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REVIEW ARTICLE

Atopic Dermatitis Across Shades of Skin

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Abstract

Atopic dermatitis (AD) is a chronic, heterogeneous inflammatory skin disease that is associated with immense patient burden globally. There is increasing appreciation of disparities among patients identified as having skin of color (SOC), which often refers to patients of non-White race or non-European ancestry, but can broadly include individuals from a number of different racial, ethnic, ancestral, and skin pigmentation groups based on definition. In this narrative review, we discuss key terminology as it relates to AD across shades of skin, including modern definitions of 'race', 'ethnicity', and 'SOC'. We then synthesize the current literature describing disparities in AD prevalence, disease recognition, and burden alongside current data regarding genetic and immunologic findings across SOC populations. In the context of these findings, we highlight key concomitant social determinants of health, including environmental factors, socioeconomic status, and access to care, for which race often serves as a proxy for true biological and genetic differences. Finally, we discuss future efforts to shift to a more inclusive understanding of AD to encompass all shades of skin, to ensure equitable representation of diverse populations in high impact research, and intensify efforts to address the critical upstream factors driving observed disparities.

Key Points

Atopic dermatitis (AD) is associated with immense patient burden globally.

There is increasing recognition of disparities affecting AD prevalence, disease recognition, and burden among patients identified as having skin of color, which can include individuals from many different racial, ethnic, ancestral, and skin pigmentation groups.

Additional efforts are needed to shift to a more inclusive understanding of AD to encompass all shades of skin, ensuring equitable representation of diverse populations, thorough understanding of biologic and genetic factors, and accurate recognition of key social determinants of health that may drive disparities in course and outcomes.

1 Introduction

Atopic dermatitis (AD) is a chronic, heterogeneous inflammatory skin disease associated with immense patient burden. AD is common across all ages and affects up to 25% of children and 10% of adults worldwide, though prevalence varies widely with geography—even within the same continent or country. In the United States (US), based on findings from multiple population-based cross-sectional studies, the estimated prevalence is approximately 13% in children and 7% in adults [1, 2].

There is increasing appreciation of disparities in diagnostic accuracy, prevalence, symptom severity, disease burden, and therapeutic management in patients identified as having skin of color (SOC), which includes individuals with racial, ethnic, and/or ancestral designations such as Black/African American, Latinx, Hispanic, Asian, or very broadly, non-White—compared with those most often identified as White and non-Hispanic. These disparities have historically been highlighted through biological interpretations of SOC, race, and ethnicity, which on the surface suggest that skin pigment, geographical ancestry, and their ensuing genetic variation account for these differences. However, currently implicated predisposing genetic factors are not able to account for many of these disparities, despite technological advances in pinpointing specific inflammatory pathways. Instead, evidence supports the critical role of upstream

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social determinants of health, including environmental factors, socioeconomic status, and access to and quality of care, in driving many of these disparities [3–5].

Here, we review the terminology of SOC in AD, summarize how various SOC designations have revealed disparities, and call for continued critical investigation into the role of systematic, upstream social determinants alongside true biological factors in SOC patients with AD (Table 1).

2 Definitions of Race, Ethnicity, and Skin of Color (SOC)

It is important to define the terms 'race', 'ethnicity', and 'SOC' to accurately interpret the existing literature, understand any shortcomings, and better design future AD studies. Race, as defined in US biomedical research, usually consists of five categories: American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, and White [6]. Race is a social construct once intended to capture genetic ancestry and phenotypic similarities, but because of the considerable variation across different social contexts, only does so partially and is no longer considered to have intrinsic biological significance. 'Ethnicity' is a social construct which groups people with common historical, national, tribal, religious, linguistic, or cultural backgrounds. Individuals within an 'ethnicity' often practice the same customs and speak similar languages, yet have highly variable overlap in genetic ancestry. In the US, ethnicity is generally separated into a Hispanic or Latino and Not Hispanic or Latino binary grouping. There are important limitations to this classification. For example, Hispanic or Latinx individuals can choose to self-identify with a variety of races. An individual who identifies as Black can also identify as having African American, African, Afro-Caribbean, or other mixed descent, which is impossible to determine from the race alone. Moreover, the amount of genetic variation within a race or ethnicity is known to be greater than variation between race or ethnicity [7–11]. Race and ethnicity may be self-reported by individuals or at other times designated by a third party, and in either case prone to subjectivity. This is further complicated in the US, where due to historical circumstances of social class, wealth, and opportunity, 'race'-based health disparities have become consequences not of the biological underpinnings of race but instead, of structural inequities [12]. Despite the heterogeneity and broad nature of these categories, biomedical researchers are obligated to use them as the most convenient method of separating and comparing study populations.

SOC is a complex concept encompassing diverse racial and ethnic backgrounds. Most simply, 'SOC' is pigmented skin or skin particularly prone to post-inflammatory pigment alteration (PIPA) (hyper- or hypopigmentation). SOC has colloquially been translated to specific racial groups, non-White individuals, or higher Fitzpatrick skin phototypes (FST) beyond II or III. Some patients may also self-identify as having SOC, despite not having heavily pigmented skin. In practice, because FST is commonly assigned by a clinician via their subjective visual inspection, there is significant interobserver variability when used in non-White populations [13–15].

Race, ethnicity, SOC, and FST type are the common and distinct categories conventionally used in biomedical discourse to group individuals based on their skin tone, presumed biological ancestry, and cultural backgrounds. There is no one universally accepted definition of these terms among all patients, clinicians, and researchers [16]. It is critical to consider the structural and social determinants of health inherent to these concepts to avoid inadvertent pathologization and biologization of race/ethnicity [3]. We synthesize and present here the available data on AD in patients with SOC. Most studies discussed here use variable definitions or a combination of race, ethnicity, or FST to describe SOC. Thus, we also highlight the conflicting conclusions of studies that attempt to identify biological differences with socially constructed terminology and identify possible gaps in study design. We are hopeful this may serve as a guide for how to incorporate the social determinants of health and other environmental factors into future, more complete studies of AD in populations with SOC.

3 Prevalence

Within the US, there are well-documented differences in the incidence and prevalence of AD among certain racial and ethnic groups, especially in the pediatric population. In a pooled analysis of the National Survey of Children's Health (NSCH) 2003–2004 and 2005–2006, National Health Interview Survey (NHIS) 2008–2012, and National Health and Nutrition Examination Survey (NHANES) 2003–2004 and 2007–2008, African American/Black and multiracial/other children had 1.5- and 1.3-fold increased odds of having AD, respectively [17]. Data on AD prevalence by race and ethnicity are more mixed among adults. For example, a meta-analysis using NHIS 2010, 2012 and NHANES 2003–2004 and 2005–2006 found that African American/Black, Hispanic, and Asian adults all had significantly lower odds of AD when compared with White adults [17]. The disparity in prevalence reporting between children and adults may indicate that there are other factors at play, including potential underdiagnosis of adult AD in patients who are non-White.

Table 1 Key considerations and recommendations for atopic dermatitis (AD) across shades of skin

Language	SOC is pigmented skin or skin prone to post-inflammatory pigment alterations, but often in practice translates to specific racial/ethnic groups, non-White patients, Fitzpatrick types beyond II or III Race is a construct partially based on geographic ancestry and physical similarities Ethnicity is a construct based on common historical, national, or cultural backgrounds Standardization of terminology is needed to avoid confusion between social and biologic concepts Avoid pathologizing diversity (e.g., SOC) by associating cutaneous findings with terminology such as 'atypical' or 'normal'
Prevalence	Within the US, particularly in pediatric patients, AD appears to be more prevalent among non-White patients The prevalence of AD can vary widely within the same region, country, and continent, suggesting the key role of environmental factors Future studies should include more granular data on social determinants of health driving differences in prevalence alongside race and ethnicity
Long-term course	Persistence of AD beyond childhood has shown association with Black race, Hispanic ethnicity, urban environment, and lower socioeconomic status, supporting the significant influence of structural factors Persistent AD is associated with disease burden, severity, atopic comorbidities, and impaired overall health
Quality of life	Non-White children are more likely to miss school Non-White patients account for a greater utilization of emergency department and inpatient care, with increased costs of care and longer hospital stays, reflective of lack of access and underdiagnosis in the primary care setting Even among Black patients with equal access to care, patients are subject to higher costs and more prescriptions
Diagnostic criteria	Current AD diagnostic criteria using 'typical' involvement of flexural surfaces in adults and face or extensors in children inadequately captures AD across diverse skin types, which are often characterized as featuring 'atypical' distribution or morphology Conventional diagnostic criteria have been validated as highly sensitive in some geographic areas but less sensitive in certain Asian, African, and non-European White populations There should be increased effort to redefine 'typical' features in AD diagnostic criteria to reflect the breadth of presentation more accurately
Severity	Erythema may appear violaceous, purple, or brown instead of pink or red. Closer inspection should be prompted by other clues of active disease such as warmth, edema, and scale Xerosis and post-inflammatory pigmentary alterations are important in assessing the severity of AD and can be more stigmatizing for patients with darker skin tones Limited research suggests pruritus may present with increased severity and impact on quality of life in certain groups
Distribution	Beyond flexural skin, other important areas of AD activity in diverse populations can include extensors, head/neck, trunk, and hands/feet
Morphology	Additional morphologies of AD that can be more common across diverse populations include perifollicular accentuation, lichenoid papules, nummular/psoriasiform plaques, and prurigo nodules
Genetics	GWAS studies have not revealed racial/ethnic differences in AD, although they inadequately capture patients with non-European ancestry Loss-of-function variants in *FLG* are reported in some AD patients of European and Asian ancestry but not in AD patients of African descent, suggesting that the utility of this is limited in diverse populations *FLG2* mutations have been identified in African American AD patients, but the function and role of *FLG2* in disease is not well understood The genetic factors in AD require more study, particularly with an eye towards including diverse populations
Barrier dysfunction	TEWL is a biomarker for AD severity and treatment response. Studies of differences in TEWL by race have not been conclusive and TEWL is subject to many environmental influences not captured in these studies Ceramide levels are inversely correlated with transepidermal water loss. Recent studies indicate ceramide levels may be lower in Black skin, however, the impact of extrinsic factors on this difference is not known
Immune dysregulation	Small studies have shown increased Th17/Th22 activation in the skin of Asian patients and psoriasis-like features in the skin of Han Chinese patients compared with African American and European American patients. However, serum levels of Th2 markers were similar African American patients have been found to have higher serum IgE levels than Asian and European Americans, which is associated with greater disease severity and atopic comorbidities Studies investigating immune skewing among races are inconclusive and limited to small, narrow samples
Environment	Air and other outdoor pollution is associated with AD prevalence and severity across populations. This may be an important driver of perceived differences across diverse populations Prenatal stress may be a proxy for the physical environment and SES and has been associated with an increased risk of AD in children More detailed studies are needed to explore these factors as well as water quality and nutrition

Table 1 (continued)

Socioeconomic status	SES is a complex variable closely tied to historical and structural factors, with mixed findings in relation to AD The history of housing discrimination and redlining is of particular importance in the US for limiting the SES of Black patients. SES overlaps with healthcare access and exposure to pollution Higher SES is also associated with increased AD prevalence in adults, which may reflect increased access to care Lower SES is associated with increased severity, persistence, and costs in AD, even independent of access, suggesting additional structural factors
Response to therapy	Limited data has been published on treatment response in AD patients with SOC and suggests no significant differences among racial or ethnic groups in topical or systemic therapies Systematic initiatives should continue to promote the equitable inclusion of SOC patients and reporting of race/ethnicity in basic, translational, and clinical research

AD atopic dermatitis, *GWAS* genome-wide association studies, *SES* socioeconomic status, *SOC* skin of color, *TEWL* transepidermal water loss

The interchangeable use of designations such as African American and Black, Latinx and Hispanic, and Asian and Pacific Islander in these and other studies disregards the heterogeneity within these groups and has likely prevented more comprehensive analysis of AD in specific populations. Black Americans include African Americans but also encompass recent African immigrants or those of mixed descent. These populations have significant differences in health behaviors and health outcomes, as evidenced by research in other specialties of medicine [18–20]. Few studies have analyzed the heterogeneity of AD within broad racial or ethnic groups in the US. For example, two studies investigating the prevalence of AD in school-aged children in Puerto Rico and Mexico (both often included in the 'Hispanic' group) showed rates of 25.8% and 3.4%, respectively [21, 22]. Interpretation of this large gap in prevalence is limited by the differing study designs and potentially driven by lesser-studied differences in socioeconomic structure, cultural practices, and physical environment, with likely lesser contribution of innate genetic differences. For this reason, for the future of AD research, it will be important to tease out these differences rather than group them together under umbrella terms such as 'Hispanic'.

The International Study of Asthma and Allergies in Childhood (ISAAC) represented an effort to analyze prevalence rates across the globe using consistent sampling methodology, though was still limited by categorizing based on region [23]. In their global synthesis study, they reported that in the 6- to 7-year-old age group, the highest prevalence of AD ($\geq 15\%$) was in Asia-Pacific (Thailand), Latin America (Colombia, Cuba, Ecuador, Honduras, and Nicaragua), Northern and Eastern Europe (Sweden), Oceania (Australia, New Zealand, and Niue), and Western Europe (United Kingdom) [24]. A lower ($<5\%$) prevalence of AD was found in Asia-Pacific (Hong Kong, Indonesia, and Vietnam), Eastern Mediterranean (Iran, Malta, Pakistan, Sultanate of Oman, and the Syrian Arab Republic), India, Latin America (Argentina and Mexico), Northern and Eastern Europe (Albania, Bulgaria, Croatia, Georgia, Hungary, Kyrgyzstan, Lithuania, and Ukraine), and Western Europe (Greece and Spain) [24–26]. Differences were frequently seen between cities within the same country and underscore the need to be granular in the collection and analysis of AD epidemiologic data. By aggregating heterogenous groups under overarching racial or broad geographic categories, the opportunity to understand true causative and exacerbating factors associated with AD are limited.

4 Severity of AD Signs and Symptoms

Along with increased prevalence of AD in certain racial and ethnic groups, accumulating evidence reflects increased severity and symptom burden of AD in Black, Latinx, and Asian/Pacific Islander populations [4, 27].

Disease severity in AD is evaluated using objective exam findings including erythema, edema/thickening, lichenification, excoriation, xerosis, and PIPA. Erythema (or "redness") can be easily underappreciated in SOC and darker skin tones, since it may appear more violaceous, purple, or brown instead of pink or red (Fig. 1) [24, 26]. Several AD clinical scoring tools, including the Eczema Area and Severity Index (EASI) and SCORing Atopic Dermatitis (SCORAD) index, include erythema as a major component, which can engender underestimation of disease severity and undertreatment in SOC [28]. In a longitudinal study investigating the inclusion of erythema in assessing AD severity with SCORAD, the authors found that Black children with AD were at higher risk for more severe disease after adjusting for the erythema score [29]. Reliance on erythema as a measure of disease severity is likely to mask severe AD in patients with darker skin tones, unless the reliability of the assessors can be assured. Alongside targeted educational interventions to better appreciate diverse signs of cutaneous inflammation, attention to qualities such as warmth of skin, edema, and overlying scale may help in identifying erythema in SOC patients [30].

Associated skin findings that both measure disease severity and are more stigmatizing in darkly pigmented skin include xerosis and PIPA. AD patients with darker skin

tones are more likely to experience PIPA; one Nigerian study found PIPA in 63% of studied AD patients [31]. PIPA may resolve over the course of months, but in cases of pigment alteration due to chronic and persistent excoriation, the changes may be permanent. Because these skin findings may be more distressing than other cutaneous symptoms of AD, especially for SOC patients, dermatologists should address this with their patients as it can greatly improve quality of life (QOL) [32].

Subjective patient-reported outcomes such as pruritus can also be used to measure disease severity. In one cross-sectional study of US military veterans, itch scores in non-White patients with AD were significantly higher than those of White patients [33]. Additionally, African American patients reported significantly higher emotional impact from their itch than their White counterparts [34]. Another study found pruritus was the most common skin concern among African Americans [35], despite being less likely to have a documented skin exam or dermatology visit [36]. Studies from Southeast Asia and Africa show a higher degree of lichenification in AD patients [37], and atopic prurigo or the prurigo phenotype of AD is more common in African Americans [38]—both physical signs of an increased itch burden. Examined together, these studies suggest potential disparities in itch burden among SOC populations, but additional research is needed.

5 Long-Term Course of AD

Though not often addressed clinically, the longitudinal course of AD fluctuates in severity and can range from transient to persistent [39]. In a systematic review and meta-analysis examining the persistence of childhood AD, the authors found that 80% of childhood disease did not persist by 8 years of age [40]. However, more persistent disease is associated with several extrinsic factors including non-White race, Hispanic ethnicity, urban environment, and low income [39, 40]. A prospective study using a pre-birth cohort found that Black and Hispanic children had the highest odds of persistent AD into mid-childhood [41], suggesting that additional investigations are needed for the systemic, environmental, and socioeconomic factors that may lead to these findings. Persistent AD is also associated with increased disease severity, odds of asthma and allergic sensitization with positive IgE testing, disease burden, and overall impaired health [40].

6 AD Quality of Life Burden

AD imposes an immense QOL burden on both patients and caregivers. Individuals with AD have impaired physical health, mental health, and life satisfaction [27]. Among SOC patients, Black and Hispanic children are 1.5-fold and 3-fold more likely to miss school, respectively, than their White counterparts [42]. The financial burden and health care utilization for non-White patients with AD appears to be greater as well. Black AD patients report higher out-of-pocket expenses for prescription medications, emergency room visits, and outpatient laboratory testing compared with non-Black AD patients [43]. In one population-based study examining health care utilization for AD among racial/ethnic groups, office visits were 2 times more frequent for African American/Black children and 7 times more frequent for Asian/Pacific Islander children than White children [44]. Despite this, the overall number of visits per capita was lower, suggesting that there is a lack of access and/or underdiagnosis in the primary care setting. This translates to greater rates of emergency department (ED) visits (which have increased over the last decade for AD) and hospitalizations for chronic disease management, resulting in an increased financial burden for patients and hospital systems [43, 45]. A study investigating primary AD hospitalizations found that Black patients were more likely to be hospitalized with AD and non-White races were associated with increased cost of care and prolonged length of inpatient stay [46]. Black AD patients are less likely to have insurance and

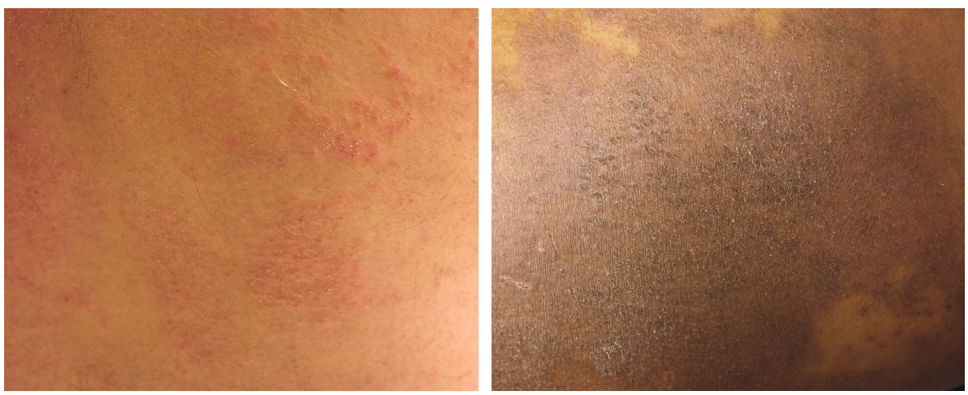

Fig. 1 Active atopic dermatitis with erythema presenting with redness (left) or violaceous and brown colors (right)

access to medical care, which increases financial burden, but even among insured non-Hispanic Black children with Medicaid, there are an increased number of prescriptions and greater out-of-pocket costs [43, 47]. While there are frequent anecdotal reports of 'treatment-resistant' AD in those with SOC, disease presentation is intertwined with structural and historical inequities leading to many of the associations noted above.

7 Morphology and Topography of AD

7.1 Diagnostic Criteria

Often, the 'classic' morphology of AD is described as erythematous, scaly papules and plaques involving flexural sites, while other cutaneous findings are considered to be 'atypical' [48, 49]. This 'classic' morphology of AD is based on historical observations in predominantly White, European populations, whereas the description of 'atypical' features is a subsequent effort to describe the diverse range of morphological presentations, of which many are more prevalent in SOC populations [49, 50].

Current existing formal diagnostic criteria, including those of the United Kingdom Working Party (UKWP) [51], ISAAC, and the American Academy of Dermatology (AAD) [52] are heavily grounded in the Hanifin and Rajka (H-R) criteria originally proposed in 1980 [48]. These criteria require at least three of four major features: (1) pruritus; (2) typical morphology and distribution (with flexural lichenification in adults and facial/extensor eruptions in infants and children); (3) chronic or relapsing dermatitis; and (4) personal or family history of atopy. The AAD guidelines for AD attempt to encompass the full age range of patients by expanding the definition to include flexural lesions in any age group. However, the AAD explicitly acknowledges that its diagnostic criteria have not been experimentally validated and are instead based on expert consensus. In contrast, the Japanese Dermatological Association's (JDA) definition of eczematous features explicitly outlines a predilection for adults to develop eczema on the face, neck, chest, back, and outside of the antecubital/popliteal fossae on the extremities [53].

The danger in normative classification is that it ignores a more realistic, heterogenous perspective of dermatitis location and morphology [54]. For example, a recent systematic review and meta-analysis of global AD studies showed that over half of AD patients had involvement of the extensor surfaces of the upper extremities and another quarter had involvement of the lower extremity extensors—locations that are more often associated with psoriasis rather than AD [37]. More than one third of AD patients had dermatitis of the head/neck, hands/feet, and scalp in the same study [37].

Though the guidelines from Japan are likewise not externally validated, multiple attempts at validation across systems have made clear that the most used diagnostic criteria inadequately embrace the full range of clinically evident AD, thus limiting their sensitivity, despite consistently exceeding 90% specificity. This is not to say that current diagnostic criteria have not been validated in certain populations. In North India, the H-R criteria had a 96% sensitivity, while the UKWP criteria had a sensitivity of 86% [55], and in Denmark an adaptation of the H-R criteria had a 90% sensitivity among children [56]. In another study among Romanian schoolchildren, a sensitivity of 74% was interpreted as 'good' for the H-R criteria, but this was in relation to the sensitivity of the children's parental report of eczema [57]. The UKWP criteria was determined to be valid with a high sensitivity and specificity across three hospitals in China—however, this was in comparison with the H-R criteria, which likely reinforces the fact that the UKWP criteria is derived from the H-R criteria [58].

Across several other studies, the sensitivity of these criteria has proven to be lower. When the UKWP criteria was applied to Japanese elementary schoolchildren, the sensitivity was 71.8% [59], and among nursing staff at a university hospital in Taiwan, the sensitivity of the UKWP criteria was only 42.2% [60]. Among children in China, a 'typical morphology and distribution' as defined by visible flexural eczema or eczema involving the face and extensor limbs only captured 69.9% of 1811 children. In contrast, 41.7% of the children presented with an 'atypical morphology and distribution', the most common of which included hand/foot dermatitis, pityriasis alba, and nail/paronychial eczema [61]. Beyond Asia, in a Xhosa-speaking African pediatric population, the sensitivity of the UKWP criteria was 43.7%. The investigators hypothesized that the performance of the criteria may have been lower than expected due to linguistic and cultural issues [62]; however, even among schoolchildren in Australia, a similar sensitivity of 42.8% was assessed by English-speaking dermatologists [63]. Though the Australian study did not report racial demographics, the authors did state that 96% of subjects were born in Australia in the predominantly White state of Victoria. As others have proposed, the distribution and morphology of AD in non-European White patients may differ around the world.

Chalmers et al. argued that new criteria for AD in different countries would "turn back the clock of atopic eczema research back 30 years…[and] hamper efforts at international standardization and comparison." [62]. Across the cited studies, the gold standard for diagnosis used was a clinical diagnosis by an experienced dermatologist. If individual clinicians can accurately diagnose AD, then it may be time to advance AD diagnosis and consider redefining 'typical' features of AD to reflect true morphologic and topographic variation.

7.2 Distribution

The distribution of AD appears to vary based on geographic location. Extensor lesions are more frequently reported in Indian, Iranian, and East Asian studies (Fig. 2) [37, 64–66]. A Turkish study described 49.5% of 321 patients with an 'atypical' presentation, the majority of which were infants or young children with flexural instead of the expected cheek or extremity involvement [67]. This contrasts with the 96.6% of children with 'typical' atopic dermatitis reported at an academic center in Bosnia and Herzegovina [68]. Other studies have demonstrated differences in lesional distribution based on race/ethnicity. One US study found that trunk involvement was more common in Black and Hispanic patients [69]. However, the methodologies of these studies vary widely both in patient selection and clinical definitions. For example, a study of 1008 Han Chinese individuals with AD in Shanghai described facial dermatitis in 86% of patients overall and 72.2% of adults specifically, while another Chinese study of 407 adult patients with AD across 15 provinces described a 'red face' in only 9.8% [70, 71].

7.3 Morphology

AD morphology varies considerably across diverse patient populations, and this may be a major contributor to delayed diagnosis or underdiagnosis across different SOC groups. Relevant lesional morphologies include perifollicular accentuation, lichenoid papules, nummular/psoriasiform plaques, and prurigo nodules (Fig. 3). Each of these morphologies has been historically underrecognized in the US.

Perifollicular accentuation, or dermatitis enhanced around the hair follicles, can be subtle in darker skin, though it is featured as a minor criterion in the H-R criteria for AD [17, 48]. While commonly found in all patients, it has been reported in up to 70% of patients with AD in Nigeria and India [65, 72]. In one Thai study, follicular lesions were more commonly found in association with intrinsic AD compared with extrinsic AD [66].

Lichenoid papules can often be present on the extensor surfaces [50]. They have been well described in SOC patients in the US and globally, including a study highlighting 54% of Nigerian patients with AD [65, 73]. A systematic review of AD characteristics by region similarly found an increased report of lichenoid papules in African studies [74]. Though lichenoid papules share features with the lesions of lichen planus, notable differences include lack of Koebnerization, Wickham's striae, and typically round shape in the lichenoid papules of AD [73].

Also found on the extensors and trunk, nummular and psoriasiform plaques can be obscured by hyperpigmentation [75]. Nummular lesions may present clinically as red, oozing, excoriated, and/or studded with pustules [50]. Studies from the US and Mexico show a prevalence of 15–17% for this morphology in patients with AD [73, 75]. Like follicular lesions, they are associated with intrinsic AD in Thai adults [66]. Psoriasiform

Fig. 2 Atopic dermatitis presenting on the extensor surfaces of the elbow (left) and knee (right)

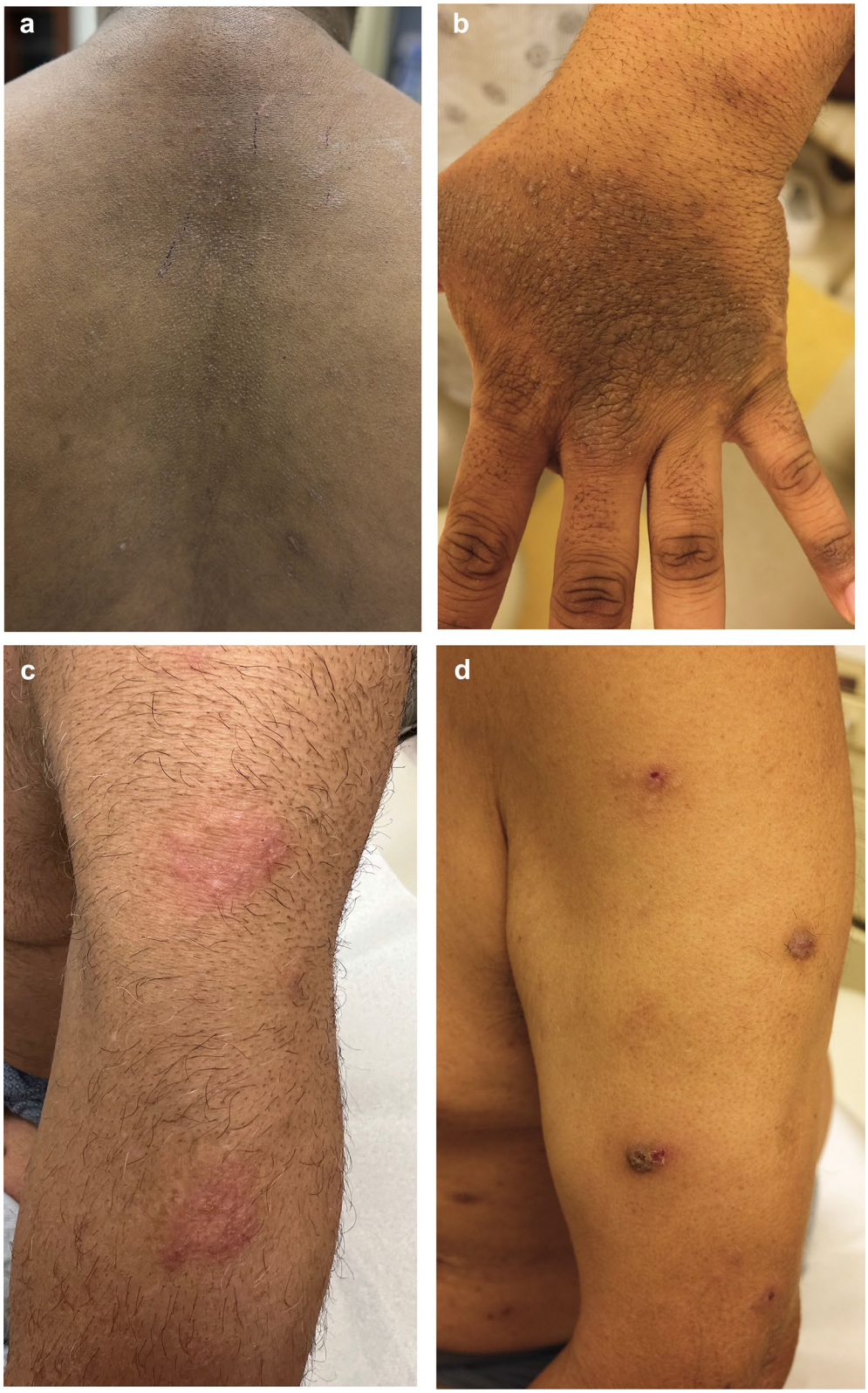

Fig. 3 Atopic dermatitis presenting with perifollicular accentuation (**a**), lichenoid papules (**b**), nummular/psoriasiform plaques (**c**), and prurigo nodules (**d**)

lesions may be identified by their clear demarcation, prominent scaling, and lichenification [76]. Of note, the psoriasiform/nummular phenotype of AD has been proposed to be more common in Asian patients, potentially relating to cutaneous immune skewing towards IL-17 driven pathways [76]. Given that the limited number of patients described in these studies spanned several broad ancestral regions (including Japan and Korea), genetic and/or other biologic factors underlying these findings should be carefully scrutinized and reproduced with further studies.

When prurigo nodules are the dominant type of lesion observed, AD may instead be termed atopic prurigo nodularis or prurigo phenotype [5, 77–81]. Prurigo nodules are hyperkeratotic, hyperpigmented, and often excoriated secondary to intense itch. They are a common lesion associated with AD and appear to particularly affect patients with late-onset or longstanding AD [5, 82]. While prurigo nodularis (PN) is itself recognized as a distinct chronic inflammatory skin disease consisting of prurigo nodules and unbearable itch, AD is a commonly associated condition and driver of disease pathogenesis. One study of PN patients showed that 46.3% had AD or an underlying atopic predisposition [80]. Studies from southeast Asia have reported a higher prevalence of prurigo nodules, and in the US, clinical observations have noted prurigo nodules to be more common in non-White AD patients [38, 83].

8 Genetics, Barrier Dysfunction, and Immune Dysregulation

8.1 Genetics

The genetic profile of AD in SOC populations has not been well defined. Previous attempts to elucidate genetic differences based on race and ethnicity using genome-wide association studies (GWAS) have not yielded genome-wide significance [84–86], again reflecting the concept of race as a social construct rather than proxy for biologic information. However, if true genetic differences exist between racial groups, it remains a challenge to prove given that non-White populations are vastly underrepresented in current databases [84]. About 80% of GWAS participants are of European ancestry, which contributes to lower accuracy and innate bias in predicting genetic risk for disease in SOC patients [84, 85]. It is increasingly imperative to amass a wider dataset that is representative of SOC patients (or more accurately, diverse genetic ancestry) to form any conclusions about risk factors. Such risk factors should then not be used as a homogenous marker for racial differences but rather to inform patients of risk based more specifically on genetic ancestry.

The Genetic Epidemiology Research on Adult Health and Aging (GERA) project was launched by Kaiser Permanente and includes more than 100,000 multi-ethnic subjects with high quality genotyping data, as well as longitudinal clinical information from health records to study different medical conditions [87]. Recent genome-wide genotyping studies using this database have been employed in the analysis of race-based differences in AD. One study of the GERA cohort and national Pediatric Eczema Elective Registry (PEER) cohort [86] found that when self-reporting race, African American subjects had significantly higher odds of AD diagnosis and poorer disease control. However, when analyzing genetic ancestry, there were no significant differences within African American patients and between groups. Further, the risk of AD was not associated with skin pigment [86]. From an evolutionary perspective, it is thought that darker pigment was selected for to protect against toxic UV irradiation. However, in mouse models, pigmented mice display a reduced propensity for inflammatory cutaneous disease after exposure to topical irritants, which is thought to be due to cutaneous pigment-associated pH reduction [88]. Given that Black individuals with darker skin pigment are reported to have a higher incidence of inflammatory skin conditions, this may be attributable to broad environmental factors, rather than innate susceptibility to disease [88].

The Filaggrin (*FLG*) gene has been widely cited as a key marker of genetic differences between groups of individuals with AD. *FLG* is located within the epidermal differentiation complex (EDC) and plays an important role in stratum corneum (SC) structure [89]. Filaggrin loss-of-function (LoF) mutations were shown to cause epidermal barrier dysfunction and are a risk factor for developing AD. The *FLG* gene was first studied in the context of ichthyosis vulgaris in the mid-1980s. Using skin biopsies, several studies observed reduced, absent, or misshapen keratohyalin granules, as well as a reduction in filaggrin expression and profilaggrin mRNA in patients with ichthyosis vulgaris [90–98]. The profilaggrin gene was partially sequenced in 1992, however given the large, repetitive nature of the *FLG* gene, LoF mutations were not identified until 2006 [93, 98]. Notably, the single-nucleotide polymorphisms (SNPs) used to develop primers for *FLG* sequencing were studied primarily in European populations [99]. Since this time, approximately 500 *FLG* LoF variants have now been identified and are reported in 25% to 30% of individuals of European and Asian ancestry with AD [90, 100–104]. *FLG* LoF mutations are also found in about 8% of the general European population, regardless of diagnosis with AD [12, 90, 105, 106]. Given the skewed focus of *FLG* mutations in European populations, it is postulated that identifying *FLG*

mutations may be difficult and inaccurate in populations with more diverse ancestry [90].

Using newer sequencing techniques, *FLG* LoF variants have been identified in AD patients of African descent, however their frequency was reported to be < 2% [12, 101]. A recent study using the PEER database identified *FLG* LoF mutations in 23.9% of the total population, with White children having 2.44 higher odds of carrying any *FLG* LoF mutation [12]. However, within this population, African American children had more persistent disease regardless of a *FLG* LoF mutation [12]. Thus, *FLG* mutations do not fully capture disease onset and severity.

Interestingly, Filaggrin 2 (*FLG2*) mutations have been reported in African American individuals with AD, but not in Europeans [100, 107]. *FLG2* encodes a protein closely related to filaggrin, though its function is not entirely clear. Future studies could seek to explore the role of *FLG2* in AD onset, persistence, and severity. However, genetic differences, such as those seen with *FLG* mutations, do not appear to broadly account for racial disparities in AD patients. Examining upstream environmental and structural factors is likely to be far more fruitful when trying to understand these disparities and their relationship to clinical presentation and outcomes. Once representative, diverse samples have been collected, GWAS may eventually be useful in counseling patients on their risk factors for AD in the context of their environment.

8.2 Barrier Dysfunction

The skin barrier has been studied in different racial and ethnic populations, particularly in relation to impact of stratum corneum (SC) lipid composition—though results have been conflicting [108–112]. Ceramide levels are directly correlated with water content of the SC and inversely correlated with transepidermal water loss (TEWL) [83, 113]. Early studies investigating racial differences in the SC suggested that Black individuals had a higher lipid content than White individuals; however, more recent data indicates that ceramide content may be lower in Black skin when compared with Hispanic, White, and Asian skin [83, 108, 113]. A US study of 341 healthy subjects reported lower ceramide content in African American skin, as opposed to Caucasian and Asian participants; however, TEWL was highest in Caucasian skin [83]. Another study of 71 healthy university students in Denmark showed no significant differences in the amount of ceramides between White, Asian, and African descendant participants. However, there was a lower relative ceramide-to-cholesterol ratio in individuals of African descent [108]. Pediatric studies have shown similar results using tape-stripping [74]. Future studies investigating cutaneous lipid composition should include a larger sample size with additional demographic data in order to understand other external factors that may have contributed to these findings.

TEWL is a commonly used biomarker for barrier integrity and thus AD severity and treatment response. However, studies conducted to examine TEWL differences in AD patients based on race have been inconclusive. Most of these studies had small sample sizes and differing methodology. Two earlier studies utilized skin biopsies and tape stripping and found higher TEWL in Black and Asian patients, respectively [113, 114]. Another studied TEWL at various depths of the SC after tape stripping and reported greater TEWL in Black subjects in the superficial SC, but not the deep SC [113, 115]. Induced skin irritation with applied sodium lauryl sulfate has also been shown to increase TEWL in Black patients more than White patients [25, 113]. However, many studies also reported no difference in TEWL between Black and White subjects [113, 115–121] and others reported a decreased TEWL in Black subjects [83, 113]. Overall, TEWL studies may have high levels of inter-rater variability and can be influenced by humidity levels, anatomic location, type of device used, and physiological factors. Additionally, many other uncontrolled variables may influence TEWL values. These include mask-wearing, dry-eye disease, chronic vascular diseases, age, stress, body mass index, bathing habits, a history of scratching, genetic factors, and nutritional status [122]. Based on these data, it may be difficult to extrapolate TEWL as an independent biomarker for disease activity across AD patients, and instead, differences should be analyzed in the context of other patient factors.

8.3 Immune Dysregulation

Differences in cutaneous immune skewing based on race have been described to explore potential differences in clinical presentation, severity, and treatment response. Type 2 inflammation consisting of type 2 T-helper cell (Th2) activation appears to be a consistent and central finding among AD patients of all races and ethnicities [76, 123]. In one study, Asian Americans with AD were shown to exhibit increased Th17/Th22 activation when compared with African American and European American AD patients [76, 124]. Real-time PCR and immunohistochemistry-based analysis of 27 Asian-American AD patients—12 with Japanese and 15 with Korean ancestry—showed higher Th17 and Th22 and lower Th1 cytokine signatures than the European American cohort, which is more consistent with the immune signature of psoriasis [76]. Interestingly, a study correlating these skin biopsies to the serum of 15 Asian AD patients did not find any correlation between lesional skin and nonlesional skin biopsies and serum Th1 and Th17 markers [125]. Th2 serum markers were increased in both European and Asian AD patients [125]. It is important to note that these studies

had fewer than 30 individuals in both the European and Asian American groups, with only two Asian ethnicities represented.

These findings have subsequently been used to support clinical observations of increased psoriasiform and nummular AD presentations among Asian individuals. However, these preliminary findings need to be reproduced and their relationship to meaningful clinical outcomes of AD are not yet evident. For example, another study utilizing lesional biopsies from Han Chinese patients with AD found an increase in psoriasis-like features when compared with European AD skin, including increased tissue Th17 cells, neutrophils, and parakeratosis [126]. However, in contrast to apparent phenotypic and histologic differences, Han Chinese and European American AD patients had similar levels of the Th2 marker CCL26 [126, 127]. In this study, CCL26 levels could be used to discriminate AD from psoriasis biopsies with 100% accuracy [126]. A phase II clinical trial of the IL-17 inhibitor secukinumab for the treatment of moderate-to-severe AD failed to show significant improvement in multiple measures of disease severity [128, 129].

When comparing the immune profile of African American versus European American AD patients with similar clinical severity, one study demonstrated reduced expression of Th1- and Th17-related markers in the African American group but similar Th2 skewing [130]. Dendritic cells exhibiting high-affinity IgE receptors were significantly increased in African American AD lesional skin, which was associated with higher serum IgE [130]. Eosinophil levels were similar in both groups. An important caveat to these findings is that this study only included 15 African American patients in a racial category that has numerous limitations for capturing biological differences as discussed earlier. However, racial differences in serum IgE have been reported in AD patients and have been linked to worsened disease severity, specifically in African American patients [131]. Elevated IgE in AD patients is thought to be a product of the impaired skin barrier leading to transcutaneous sensitization to allergens [17, 132]. One pediatric study in the Detroit metropolitan area found that Black children were at higher risk of having an allergic phenotype and being diagnosed with AD [133]. Several studies have shown that African American individuals with AD appear to have higher IgE levels than their Asian and European American counterparts [130, 131, 134–137].

Differences in immune phenotypes observed in AD and other allergic disorders may be related both to genetic predisposing factors as well as individual environmental exposures and consequences of socioeconomic status (SES). Children with uncontrolled asthma living in urban environments have more *Moraxella* infections and eosinophilic inflammation [138, 139]. Asthmatic children from low-income backgrounds show upregulation of Th17-related transcription factors [138, 140]. Water hardness showed direct correlation with AD prevalence in a study of 358 school-aged children [141]. Exposures to psychosocial stressors may also increase an individual's susceptibility to atopic disease through epigenetic changes [142]. This concept has been better studied in asthma. Specific epigenetic changes in the *ADCYAP1R1* gene were positively associated with an increased exposure to violence, as well as increased odds of developing asthma, in a study of > 500 children in Puerto Rico [143].

9 Environment and Socioeconomic Status

The sum of an individual's lifetime exposures is commonly referred to as the 'AD exposome,' which encompasses population-level exposures, specific geographic, social and physical exposures, and cellular level exposures such as the cutaneous and gut microbiota [144]. Individual exposures may play protective, harmful, or neutral roles in the development and persistence of AD. One proposed mechanism of their direct influence on genetics is via induction of epigenetic modification, which has been found in AD patients when compared with controls [144–149]. In the US specifically, race is a proxy for lower socioeconomic status (SES), poorer water and air quality, higher stress, and malnutrition, due to a history of structural racism. In other countries, there may be other historical and cultural factors that drive disparities in AD impacting individuals who are not part of a specific racial group but similarly subject to systemic discrimination.

SES is an important health determinant that is usually defined by one's income, education, or occupation [150]. In general, lower SES is associated with poorer health outcomes and the development of chronic disease, which disproportionately impacts racial/ethnic minorities. Studies analyzing the prevalence of AD through the lens of SES have shown mixed results. Higher SES in some studies correlates with increased AD prevalence in adults; however, this is not reflected by severity and persistence of AD, which is associated with lower SES [4, 41, 107, 150, 151]. This may be the result of overrepresentation of higher SES patients in studies given increased healthcare access, and thus rates of AD diagnosis, while lower SES patients have significant barriers to accessing medical care [152]. In a study assessing healthcare patterns among children with AD, investigators found that Medicaid-insured children were less likely to receive specialist care, had higher utilization of emergency and urgent care, and had a greater burden of asthma and non-atopic morbidities than their counterparts, underscoring the role of socioeconomic status in healthcare access [153]. Another similar study analyzing health care utilization for AD children found that independent of SES, insurance, atopic comorbidities, or baseline demographic features,

non-Hispanic Black children were less likely to see a dermatologist in the outpatient setting, and when they did, they required more visits and more prescriptions [154]. These results suggest that there are underlying structural issues co-existing with race that present barriers to care and must be further investigated. In a study of prevalence of atopy among Korean children, the authors attributed the correlation of higher SES with higher AD prevalence to home locations closer to major roads, which are more expensive [155]. There are also conflicting studies on SES and the risk for AD, likely due to the multivariate, complex nature of this variable [153, 156, 157]. A recent systematic review of 88 studies from several continents found inconsistent associations between SES and AD, though the analysis was limited by inclusion of > 75% pediatric studies [157]. Upstream factors relating to lower SES may include housing discrimination, reduced access to healthcare resources, exposure to pollution, and job insecurity [152]. These factors should be captured when studying disparities in AD prevalence and severity and may or may not track with race or ethnicity, depending on the specific population of interest.

Some of the socioeconomic factors associated with AD severity may be related to housing discrimination, namely 'redlining,' in the US [158]. This practice started in the 1930s and affected predominantly low-income and SOC communities by categorizing them as hazardous and as such, undesirable for investment. While redlining was made illegal under the Fair Housing Act of 1968, disinvestment from affected communities resulted in a sustained legacy of significant wealth inequities and health disparities [158, 159]. Housing discrimination historically led to worse healthcare access, providing another potential explanation for increased AD burden and poorer outcomes in SOC patients. Black children are less likely to see a dermatologist, however if they do indeed present for care, they are at least three times more likely to be diagnosed with AD [89, 152, 154, 160]. Black and Latinx children are more likely to be seen in the emergency room for AD than White children [154, 160]. Such disparities must be further unraveled to understand and specifically target underlying root causes, as these factors play a major role in an at-risk individual's disease course and progression.

Highways, factories, and toxic chemical sites were built near and around redlined neighborhoods, which may have contributed to worsening rates of both asthma and AD over time. One study evaluating redlined communities in California reported increased hazardous environmental exposures, specifically citing diesel exhaust particulate emissions which were almost twice as high when compared with non-redlined areas [25, 138, 161]. In another study of nine urban US cities, historically redlined neighborhoods were associated with a lack of health insurance and negative health outcomes including increased rates of asthma and cancer [158]. For AD patients with an already impaired skin barrier, exposure to such harmful toxins and irritants may exacerbate their disease and lead to the development of other type 2 inflammatory disorders.

Water quality is often reduced in low SES communities and communities of color due to disproportionate hazardous waste treatments, polluting industries, byproducts of municipal landfills, and incinerators [162]. Studies from the UK, Belgium, and Japan have shown higher prevalence of AD in young children in urban areas and those with exposure to hard water [141, 163, 164]. However, studies examining the impact of water with high mineral content (i.e., hard water) on AD have shown mixed results. It is hypothesized that soap and detergent use increases in hard water areas, which can exacerbate AD; however, water softeners have not been shown to strongly impact AD severity [165]. More detailed investigations into water quality and hardness are needed.

Geography may also play a role in AD prevalence and severity. Individuals in urban regions tend to have a higher prevalence of eczema [166, 167]. In one nationally representative study of children in the US, those who lived in Northeastern and Midwest states had more severe disease [1]. In the same study, severity of AD increased with older age, African American race and Hispanic ethnicity, lower household income, single-mother household, lower parental education level, low maternal general health, low parental emotional health, dilapidated housing, and garbage on the streets [1]. These risk factors have generally been consistently associated with increased AD severity [4]. AD prevalence varies greatly across and even within countries. The ISAAC showed that eczema prevalence varied significantly by geographic location; for 6- to 7-year-old children, prevalence ranged from 0.9% in India to 22.5% in Ecuador [167]. One notable caveat to these data is that several countries only had representation from coastal, wealthier clinical sites [167]. However, this variation was consistently seen elsewhere, such as in Africa, with wide variation by city and country from 4.7 to 23% [168]. Interestingly, a study of foreign-born children and their parents found that Black, Latinx, and White AD patients born outside the US appear much less likely to be diagnosed with AD [1, 2, 169]. However, this risk reduction was not sustained after living more than 10 years in the US, implying an increased environmental risk of AD in the US [169]. Given wide ranges of AD prevalence across different study designs, it is difficult to directly correlate race with development of AD.

Outdoor pollution may originate from natural or man-made sources and is a major environmental factor influencing AD. Sulfur dioxide, carbon monoxide, nitrogen dioxide, and particulate matter are all associated with presentation of AD [145, 170]. In a German study investigating the relationship between traffic-related air pollution exposure and AD,

nitrogen oxides and particulate matter were associated with eczema in women aged 55 years and older, an association than was even stronger once atopic patients (with history of hay fever and IgE > 100) were excluded [171–173]. A similar study in Australia analyzing 43-year-old men and women at baseline with a 10-year follow-up found that air pollutants were associated with increased odds of eczema in males only [174]. In France, a study of nearly 5000 children found that exposure to major urban pollutants, specifically those caused by vehicle traffic, were positively associated with an increased risk of developing AD [145, 175]. Another German study showed that proximity to main roads was associated with an increased risk of AD in the first 6 years of life [145, 176]. Two South Korean pediatric reports found associations between outdoor air pollutants and AD symptoms using symptom diaries, including one study of 41 children showing that pruritus severity was significantly associated with ambient particulate matter exposure [177, 178]. A US study incorporating data from the NSCH and the Environmental Protection Agency (EPA) found that several airborne pollutants were positively associated with an increased prevalence and severity of AD, whereas others showed negative associations, suggesting a more complex relationship between AD and climate [179]. Notably, the burden of these exposure types is not shared equally among the population. Racial and ethnic minorities are disproportionately exposed to high levels of air pollution, which must be considered when considering SOC differences in AD [180–182].

Psychological stress is not innately an environmental exposure, however it may serve as a proxy for one's physical environment and presents with a higher burden in lower SES communities [150, 183]. Prenatal maternal stress increases the risk of AD in children, specifically related to employment (high strain and job loss), as well as stressful life events such as a death or divorce [184–190]. Though the mechanism of prenatal maternal stress on AD development is unknown, it may yet be another contributor to the differences seen in the immune phenotype of Black patients with AD [145, 191]. Maternal stress has been shown to lead to an increased IgE in children who develop AD, which has been reported to be higher in African American patients [124, 145, 152]. Maternal and postpartum depression and anxiety increase the risk for childhood AD [192–194]. Parental stress may be higher in children with AD, which itself may be a risk factor for the development of AD in future children [195].

Low bone mineral density associated with malnutrition has shown an association with AD [196, 197]. Though malnutrition is multifactorial, it is more commonly seen in low-income communities due to lack of access to and affordability of healthy food options [198]. While several studies link low bone mineral density to overuse of corticosteroids, others have suggested Hispanic ethnicity and malnutrition play roles, due to low BMI and low albumin in tested subjects [196, 197]. Conversely, multiple studies have shown mixed effects of obesity on the development and severity of AD [199]. Overall, more robust research is needed on the topic of diet and nutrition, with an emphasis on disparities in food access and security, in order to more precisely measure its contribution to racial differences in AD.

10 Response to Therapy

Though recent studies have attempted to delineate genetic and immunologic phenotypes of AD by race, the few studies analyzing AD treatment response in SOC groups have generally shown similar outcomes. The relationship of race/ethnicity to therapeutic response is still largely unexplored. Although non-White groups are routinely included in clinical trials, their absolute number has not typically been powered enough to perform a meaningful subgroup analysis. This dearth of evidence across studies is an amalgamation of several factors, including unclear definitions of race and ethnicity, lack of attention to reporting this data, and lack of equitable inclusion of these patient groups.

The National Institutes of Health Revitalization Act of 1993 required the inclusion of women and minority groups as subjects of clinical research. It explicitly stated that "in the case of any clinical trial in which women or members of minority groups will be... included as subjects, the Director of NIH shall ensure that the trial is designed and carried out in a manner sufficient to provide for a valid analysis of whether the variables being studied in the trial affect women or minority groups, as the case may be, differently than other subjects in the trial." [200]. In 2012, Hirano et al. analyzed clinical trials in AD in the US between 2000 and 2009. Only 59.5% of studies reported race or ethnicity, without any association with funding source, year of publication, study design, treatment type, or patient age. Only a single study provided specific definitions of how race or ethnicity was classified [201]. From 2010 to 2015, Charrow et al. found that 52.2% of 23 exclusively US clinical trials reported race or ethnicity, and as of 2021, among pediatric trials alone, only 59.3% reported this type of demographic data [202]. These consistent findings are reflective of both structural inequities that have limited the inclusion of minority groups and a lack of direct attention to the issue.

Increasing awareness of these issues in the broader healthcare community appears to have reversed some inertia over the past several years. Promisingly, during 2015–2020, reporting of race/ethnicity increased to 73.7% of 38 clinical trials in AD exclusively conducted in the US, with 71.1% of the 38 including > 20% non-White subjects [203]. In 2014, the FDA constructed an action plan for expanding diversity and industry-sponsored clinical trials and shortly afterwards

increased transparency by publishing a 'drug trial snapshot' for each new drug demonstrating the sex, race, and age of patients studied. Leading journals are beginning to enforce reporting and use of race and ethnicity [204]. The Journal of the American Medical Association issued an editorial with explicit definitions of race and ethnicity with guidance and recommendations on the use of these terms and with specific examples [205]. More broadly, the Royal Society of Chemistry brought together 54 large publishing organizations in the "joint commitment for action on inclusion and diversity in publishing"—a collective that includes the major journals read and published by dermatologists. As of April 2022, the group has published a standardized set of questions to collect gender, race, and ethnicity information for patient self-reporting [206]. Only this type of active, concerted effort by clinicians, scientists, professional societies, publications, industry stakeholders, and federal regulators will allow for continued progress in diversity efforts.

Increasing diversity in dermatology clinical trials is challenging, in part due to mistrust stemming from a history of ethical abuses of racial/ethnic minorities as well as present socioeconomic factors [207]. In one notable example, Dr. Albert Kligman, a prolific dermatologic scholar of the 20th century, performed clinical trials on predominantly Black men in Holmesburg Prison in Philadelphia with industry and government support [208, 209]. Many of these inmates were intentionally exposed to toxins (e.g. dioxin) and pathogens (e.g., herpesvirus, staphylococcus). SOC patients may be understandably mistrusting when it comes to clinical trials or institutional experimentation. More generally, patients may not believe that clinicians are competent in the care of SOC patients due to negative past personal experience. Under- or uninsured patients (a higher proportion of which are of non-White race) may not have easy access to the medical centers or clinicians who recruit subjects for clinical trials due to geographic or economic restrictions. Researchers themselves may not have multilingual and multicultural resources readily available for SOC patients. Patient transportation to and from study sites at designated times throughout the week may not be compatible with subjects' work and childcare schedules.

The existing but limited published data for the efficacy of topical and systemic AD treatments suggest that there is not a significant difference in efficacy among racial or ethnic groups. Topical corticosteroids, the most common first-line AD therapy, have not been formally studied among most groups, presumably because of longstanding clinical experience demonstrating effectiveness across patients. Among other commonly used topical therapies, equivalent treatment efficacy and safety profiles have been demonstrated between White and non-White patients. These include a pooled analysis of tacrolimus in adults and children in Asia and subgroup analyses in the pivotal clinical trials for pimecrolimus cream in children, crisaborole ointment in children, and ruxolitinib cream in adults [210–215]. These types of data for advanced systemic AD therapies are sparse. NBUVB has shown improvement in a small study of children in Singapore and among darker skin types in the US, although with the latter requiring a higher dose [216–219]. Among nine exclusively US studies of systemic therapy encompassing phototherapy, cyclosporine, azathioprine, methotrexate, and mycophenolate mofetil, only two reported the presence of non-White race, and there was no difference between groups [220]. In the key phase III clinical trials SOLO1, SOLO2, and CHRONOS, dupilumab was shown to be similarly efficacious and safe across multiple races/ethnicities in 128 Black/African American patients (6.2% of 2058 pooled patients) and 250 Japanese patients [221, 222].

Despite the possibility of different clinical phenotypes of AD among different SOC groups, no published evidence has yet to convincingly demonstrate drastically reduced efficacy or lack of efficacy for available topical and systemic therapies. While further studies are needed, particularly regarding safety and tolerability, the equivalent treatment outcomes suggest similar underlying mechanisms of inflammation across patients of all skin tones.

11 Conclusion

Our current understanding of racial differences among AD patients is both lacking and at times, misleading. As a social construct and not a biologic attribute, race is often utilized as an imperfect proxy for one's genetic ancestry, and in medicine, genetic findings require appropriate social and historical contextualization for clinical relevance. Race and ethnicity as they are used do not adequately capture intra-group heterogeneity—'Hispanic' ethnicity and 'Black' race both represent a broad group of culturally distinct individuals. Language about race and ethnicity should be defined, standardized, and consistently reported in high impact publications, with additional attention paid to ensuring equitable inclusion of patient populations in pivotal clinical trials. As clinicians and scientists expand recognition of AD in populations across the globe, defining features of AD should be updated and better taught to capture the complete range of morphologic and topographic variation. SOC populations have been historically underrepresented in GWAS, and polygenic risk scores have achieved accuracy mainly in White patients of European descent. Epidermal and immunologic characterization of SOC groups is only in its infancy, and we are only beginning to understand the relevance of the AD exposome. Ultimately, the upstream factors that contribute to inequities in AD should receive renewed focus, even beyond racial categories, to characterize true differences in disease presentation, burden of disease, and response to therapy.

One of the ways in which we can begin to shift our understanding of AD is to make educational curricula more inclusive. Increased inclusion of representative dermatologic images and texts in the training of physicians, physician assistants, nurses, and other healthcare workers represents one important step forward. However, language regarding skin pigment, race or ethnicity, and SOC itself should also be standardized to avoid vague or misleading terminology that muddles social and biologic attributes [3]. Race itself does not put patients at risk for AD and race-based bias may be perpetuated by this misconception. Race must instead be considered in the context of socioeconomic, cultural, and historical factors that play a significant and potentially more prominent role in dictating disease onset and its management. This will be especially important as we progress toward a world of personalized medicine, where genetic risk factors may also be considered within this context for each patient.

Our language when describing dermatologic conditions in SOC should be intentional and informed. We should avoid pathologizing SOC by associating cutaneous findings with terminology such as 'atypical'. It is imperative that trainees have exposure to all clinical phenotypes of dermatologic disease to prepare them to treat patients competently, compassionately, and with respect. Medical school and residency training should incorporate lectures on structural discrimination, including the history of housing, wealth, and health inequities that disproportionately impact SOC populations [3]. This is equally important not only within dermatology but also in other specialties to prevent delays in diagnosis and referral.

In summary, we are now uniquely positioned to reshape and redefine our approach to understanding AD across shades of skin (Table 1). To gain a deeper understanding of the clinical diversity of AD, the next generation of research and clinical care must take additional steps beyond characterization of AD by broad demographic variables, and instead, investigate disease pathogenesis, progression, and treatment in the context of both diverse structural and environmental factors alongside traditional biologic features.

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