research in order to develop targeted treatments.

**KEYWORDS**

Asia, atopic dermatitis, child, eczema, environment, ethnic diversity, genetics, global, immuno-phenotypes, tailored treatment

## 1 | INTRODUCTION

Atopic dermatitis (AD) is one of the most common chronic inflammatory skin disorders, which often develops in early infancy and may persist into adulthood.[1] The pathogenesis of AD has yet to be fully elucidated, but it is considered to be complex and multifactorial, attributed to an interplay of genetics, immune, and environmental factors.[1,2] The International Study of Asthma and Allergies in Childhood (ISAAC) Phase 3 indicated the Asia Pacific region as an area of increasing AD prevalence.[3]

However, the epidemiology of AD is highly variable worldwide and most of the published literature has so far focused mainly on Western populations. The risk factors contributing to the ethnic and geographical differences in AD are also not well established. Recent studies have shown variability in the immuno-phenotypes of AD among different ethnic groups and populations. These differences may in turn affect responses to treatment which are tailored mainly to a specific immuno-phenotype (T-helper type 2 (Th2) dominant).

This review therefore seeks to collate existing literature on the prevalence of AD internationally; highlighting differences, if any, in the clinical and immuno-phenotypes of AD between different ethnicities and discusses possible factors accounting for the observed differences.

## 2 | PREVALENCE OF ATOPIC DERMATITIS

The rising prevalence of AD in recent years has been demonstrated in several studies, notably the ISAAC, one of the most comprehensive global epidemiological studies on allergic diseases available to date.[4,5] The study estimated a self-reported AD prevalence of 15%-20% in children and an increment of 1.8% over an average of 7 years.[5] However, prevalence rates vary significantly between countries, ranging from as low as 0.9% (India) to 22.5% (Ecuador) in 6- to 7-year-old children; and from 0.2% (China) to 24.6% (Colombia) in 13- to 14-year-old children.[5] Generally, self-reported AD prevalence in Scandinavia, Northern and Western Europe, Australasia, and urbanized African regions were ascertained to be higher than those in Eastern Europe, Middle East, China, and Central Asia.[4,5] The follow-up study also indicated stable prevalence rates in urban nations such as UK and New Zealand, while prevalence rates were surging in low-income countries such as Latin America or South-East Asia.[5]

AD prevalence has also been found to vary significantly between diverse ethnic groups within multi-ethnic countries, highlighting the role of genetics in AD etiology.[6] A population-based study in the United States (US) has demonstrated higher self-reported doctor diagnosis of AD prevalence in African American children in comparison with European American children.[7] Project Viva, a prospective US pre-birth cohort, showed higher childhood AD prevalence based on self-reported doctor diagnosis, in non-Hispanic Blacks, and other non-Hispanic ethnic groups compared to Hispanics and non-Hispanic Whites.[8] However, the odds of persistent AD were higher in non-Hispanic Blacks and Hispanics than non-Hispanic Whites. Similar findings were observed when AD diagnosis was made by a physician using the UK Working Party criteria (UKWP).[9] Multiracial, non-Hispanic participants had an increased odds of AD [OR 3.36 (1.31-8.58)] compared to White, non-Hispanic individuals. Among US adults whose age of AD onset was less than 2 years, the study reported an AD prevalence of 7.3%. Clinical data from a national survey of children's health also reported increased medical utilization in Blacks and Asian/Pacific Islanders in comparison to Whites.[7] Additionally, a population-based study of 15 000 Chinese preschool children reported the prevalence of AD based on clinical diagnosis of 12.94% compared to 4.76% when diagnosis was made by a physician based on UKWP diagnostic criteria and 3.51% when using Hanifin and Rajka criteria.[10,11] Collectively, these ethnic and racial disparities, compounded by differing methods of AD diagnosis signify the complexity of AD.

The inconsistencies and differences in AD definitions among the studies render comparisons and reconciliation of current evidence challenging. Previous studies lacked a standardized nomenclature for AD, resulting in terms such as "AD" and "atopic AD" or "atopic dermatitis" being used interchangeably.[12,13] A comprehensive review by Kantor et al in 2016 reported that out of 33 060 identified relevant publications, publications using terms such as "atopic dermatitis", "AD," and "atopic AD" were 21 299 (64.4%), 15 510 (46.9%), and 2471 (7.5%), respectively.[12] Comparatively, alternative terminologies such as "flexural AD", "childhood AD," and "infantile AD" were also used to describe phenotypes of AD.[13] While some authors defined AD according to clinical diagnostic criteria regardless of atopic status, others proposed segregation into intrinsic (non-atopic) and extrinsic (immunoglobulin E associated) subgroups to account for underlying mechanisms.[14]

**Key Message**

Our review highlights atopic dermatitis as a disease with ethnic-dependent clinical and immunological heterogeneity. Better understanding of the clinical, genetic, and molecular aspects of atopic dermatitis across various ethnic groups is essential to guide targeted approaches for treatment of atopic dermatitis specific to each ethnic population. In order to do so, greater inclusion of ethnic diversity in future research is necessary.

Large epidemiological studies on AD prevalence often utilize self-reported data that could be less accurate due to reasons like recall bias, rather than objective clinical assessments by clinicians.[15] Of the various objective clinical assessments for AD severity, multi-item scores such as Eczema Area and Severity Index (EASI) and Severity Scoring of Atopic Dermatitis (SCORAD) are two of the most frequently validated tools.[16] Both are clinical tools used to assess the extent and severity of eczema by grading the physical signs of AD lesions. Other commonly used tools are the Nottingham Eczema Severity Score (NESS) [17] and a global scale assessment, Investigator's Static Global Assessment (ISGA).[18] While NESS is an index that evaluates chronicity, extent, and intensity of AD,[17] the ISGA is a 5-point ordinal scale commonly used to provide an overall snapshot of AD severity in randomized control trials. Collectively, these differences in reporting styles, adoption of different clinical tools which are not standardized or validated, and inconsistencies in the definition of AD between studies can contribute to potential mis- or under-recognition and inaccurate reporting of the true AD prevalence.

There is a growing interest in the role of the environment impacting AD pathogenesis.[19] Migrant studies are considered to be a potential tool in epidemiological studies to elucidate the environmental effects on AD pathogenesis. By eliminating the variability of genetic determinants, observations derived from a population with similar genetic makeup who migrated and acquired disparate disease risk can implicate the strong role of environmental effects on AD development.[20] Disparities in AD prevalence between migrants and native-born residents within the same geographical location have been illustrated in a few studies.[21,22] Immigration from a less developed/affluent country into a more developed/affluent country with higher AD prevalence rate was observed to correlate to a lower incidence of AD in migrants when compared to the native population.[23] In Australia, children born in Asia who subsequently migrated to Australia also had a lower risk of self-reported AD than their East Asian peers who were born in Australia.[24] Additionally, a study by

Ernst et al found self-reported doctor diagnosis of AD prevalence to be one-third lower in German children and adolescents with two migrant parents.[21] However, an Australian population-based study by Martin et al showed that 12-month-old infants with parents born in East Asia had a higher prevalence of self-reported doctor diagnosis of AD than infants of Australian-born parents.[25] At age 6 years, self-reported doctor diagnosis of AD was still more common in the children of East Asian background compared to those of Caucasian background.[26] Data from the ISAAC study likewise revealed a protective pre-migration environment that diminishes over time in the host country, which suggests the importance of environmental factors in AD pathogenesis.[22]

### 2.1 | Ethnic differences in AD-associated food allergy risk

Previous studies have established AD as a well-known strong risk factor for food allergy, with AD severity and early age of onset as significant modulators of food allergy risk.[27,28] A systematic review and meta-analyses of 66 studies found 16 studies supporting the association between food allergy and severe AD and six indicating association between early onset AD and food allergy.[28] Based on the population-based studies included in the systematic review, up to 15% of children with AD also had food allergy. However, the systematic review did not address differences, if any, in ancestry.

These associations may be attributed to the dual allergen hypothesis that was first proposed by Gideon Lack.[29] The hypothesis stipulates that a disrupted skin barrier function caused by AD can promote allergic sensitization due to low-dose epicutaneous exposure to allergens. Without timely introduction of food into the diet, oral tolerance induction does not occur and consequently, food allergy develops. Even in this regard, there exist ethnic differences in the risk of food allergy associated with AD. Australian-born children with AD whose father was born in East Asia had an increased risk of food allergy.[30] Ethnic differences in AD and food allergy were also observed in a study carried out among African American, Hispanic, and White children. Another study found that African American and Hispanic children had higher rates of both food allergy and AD compared to White children.[31] In children with moderate-to-severe AD, peanut allergy was reported in 15% of those of Black South African (Xhosa) origin compared to 38% of those with mixed Caucasian/Black ancestry.[32] However, this ethnic difference was not observed for egg sensitization and egg allergy, suggesting that different mechanisms may impact the pathogenesis of allergy to different food allergens.[33] Collectively, existing literature highlight the presence of ethnic differences among children with AD as a high-risk group that can be targeted for closer monitoring to prevent development of food allergy.

The co-existence of AD and food allergy has also been attributed to their shared genetic makeup, particularly loss of function of filaggrin (*FLG*) variants.[34,35] Interestingly, increased transepidermal water loss (TEWL) was observed in both AD patients with and without *FLG* mutations, even in non-lesional skin.[36] In another study, TEWL was found to be associated with food sensitization in the absence of AD.[37] These two studies imply that while skin barrier impairment may be a precursor to AD skin lesions and/or inflammation, skin barrier impairments not specific to AD can also contribute to sensitization and possibly, food allergy development.[36,37]

## 3 | VARIED CLINICAL PHENOTYPES

There also appears to be ethnic-dependent heterogeneity in AD clinical phenotypes. In a genomic profiling study utilizing lesional biopsies from AD patients, Asian patients tended to have well-demarcated, erythematous plaque-like lesions, whereas Caucasian patients typically have ill-defined, flatter erythematous skin lesions.[38] In a cross sectional study of 602 adults with AD, skin lesions were most commonly found at the popliteal fossae, lower legs, dorsal feet, and antecubital fossae.[39] Lesions on the trunk were more common in Blacks and Hispanics than in other ethnicities and were associated with a poorer quality of life.

AD lesional distribution was also found to differ by study region according to a recent systematic review and meta-analysis of 101 studies.[40] Notably, the studies were carried out across 28 countries of which, 29 studies were from East Asia, 48 from Europe, 4 in South-East Asia, and the rest distributed among Americas, Africa, Australia, India, and Iran. In studies originating from East and South-East Asia, truncal involvement was more common, whereas in Australian studies, flexural involvement was more prevalent. When compared to European studies, erythroderma and truncal, extensor, scalp, and auricular involvement were more common in East Asia. On the other hand, studies from South-East Asia had higher prevalence of exudative AD, immediate skin test reactivity, truncal involvement, lichenification, and prurigo nodularis. In addition, itch was reported to be aggravated by sweating in South-East Asia, America, East Asia, Europe, and India to a similar extent. Although the underlying reason for the observed variations is unclear, it may be due to the interplay between genetic and environmental risk factors.

## 4 | IMMUNO-PHENOTYPES

An imbalance in T-helper 1 (Th1)/Th2 responses is one facet of the pathological processes of AD. While the Th2 pathway activation is relevant to the various subtypes and phenotypes of AD, other hallmarks of T-helper cells have also been reported in different AD populations. The skin immune response in Asian AD has been shown to be driven by a combination of Th2 and T-helper 17 (Th17) (another T-cell effector subset) cytokines, while in Europeans the immune response is primarily Th2-mediated.[38]

Evidence also suggests that there are significant differences in the skin immune response as well as epidermal morphology and dermal composition between Asians, Caucasians, and African Americans.[41-43] In a group of females aged between 18 and 45 years,

East Asians and Caucasians were reported to have higher baseline levels of TEWL compared to African Americans, indicating that the latter may have a more intact skin barrier demonstrating resistance to mechanical challenge.[41] Baseline TEWL of Caucasians was slightly higher compared to East Asians. Despite this, Caucasian skin was shown to have a significantly stronger barrier function than East Asian skin, measured by a greater number of tape strips required to disrupt the skin barrier.[41]

African Americans were also found to have several differences in barrier characteristics compared to Caucasians.[44,45] A key skin barrier protein, Loricrin, was not consistently distributed and expressed in biopsy samples from African Americans compared to Caucasians.[44] The African American skin biopsies were also marked by dendritic cells of the high-affinity IgE receptor (FceRI+). This significant increase in FceR + dendritic cells correlated with higher serum IgE levels and SCORAD in African American but not Caucasians. African Americans also demonstrated a skewed Th2/Th22 disease profile combined with an attenuated Th1/Th17. Upregulation of Th22 known to be associated with hyperplasia and keratinocyte proliferation was more prominent in African Americans,[46] while Th17 markers which play a significant role in Caucasian AD were downregulated in African Americans. This is also accompanied by a lack of induction of Th1 markers in African Americans, which are drivers in AD pathogenesis in the Caucasian population.[44] Additionally, peripheral blood from Japanese/Korean patients with AD demonstrated higher Th17 and Th22 and lower Th1 skewing compared to European Americans.[38] Th2 activation were, however, similar in the European Americans and Japanese/Korean patients. An overview of the clinical and immuno-phenotypes illustrated by Czarnowicki et al[45] is shown in Figure 1.

## 5 | POSTULATED REASONS FOR OBSERVED DIFFERENCES

The global differences in AD prevalence and phenotypes may be attributed to a combination of underlying genetic disposition as well as environmental factors such as climate, humidity, temperature, and water hardness.

### 5.1 | Genetic effects

*FLG* is the most well-studied gene in AD. Loss-of-function mutations have been reported to be a significant risk factor for the pathogenesis of AD.[47-50] *FLG* encodes a key epidermal barrier protein and mutations in this gene disrupt the skin barrier,[51] enhancing epicutaneous

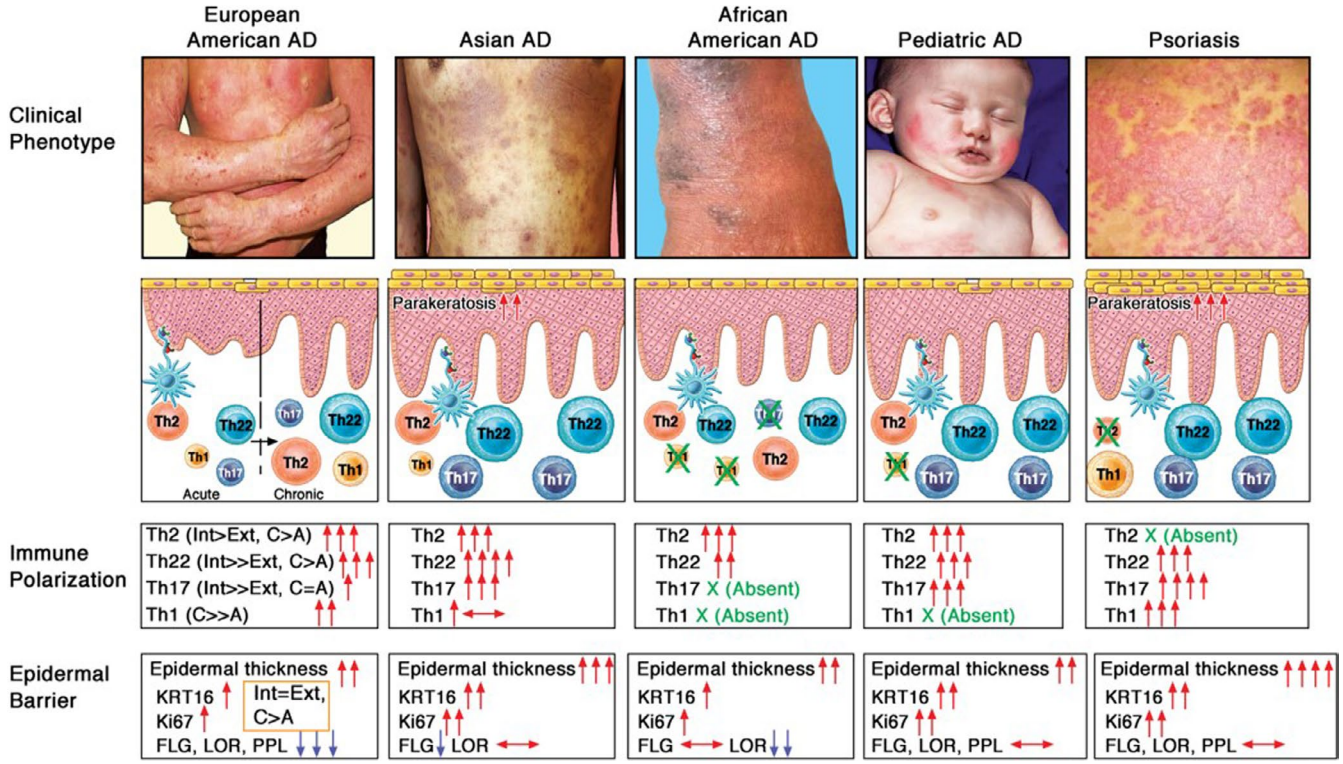


**FIGURE 1** Clinical and immuno-phenotypes of AD[45] [used with permission from Elsevier]. Clinical phenotypes, cytokine activation pathways, immune polarization of T-cell subsets, and epidermal barrier changes for each AD phenotype are shown. Pediatric AD and psoriasis phenotype comparisons were not addressed in this review. Intrinsic (Int), extrinsic (Ext), acute (A), and chronic (C) subtypes were characterized only in European American patients with AD and thus appear exclusively under this category. Epidermal barrier measures, including epidermal thickness, keratin 16 (*KRT16*), Ki67, filaggrin (FLG), loricrin (LOR), and periplakin (*PPL*), were similar in patients with intrinsic and extrinsic AD but more evident in European American patients with chronic versus acute AD.

allergen exposure which results in increased TEWL and exposure to irritants and allergens.

The frequency and type of *FLG* mutations differ between Asians and Caucasians. Polymorphisms accounting for AD in Singapore are more diverse compared to that in Ireland.[52] The top seven most frequent *FLG*-null mutations (c.3321delA, c.6950_6957del8, p.S1515X, p.S2706X, p.Q2417X, p.E2422X, p.G323X) found in the Singapore population accounted for almost 80% of *FLG* mutations associated with AD. In comparison, only two *FLG*-null mutations (p.R501X and c.2282del4) accounted for 80% of mutations in Ireland. While three *FLG* mutations, R501X, 2282del4, and E2422X, were common in both European and Asian populations, the most common mutation in the Asian population, 3321delA, was not present in the European population.[53] Moreover, loss-of-function *FLG* mutations are not as prevalent in African Americans compared to European Americans.[49] Even then, the loss-of-function mutations were associated with persistent AD rather than AD onset in African Americans. This suggests that there may be other attributable skin barrier genes that contribute to the pathogenesis of AD in this ethnic population.

Through genome-wide association studies (GWAS), a hypothesis-free driven approach, novel genetic associations for AD were also identified. The first GWAS carried out in 2009 in a German cohort (939 individuals with AD and 975 controls), replicated *FLG* as a susceptible gene, and also identified rs7927894 on chromosome 11q13.5 as a new susceptibility gene.[54] The first AD GWAS in a Chinese Han population was later carried out in 2011, where *FLG* was again replicated as a susceptibility gene and two new susceptibility loci were identified.[55] Loci 5q22.1 (*TMEM232* and *SLC25A46*, rs7701890) and 20q13.33 (*TNFRSF6B* and *ZGPAT*, rs6010620) were both associated with an increased risk of AD. Within the same year, a more statistically powered GWAS was carried out by Paternoster et al in 26 171 European subjects across 16 population-based cohorts.[56] Three SNPs (rs479844 upstream of *OVOL1*, rs2164983 near *ACTL9* and rs2897442 in *KIF3A*) reached genome-wide significance in the combined analysis of discovery and replication cohorts. Since then, eight more GWAS have been published, [57-64] the most recent of which was by Marenholz et al, [61] which investigated genetic associations with atopic march, and the notion of AD preceding development of asthma.

Untangling genetic determinants specific to AD may be challenging given that there are shared genetic components among various allergic diseases. Several studies have highlighted genes shared among several allergic diseases which modulate adaptive and innate immune response and skin barrier dysfunction.[34,65] However, genetics alone do not explain the differences in AD susceptibility across different populations. A genetic study carried out in two cohorts of US AD subjects of African American did not detect any associations between African genetic ancestry or genetic skin pigment score with AD risk among the African American population,[66] suggesting that social and environmental factors also play important roles in AD pathogenesis.

## 5.2 | Environmental effects on atopic dermatitis

A growing body of evidence has suggested the involvement of environmental factors in the rapid rise in prevalence of AD worldwide. The prevalence of AD is also reported to be higher in more developed parts of the world compared to developing areas.[67,68] These differences cannot be due to genetics alone. In this section, we discuss the different environmental factors and their role in AD pathogenesis (Figure 2).

### 5.2.1 | Socioeconomic status and the hygiene hypothesis

Evidence from a number of studies has shown the association between higher socioeconomic status and increased AD rates. Results from the National Health and Nutrition Examination Survey showed that AD was more common in children from families with higher household income and education.[69] Similar findings were reported from the UK Millennium Cohort Study which showed that children from more highly educated mothers were at increased risk of developing AD.[70] This may in part be attributed to better living conditions and may be explained by the hygiene hypothesis which postulates that exposure to microbes, allergens and endotoxins in early life is protective against the development of allergic diseases in later life.[71,72] Supporting evidence for this hypothesis is provided by the observation of lower rates of AD in less developed countries compared to developed counties such as the US.[73] Similarly, rural living is associated with lower odds of AD compared to urban living.[74] The PARSIFAL (Prevention of Allergy—Risk Factors for Sensitization Related to Farming and Anthroposophic Lifestyle) cohort [75,76] and GABRIELA (Multidisciplinary Study to Identify the Genetic and Environmental Causes of Asthma in the European Community [GABRIEL] Advanced Study) cohort showed that the prevalence of AD is lower in children living on farms compared to children from suburban areas due to increased exposure to the environmental microbiome present in farming environment.[75,77,78]

### 5.2.2 | Climate (UV exposure, latitude, humidity, temperature)

Meteorological factors such as latitude, UV radiation, humidity, and temperature are several key environmental exposures affecting AD development and severity.

Latitude increases with distance from the equator and AD severity has been shown to be positively associated with latitude and negatively with UV light exposure and outdoor temperature. AD prevalence was found to be higher in states with increased stratospheric ozone which blocks UV radiation.[79] Beneficial effects of UV radiation include stimulation of previtamin D synthesis as well as facilitating the conversion of breakdown product of filaggrin,

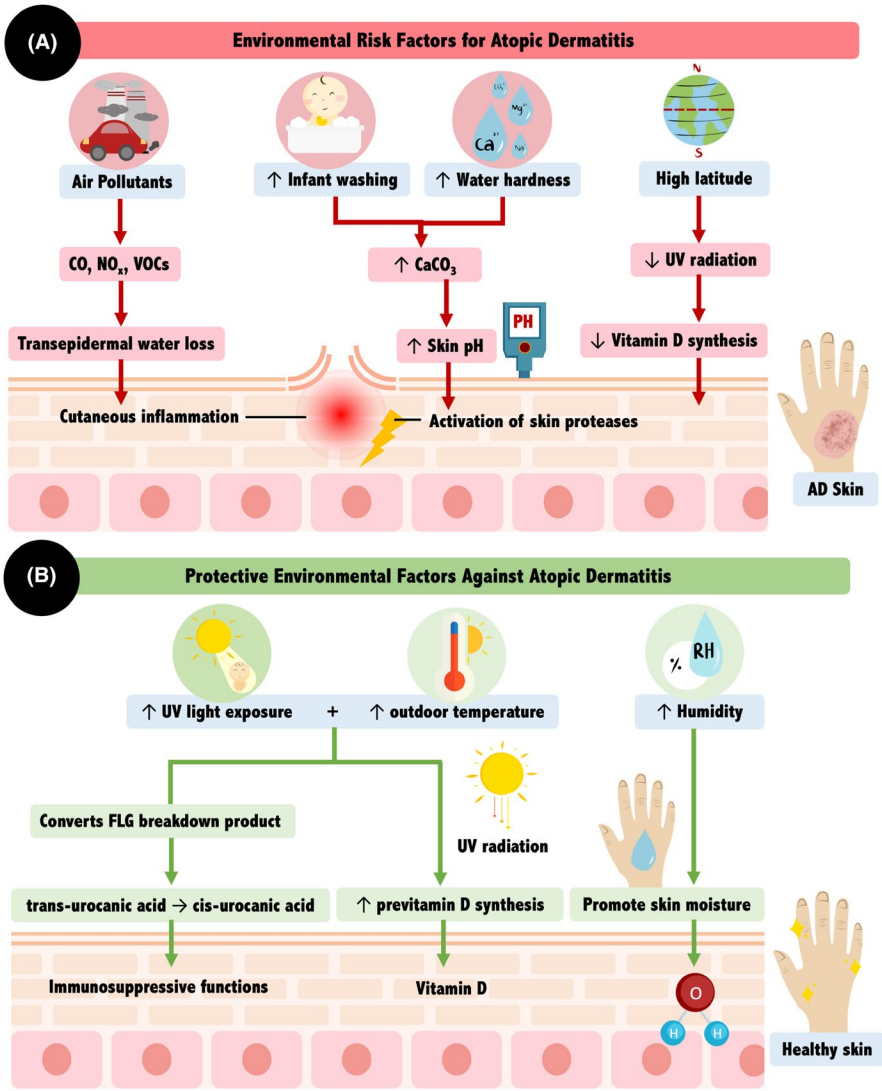


**FIGURE 2** Environmental risk factors (A) and protective factors (B) for atopic dermatitis. (A) Environmental risk factors for atopic dermatitis include air pollutants, increased infant washing, and water hardness as well as high latitude. Collectively, these can lead to cutaneous inflammation and activation of skin proteases that contribute to the development of atopic dermatitis. (B) Conversely, increased ultraviolet exposure, coupled with high temperature and humidity enhance vitamin D exposure as well as promote skin moisture, in a bid to prevent the development of atopic dermatitis.

trans-urocanic acid into the cis-urocanic acid isoform with immunosuppressive functions.[80] Epidemiological studies have shown that non-White children have higher rates of AD compared to White children.[81] Studies in cohorts have demonstrated the protective role of vitamin D in the development of AD.[82,83] The geographical and ethnic disparities in AD prevalence may thus be attributed to a combination of UV exposure with latitude and skin pigmentation, as increased pigmentation decreases the production of vitamin D in the skin.

While sun exposure/UV radiation impacts upon the risk of AD development, temperature and humidity impact upon skin moisture retention and TEWL which in turn modulate- AD risk and severity. In observational studies, however, the distinction between the contribution of UV exposure, temperature, and humidity toward AD pathogenesis cannot be clearly distinguished as these factors typically co-exist. The National Survey of Children's study in the US on 91,642 children aged 0-17 years reported that AD prevalence was decreased with higher UV index, relative humidity, and mean temperatures.[81] Similar findings were shown by another Australian study where prevalence of AD was found to be lower in regions with high sun exposure and warmer climate, such as those that are closer to the equator.[84]

Studies investigating the effects of temperature on existing AD, however, indicate that AD severity may be aggravated by higher temperatures and humidity. In a German study of children with AD followed up over 6 months from spring/summer to autumn, 21 children experienced AD exacerbations that were alleviated following rising temperatures. [85] The remaining 18 children in the study had symptoms during summer months which were aggravated by higher temperatures. Humidity however had no significant effect on severity of symptoms in this study. Poorly controlled AD has been shown to be associated with geographic areas with increased temperature, sun exposure (total, UVA, and UVB), and humidity.[86] Langan et al proposed that the increased sweating due to the higher humidity may have an irritant effect on the skin due to its acidic pH, [87,88] activating Th2- and Th17-mediated inflammation, which downregulate the expression of *FLG*.[89,90] Although the humidity may promote skin moisture, ironically, it also promotes the evaporation of water on the skin surface, further exacerbating xerosis.[86] These findings suggest that

meteorological factors play different roles in modulating AD onset and control of existing AD.

### 5.2.3 | Irritants and water hardness

The impairment and/or permeability of the skin barrier can be affected by infant washing practices such as bathing frequency, types of soap, and detergents used or even water hardness which may affect skin barrier permeability.[91] Studies in UK, Spain, and Japan have shown that increased water hardness elevated the risk of AD development in children.[92-94] In another study conducted in infants from UK, exposure to higher levels of water hardness increased the risk of developing AD at 3 months of age.[95] The Danish Birth Cohort also showed that early life exposure to hard domestic water and birth in fall/winter seasons increased the risk of development of AD in the first 18 months of life.[96] Increased calcium carbonate levels in water may lead to higher pH with activation of skin proteases and triggering of cutaneous inflammation.[97] Regions with increased ground water hardness may thus experience a higher prevalence of AD, though more mechanistic studies are required to conclusively prove this link.

The East Asian skin has also been reported to be more sensitive and reactive to irritants and environmental agents,[98] possibly due to the thinner stratum corneum of East Asian skin.[99-101] This provides further support to the theory that the weaker barrier function in East Asians may be contributing to the high prevalence of AD in this group.

### 5.2.4 | Air pollutants

Studies suggest that exposure to environmental pollutants may also increase AD risk. A study involving 317 926 Taiwanese schoolchildren found a positive correlation between flexural AD and exposure to traffic-related air pollutants such as carbon monoxide and nitrogen oxides.[102] Increase in exposure to volatile organic compounds - such as benzene was also associated with severity of AD symptoms.[103] Clinical studies have also demonstrated exposure to airborne formaldehyde and $NO_2$ elevated TEWL and skin barrier impairment in AD subjects.[104,105] No studies examining geographical or ethnic differences in pollutant exposure on AD have yet been performed.

## 6 | IMPLICATIONS FOR AD MANAGEMENT

Given the variability in prevalence and phenotypes of AD across different ethnic populations, it is surprising that little literature exist on the efficacy of therapies across the various ethnic populations and/or minority ethnic groups. We have discussed earlier that skin physiology differs across ethnic groups[38] and these differences may affect treatment response. It remains to be seen whether these differences across ethnic groups are clinically significant and affect treatment outcomes. Additionally, the lack of a published standard on management of AD in the Asia Pacific region prompted the development of a consensus guideline to provide evidence-based recommendations for general practitioners and dermatologists in the Asia Pacific region.[106] Even within the Asia Pacific region alone, management of AD can be influenced by variations in the healthcare systems, climate, access to medical care, and diversity in cultural practices and preferences.[106]

Despite this, the first-line therapy for AD across various ethnic populations is still topical anti-inflammatory drugs such as corticosteroids.[107] More recently, Crisaborole ointment, a non-steroidal phosphodiesterase 4 inhibitor for the treatment of mild-to-moderate AD, has been shown to be efficacious in the treatment of mild-to-moderate AD in all racial groups (White vs non-White: made up of Asian/native Hawaiian/other Pacific Islanders; Black/African Americans; and others/American Indian/Alaskan natives).[108] In this study, two randomized controlled trials on Crisaborole which performed post hoc analysis by ethnicity observed that more Crisaborole-treated, compared to vehicle-treated patients, achieved ISGA scores of "clear" or "almost clear" in all racial and ethnic groups.

Dupilumab is another biologic that has been shown to be effective in treatment of severe AD. It is a monoclonal antibody that acts by inhibiting signaling to IL-4 and IL-13 receptor, reducing IL-4 and IL-13 production, the two key mediators of AD and thereby reducing Th2 type inflammation seen in AD. The efficacy of dupilumab for AD treatment has been well established—a systematic review and meta-analysis of dupilumab clinical trials showed successful reduction in skin infections and AD herpeticum in adults of moderate-to-severe AD.[109] However, it is worth noting that the studies included in the systematic review were carried out in predominantly White populations (>57% of patients in each included study). Just a single clinical trial in White, Asian, and African American patients with moderate-to-severe AD found that dupilumab, with or without concomitant topical steroids, significantly improved AD signs, symptoms, and quality of life across all racial subgroups.[44,110] The overall lack of representation of the minority ethnic groups in published AD studies has also been highlighted in systematic reviews carried out by Hirano et al.[111] and Charrow et al.[112] Ensuring ethnic diversity in research is essential in delivering management, prevention, and access to AD treatment across various ethnic groups.

## 7 | CONCLUSION

The differences in Asian, Caucasian, and African American populations discussed in each section of this review are summarized in Table 1. With an increasingly globally mobile society, it is imperative to have an understanding of the clinical, genetic and molecular aspects of AD across various ethnic groups to guide targeted approaches for treatment of AD that can be tailored to each ethnic population. While the Th2 cytokine axis appears to be the common

**TABLE 1** Summary of global differences in atopic dermatitis (AD)

| | Asian population | Caucasian population | African American population |
|---|---|---|---|
| AD prevalence | ↑ (10.1% (3.7% –13.5%)[5] | ↑↑ than Asian | ↑ than Caucasian |
| Food allergy associated risk | ↑↑ in Australian-born infants of Asian ancestry | ↑ | ↑ |
| Clinical phenotypes | - Well-demarcated, erythematous plaque-like lesions<br>- Erythroderma and truncal, extensor, scalp, and auricular involvement | Ill-defined, flatter erythematous skin lesions | Lesions on the trunk more common |
| Immuno-phenotypes | Involvement of Th2, Th22, Th17, and Th1 | Involvement of Th2, Th22, Th17, and Th1 | Involvement of Th2 and Th22 |
| Genetic effects | *FLG* variants R501X, 2282del4, and E2422X common in both populations | | |
| | *FLG* genetic makeup more diverse. Seven *FLG* LOF variants (c.3321delA, c.6950_6957del8, p.S1515X, p.S2706X, p.Q2417X, p.E2422X, p.G323X) make up 80% of mutations associated with AD.<br>GWAS identified rs7701890 (*TMEM232/SLC25A46*), and rs6010620 (*TNFRSF6B/ZGPAT*) as susceptible variants. | Two *FLG* LOF variants (p.R501X and c.2282del4) make up 80% of mutations associated with AD.<br>GWAS identified rs7927894 (near *C11ORF30*), rs479844 (upstream of *OVOL1*), rs2164983 (near *ACTL9*), and rs2897442 (*KIF3A*) as novel susceptible variants. | *FLG* variants (composite based on p.R501X, p.R826X, p.R2447X, p.Q3818X, p.Q570X, p.R3409X, p.S3247X, p.S3316X, p.H440fs) more associated with persistence of AD. |

Abbreviation: AD, Atopic Dermatitis; ↑ increased/higher levels/rates.

mechanism of action for AD development across the ethnic populations, the discovery of involvement of other cytokine axis such as Th22 and Th17 represents a promising target for precision medicine in patients presenting with a distinct phenotype.[45] It is likely that an integrated model of lesional and non-lesional skin along with blood measures will best reflect disease severity for accurate AD diagnosis and inform tailored treatment of AD.

## CONFLICTS OF INTEREST

The authors declare that they have no relevant conflicts of interest.

## AUTHOR CONTRIBUTIONS

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## PEER REVIEW

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