

Potential role of reduced environmental UV exposure as a driver of the current epidemic of atopic dermatitis

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The basis for the sudden and dramatic increase in atopic dermatitis (AD) and related atopic diseases in the second half of the 20th century is unclear. The hygiene hypothesis proposes that the transition from rural to urban living leads to reduced childhood exposure to pathogenic microorganisms. Hence instead of having the normal T_H1 bias and immune tolerance because of repeated exposure to pathogens, urban dwellers have T_H2 cell immune activity and atopic disease in a more sterile environment. Various other environmental exposures have been implicated in the explosion of AD (and atopic disorders in general), including breast-feeding, tobacco smoking, alcohol consumption, and exposure to domesticated furry pets. Notably, the key role of a compromised barrier of neonatal skin as a predisposing factor in the development of childhood AD has recently been demonstrated. In this article we review the salubrious effects of suberythemogenic doses of UVB irradiation for the skin barrier. We then discuss how the lack of sufficient UVB exposure could have contributed to the rapid increase in the incidence of AD in developed countries. This hypothesis offers a separate but not competing partial explanation, which should be viewed as not discounting the role of the etiopathogenic factors that also could influence the prevalence of atopic disorders. (J Allergy Clin Immunol 2015;■■■:■■■-■■■.)

Key words: Atopic dermatitis, filaggrin, irradiation, pathogenesis, phototherapy, skin, UV

Atopic dermatitis (AD) is a chronic relapsing inflammatory skin condition characterized clinically by pruritic and xerotic skin, with dermatitis typically accentuated in flexural anatomic sites. Because several genetic mutations are now associated with

Abbreviations used

AD: Atopic dermatitis
AMP: Antimicrobial peptides
TSLP: Thymic stromal lymphopoietin
VD3: Vitamin D₃

AD¹ and the phenotype can be heterogeneous, perhaps AD should best be applied as an umbrella term. Early-onset AD is caused primarily by skin barrier abnormalities commonly caused by filaggrin gene (*FLG*) mutations in Northern Europeans and Asians, which lead to downstream immunologic activation, including both the synthesis and secretion of specific IgE against absorbed allergens, again contributing to the barrier abnormalities.² Although AD is immunologically characterized by T_H2 predominance in the acute phase, additional pathogenic roles for T_H1 and T_H22 cells emerge in chronic disease.³

The basis for the sudden and dramatic increase in AD and related atopic diseases in the second half of the 20th century is unclear. Various exposures have been implicated in the etiopathogenesis of AD (and atopic disorders in general), including breast-feeding, tobacco smoking, alcohol consumption, and exposure to domesticated furry pets,⁴ but none of these account for the recent explosion of AD. Nonetheless, before focusing on our new hypothesis, some of these older hypotheses are worth examining here.

The hygiene hypothesis proposes that the transition from rural to urban living leads to reduced childhood exposure to pathogenic microorganisms.⁵ Hence instead of having a normal T_H1 bias and immune tolerance caused by repeated exposure to pathogens, urban dwellers have T_H2 cell immune activity and atopic disease in a more sterile environment. A crucial component of this hypothesis is the observation that first-born children are more prone to atopic disease in comparison with their younger siblings, presumably as a result of reduced spread of infections.

Another recently proposed hypothesis suggests that the natural T_H2 skewing that occurs during pregnancy and early life is accentuated by increased environmental exposure to chemical allergens and irritants from cosmetic products, providing a potential link to the subsequent development of AD and associated allergies.⁶ Here, the higher prevalence of AD in the first-born child is explained by greater T_H2 skewing during first compared with subsequent pregnancies.

Finally, a converse of the hygiene hypothesis links the primary abnormality in barrier function to the pathogenesis of AD. According to this view, genetically at-risk subjects living in increasingly crowded urban settings are continuously bombarded by proteolytic dust mites, which together with prolonged exposure to low relative humidity because of radiant indoor

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heating, more frequent bathing habits (often with high pH soaps), or both,⁷ further compromising the barrier, ultimately have T_H2 immune reactivity.

In this article we briefly review the role of the naturally compromised barrier of neonatal skin as an additional predisposing factor in the development of childhood AD and, conversely, the salutary effects of suberythemogenic doses of UVB irradiation for the skin barrier. We then discuss how the lack of sufficient UVB exposure could have contributed to the rapid increase in the incidence of AD in developed countries.⁸

SKIN BARRIER PHYSIOLOGY IS ABNORMAL IN NEONATES AND INFANTS

The transition from an aqueous *in utero* environment to the challenging arid conditions of postnatal life requires rapid adaptations at birth. Skin surface pH remains markedly increased during the first 2 postnatal weeks (approximately pH 6),⁹ paradoxically at a time when increasing levels of acidic natural moisturizing factor concentrations become available to acidify the stratum corneum pH.^{9,10} However, thereafter, pH slowly decreases, stabilizing at around 5.1 over subsequent weeks to months.^{9,10} The increased pH of neonatal skin has multiple negative consequences, including abnormal permeability barrier recovery after acute insults, suboptimal stratum corneum cohesion, a propensity for microbial pathogen colonization, and reduced inflammatory thresholds, largely because of activation of serine proteases (kallikreins).¹¹ Thus the high pH of neonatal skin stimulates kallikrein activity, which in turn activates the protease-activated receptor 2, thereby downregulating lamellar body secretion and activating thymic stromal lymphopoietin protein (TSLP) secretion from keratinocytes.¹² However, kallikreins also are locally destructive, degrading corneodesmosomes while promoting inflammation through activation of IL-1 α / β .^{13,14} The high stratum corneum pH can also negatively impair ceramide production through kallikrein-mediated degradation of ceramide-generating enzymes^{11,13} while at the same time favoring the growth of pathogenic microorganisms, such as *Staphylococcus aureus*.^{15,16}

Important adaptations take place during the first months of life that allow life in a dry environment. Although both the water content of the stratum corneum and the absorption and desorption of experimentally applied water remains increased in full-term neonates, concentrations of natural moisturizing factors are significantly reduced when compared with adult skin.¹⁷ Although further optimization of barrier homeostasis occurs thereafter, during this neonatal period of suboptimal skin barrier function, environmental exposures can indeed cause further problems. Thus exposure to alkaline soaps, frequent bathing, or chemicals likely provoke skin inflammation more readily in neonates, particularly when superimposed on their inherent skin barrier abnormality. Indeed, the hardness of bathing water significantly correlates with AD prevalence in infants,^{18,19} and increased epidermal water loss at day 2 after birth predicts the incidence of AD.²⁰

AD IS INVERSELY ASSOCIATED WITH GESTATIONAL AGE: POSSIBLE BENEFITS OF BLUE-LIGHT THERAPY OF NEONATES

A possible relationship between gestational age and AD was recently investigated in 2 independent French cohorts.²¹ The lowest prevalence of AD was observed in a group of extremely

preterm infants compared with those born at a later gestational age, and this effect appeared to be prolonged. This observation is consistent with previous studies that showed a similar inverse association of preterm birth with AD.^{22,23} Multiple mechanisms could explain this inverse association, including facilitated penetration of allergens across an immature skin barrier, leading to induction of immune tolerance and reduced diversity of the intestinal microflora and possibly affecting the development of tolerance; shorter periods of exposure to T_H2 cytokines during pregnancy, which could bias the immune system beneficially; or both.²¹ Although blue-light therapy, which is often administered to preterm infants to treat hyperbilirubinemia, appears to delay skin barrier recovery after tape stripping in mice,²⁴ this treatment could also, at least in theory, delay AD onset by means of unrelated immune suppressive mechanisms. For example, the prevalence of melanocytic and halo nevi correlates positively with blue-light exposure, suggesting that the levels of irradiation achieved with blue light are significant.^{25,26} Thus blue light emits low levels of UVA irradiation, which appear to induce melanocyte proliferation. Yet the wavelengths of blue light and UVA irradiation are adjacent, likely leading to an overlap of their biological effects. Therefore one might speculate that the observed inverse association between gestational age and AD²¹ could be explained, at least in part, by the use of blue-light therapy in preterms, which could prevent inflammation.

SUBERYTHEMOGENIC UVB IRRADIATION IMPROVES THE SKIN BARRIER AND REDUCES INFLAMMATION

Because of upper atmospheric filtering, UV irradiation on the Earth's surface is limited to UVA and UVB. Although UVB reaches epidermal keratinocytes and Langerhans cells, UVA extends deeper into the dermis, potentially affecting mast cells, T cells, and dermal dendritic cells.²⁷ Toxic doses of acute UVB cause inflammation, apoptosis, DNA damage, and reduced barrier function. Notably, not only DNA damage but also UVB-induced barrier disruption correlate linearly with the UVB dose.²⁸ Despite the negative effects of high-dose UV irradiation, low-dose narrow-band UVB and UVA phototherapy are commonly used in the treatment of AD. Such suberythemogenic doses are beneficial to the skin barrier, and accordingly, repeated suberythemogenic UVB doses are significantly more effective in reducing AD morbidity than UVB treatment regimens that deploy stepwise dose increases.²⁹ Hence low-dose UVB irradiation positively affects epidermal permeability barrier function³⁰ while also exerting beneficial immunomodulating activity through multiple pathways. For example, suberythemogenic UVB irradiation upregulates antimicrobial peptide (AMP) production and stimulates epidermal ceramide synthesis through upregulation of serine palmitoyl-CoA transferase, the rate-limiting enzyme for the synthesis of ceramides.^{30,31} To further support this notion, a recent study showed that hairless mice experienced no inflammation after short-term daily UVB irradiation, whereas single high-dose UVB irradiation resulted in secretion of proinflammatory cytokines and chemokines that, in turn, induced the recruitment of neutrophils and macrophages into the irradiated area.³² Suberythemogenic UVA and in particular UVB irradiation also upregulate the synthesis of other important stratum corneum lipids, including free fatty acids and cholesterol esters.³³ Repeated irradiation with UVA, UVB, or both also increases the mean

epidermal and stratum corneum thickness³⁴ and inhibits histamine release from mast cells.³⁵ Medium-dose UVA phototherapy decreases the amounts of soluble receptors for the cytokines IL-2 and IL-4 in the blood³⁶ and induces apoptosis of infiltrating T cells, suppresses cytokine production, and reduces Langerhans and mast cell densities.³⁷ In line with these observations, experimental studies show that both UVA and UVB irradiation, if administered before application of skin irritants, reduce inflammation.^{38–40} Finally, trans-urocanic acid absorbs UVB photons and isomerizes to cis-urocanic acid, which has immunosuppressive functions, including the stimulation of IL-10 by CD4⁺ T_H cells.⁴¹

One potential key molecular mechanism by which UV irradiation benefits the barrier is the likely activation of the cutaneous vitamin D system, which in turn stimulates filaggrin, involucrin, epidermal lipid synthetic enzymes, and epidermal ceramide production.^{30,31} Importantly, significant upregulation of filaggrin during chronic low-dose UVA and UVB irradiation has been observed in mice, with upregulation lasting 24 weeks after irradiation was discontinued.⁴² In a recent review article we discussed the crucial devastating effects of filaggrin deficiency on the risk of AD,² emphasizing the likely preventive effects of low-dose UV irradiation. Taken together, suberythemogenic UVB irradiation improves skin barrier function and prevents inflammation.

UVB IRRADIATION IMPROVES HOST ANTIMICROBIAL DEFENSE AND REDUCES *S AUREUS* COLONIZATION

The involved skin of patients with AD is almost always colonized by *S aureus*. In fact, 90% of AD skin lesions are colonized, with a linear correlation between *S aureus* density and AD severity.⁴³ In addition, human-pathogenic *S aureus* expresses and secretes superantigens, including α -toxin, peptidoglycan, and lipoteichoic acid, all of which are implicated in the pathogenesis of AD.^{44,45} Superantigens in turn activate T cells and induce IL-31 secretion, leading to secondary pruritus and filaggrin deficiency.⁴⁶ Moreover, α -toxin preferentially targets and destroys filaggrin-deficient keratinocytes, whereas normal filaggrin levels increase sphingomyelinase secretion, thereby reducing the number of α -toxin binding sites and the risk of colonization.⁴⁷ Furthermore, superantigens stimulate the formation of IgE antibodies, levels of which correlate with AD disease severity.⁴⁸ Phototherapy appears to have independent antimicrobial effects on *S aureus* growth, with a significant reduction in numbers after low-dose UVB therapy of adults and children with AD but also with inhibition of *S aureus* proliferation *in vitro*.^{49–51} Likewise, when *S aureus* was isolated from patients with AD and irradiated *in vitro* with UVB, the production of superantigens decreased in a UV dose-dependent manner.⁵² The basis for the salutary antimicrobial activity of UVB could be attributed at least in part to the UVB-induced stimulation of cathelicidin AMP expression.³⁰ Finally, in this regard it is worth noting that cathelicidin AMP is required not only for antimicrobial defense but also for normal permeability barrier function: improving one helps the other.⁵³

UV IRRADIATION CAN REDUCE PRURITUS

Itch, which is defined as an unpleasant sensation that elicits an urge to scratch, is a hallmark of AD. Although the morphology of

subepidermal and intraepidermal free nerve endings in skin from patients with AD is similar to that found in control subjects, the distribution, density, and diameter of these fibers are greater in AD skin than in healthy skin.⁵⁴ Normally, itch sensation is initiated by the activation of peripheral nonmyelinated C-fiber nerve endings in the epidermis and dermis that trigger a cortical scratching reflex. Notably, selected cytokines released from immune cells are capable of triggering pruritus and the release of neuropeptides from sensory nerves.⁵⁵ One pertinent cytokine involved in itch pathogenesis is IL-31, which is released by T_H2 cells⁵⁶ and upregulated in AD skin lesions⁵⁷ and associated with increased IL-4 and IL-13 levels.⁵⁸ When heterodimeric IL-31 receptors are activated on keratinocytes, further recruitment of inflammatory cells takes place, thereby exacerbating AD. Moreover, PAR-2 expression in terminal C-nerve fibers in the skin, as well as on keratinocytes, is increased in patients with AD.⁵⁹ Thus kallikrein activation after skin barrier insults potentially results in itch sensation. Yet it is unknown whether suberythemogenic UV irradiation also reduces skin pH, thereby inhibiting PAR-2 expression as well.⁶⁰ Moreover, keratinocyte-derived TSLP can directly activate sensory neurons to evoke pruritus sensation,⁶¹ thereby linking TSLP secretion to the vicious inflammation-itch-skin barrier impairment cycle.

The effect of UV exposure on cutaneous nerves and itch sensation has scarcely been investigated. Although single high-dose UVA irradiation leads to a degeneration of nonmyelinated Schwann and perineural cells in the papillary and reticular dermis,⁶² repeated UVB (as well as psoralen plus UVA) phototherapy significantly reduces the density of protein gene product 9.5-positive nerve fibers in the epidermis and calcitonin gene-related peptide-positive nerve fibers in the dermis.⁶³ Also, acetone-induced stimulation of cutaneous nerve growth decreases significantly after phototherapy, with reduced epidermal expression of nerve growth factor and increased expression of the nerve repulsion factor semaphorin 3A.⁶⁴ Finally, serum IL-31 concentrations and itch sensation decrease in patients with psoriasis treated with UVB phototherapy.⁶⁵ In patients with AD, multiple studies have shown a significant reduction of pruritus after UV irradiation, perhaps with the best effect after narrow-band UVB exposure.⁶⁶ Collectively, these data suggest that UV irradiation reduces itch, potentially interdicting the vicious itch-scratch cycle that occurs in patients with AD.

INCREASED SUN-INDUCED VITAMIN D PRODUCTION COULD REDUCE THE PREVALENCE OF AD

A mistaken but often repeated assumption is that the beneficial effects of UV exposure are largely mediated by vitamin D. If that were the case, oral vitamin D supplementation should be able to replace UV exposure, but such supplementation is not known to affect disease prevalence or severity. As noted above, however, UV exerts protean effects on the skin that involve many pathways independent of vitamin D. Thus it is highly unlikely that vitamin D supplementation alone can fully reproduce the beneficial effects of UVB on AD. Nonetheless, several studies have shown an inverse association between AD severity and serum vitamin D₃ (VD3) levels,^{67,68} and low maternal fish consumption and reduced VD3 intake during pregnancy have been correlated with an increased incidence of AD in offspring.^{69,70} Recent trials have even shown that VD3 supplementation significantly improves

clinical symptoms in patients with AD,^{71,72} particularly in those with winter-related AD.⁷³

It is generally accepted that UVB exposure of the skin generates the majority of circulating VD3 as 7-dehydrocholesterol first is photoconverted to pre-VD3 and then thermally converted to VD3 in the epidermis. Pertinently, filaggrin deficiency allows more UVB to penetrate because of a decrease in levels of its downstream metabolite, trans-urocanic acid, the principal UVB filter in the skin, which should allow increased VD3 synthesis.⁷⁴ The biologically active hormone $1\alpha,25$ -dihydroxy-vitamin D_3 formed in the kidneys enhances epidermal differentiation, but importantly, it also enables keratinocytes to recognize and respond to pathogenic microorganisms through regulation of expression of cathelicidin LL-37 and Toll-like receptor 2.^{75,76} Although oral VD3 supplementation reportedly upregulates LL-37 production in lesional AD skin after 21 days,⁷⁷ a follow-up multicenter study did not confirm this finding.⁷⁸ Yet topical treatment of mouse skin with $1\alpha,25$ (OH) $_2D_3$ disrupts the epidermal permeability barrier and strongly induces expression of the pro- T_H2 cytokine TSLP in keratinocytes.⁷⁹ Moreover, undeveloped T cells mature into T_H2 cells when exposed to $1\alpha,25$ -dihydroxy-vitamin D_3 .⁷⁹ Nonetheless, the preponderance of data suggests that periodic UVB irradiation, likely in part through increased cutaneous synthesis of VD3, could improve AD, although the responsible mechanisms still remain unclear.

AD PREVALENCE AND SEVERITY IS LATITUDE AND BIRTH SEASON DEPENDENT

The detrimental effects of a desiccating climate on the skin barrier are well known. Because of a steepening of the water gradient, the skin surface becomes xerotic with exposure to low humidity, and the water content of corneocytes also decreases with a decrease in temperature.^{80,81} These observations translate into clinical and epidemiologic observations, including a higher incidence of AD among children born during the fall.⁸²⁻⁸⁵ Moreover, there appears to be a latitude-dependent increase in the prevalence of AD with greater distance from the equator. An Australian latitudinal study showed that 4- to 5-year-old and 8- to 9-year-old children furthest from the equator were more likely to have AD in comparison with age-matched children residing closer to the equator. A Spanish study showed an inverse association between AD and the number of hours of sun exposure,⁸⁶ and a recent United States-based study found that higher levels of UV exposure were associated with a lower prevalence of AD.⁸⁷ Importantly, cumulative UV irradiation during the 3 months before and after birth was inversely correlated with AD prevalence in a cohort of infants with AD,⁸⁵ and another Australian study showed that the amount of both summer and winter sun exposure correlates inversely with AD in a dose-dependent manner.⁸⁸ Even in 1-month-olds, a positive but inverse association seemed to be operative, although the correlation did not achieve statistical significance. Although it is difficult to exclude parallel changes in humidity as a possible confounding variable, these correlative data nonetheless support our hypothesis that a paucity of low levels of UVB exposure are an independent determinant of AD prevalence. Finally, the possible effect of melatonin, a hormone primarily secreted by the pineal gland during hours of darkness and that displays immunosuppressive effects, on AD is unclear. Melatonin applied on the skin in an experimental AD mouse model significantly reduced the severity of

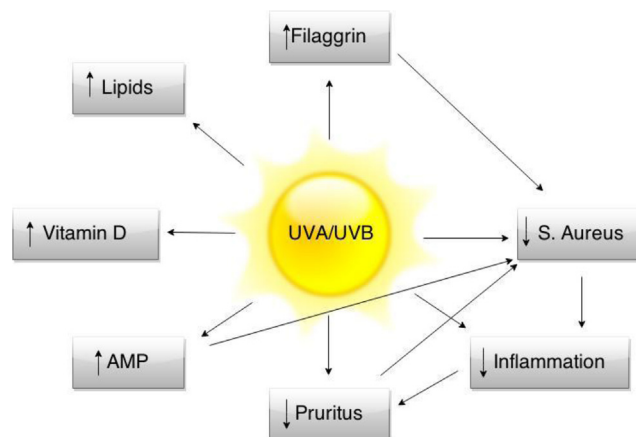


FIG 1. Positive cutaneous effects of suberythemogenic UV irradiation.

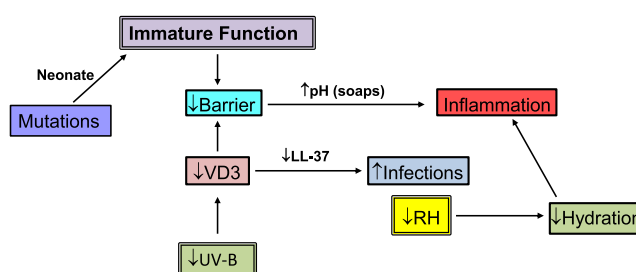


FIG 2. Factors that favor development of AD in neonates. RH, Relative humidity.

dermatitis lesions, possibly by decreasing the production of IL-4 and IFN- γ in activated $CD4^+$ T cells.⁸⁹ Also, serum melatonin levels appeared to be lower in patients with severe AD when compared with those in control subjects.⁹⁰ Reduced melatonin levels in patients with AD from seasonal sleep deprivation in summer days during which the sun sets late in the day could at least in theory influence the above observations.

DECREASED EXPOSURE TO SOLAR RADIATION COULD EXPLAIN INCREASED PREVALENCE OF AD IN URBAN CHILDREN

AD is generally more common in urban than rural children.⁹¹ In fact, a recent study showed a linear decrease in AD from the center to rural areas in Shanghai.⁹² Several critical exposures increase AD in an urban setting, such as house dust mite and cockroach antigen exposure, as well as forced indoor heating and excessive cleaning.⁷ However, the observation can also be explained in part by a reduced exposure to UV irradiation in children living in the urban settings because of less time spent outdoors and prevention of UV penetration by smog and surrounding structures that reduce sun exposure even when outdoors. Indeed, farm children who have unrestricted outdoor access and assist their parents who work outdoors receive substantial UV exposure.⁹³ In a recent study rural Danish boys received more UV exposure on their school or day care days than women who work indoors.⁹⁴ In Japan rural elementary school children receive more UV exposure than children living in cities.⁹⁵ Moreover, circulating 25-OH-VD3 concentrations are significantly higher in rural than urban

TABLE I. Key observations that support a protective role of low-dose UV irradiation on the incidence of AD

- Low-dose UV irradiation has positive immunomodulating activity, including induction of apoptosis in infiltrating T cells, suppression of cytokine synthesis, and reduction of Langerhans and mast cell densities.³⁷
- UV exposure stimulates cathelicidin AMP expression, as well as filaggrin, involucrin, and epidermal lipid synthesis, in part through increased cutaneous vitamin D production.^{30,31}
- UV irradiation reduces *S aureus* growth *in vivo* and *in vitro*.^{49,50}
- UV irradiation decreases production of superantigens in a dose-dependent manner.⁵²
- UV irradiation significantly reduces the density of dermal and epidermal nerve fibers.⁶³
- 1 α ,25-Dihydroxy-vitamin D₃ derived from UV exposure improves epidermal differentiation and enables keratinocytes to recognize and respond to pathogenic microorganisms through regulation of AMP as well as Toll-like receptor 2 expression.^{75,76}
- An inverse association between the prevalence of AD and the number of sunny hours of exposure⁸⁶ and higher UV levels was associated with a lower prevalence of AD.⁸⁷ Cumulative UV irradiation during the 3 months before and after birth is inversely correlated with AD in infants.⁸⁵
- The more common occurrence of AD in urban versus rural children can be explained in part by greater exposure to UV irradiation in rural-dwelling children.⁹¹
- Children with AD have significantly fewer nevi when compared with nonatopic children, even after stratification for pigment differences.^{105,106}

residents⁹⁶⁻⁹⁸; a finding that could be explained in part by behavioral (or cultural) differences and possible variations in levels of stratospheric ozone, which efficiently absorbs solar UVB irradiation. Children living in the country also are often members of significantly larger families than children living in cities (2.8 vs 2.1 in a United States–based study of high school students, <http://www.dst.dk/pukora/epub/upload/13788/bornfam.pdf>),⁹⁹ and an increased number of siblings likely results in more outdoor activities. Finally, reduced compliance with UV protection recommendations could also pertain to children living in the country, further increasing overall UV exposure.¹⁰⁰

ANXIETY ABOUT SKIN CANCER COULD REDUCE EXPOSURE TO SOLAR RADIATION

Because of the dramatic increase in the prevalence of skin malignancies, there appears to be a broad UV scare in the general population. This concern has led to strong recommendations to reduce UV exposure drastically because it is considered a health hazard.¹⁰¹ Interestingly, women and persons with higher educational levels and income are more likely to use sunscreen,^{102,103} and children's risk behavior seems to relate to the extent of their mothers' sun exposure and protective behavior.⁹³ Yet the risk of AD increases in these same populations of affluent children with parents who also have a higher education.¹⁰⁴ Pertinently, children with AD have significantly fewer nevi when compared with nonatopic children, even after stratification by skin pigmentation and hair color.^{105,106} Although we acknowledge that excessive sun exposure is mutagenic, resulting not only in premature skin aging but also an increased risk of nonmelanoma skin cancer, low doses of UV irradiation improve the skin barrier and antimicrobial defense through several independent pathways, as discussed. Likely, UV exposure also displays other positive effects on human health, which have not yet been fully elucidated¹⁰⁷; for example, UV exposure seems to influence mortality rates in an inverse and dose-dependent manner.¹⁰⁸

In summary, in this article we have raised the possibility that a reduction of exposure to UV light in the last 50 years has contributed to the current AD epidemic (Figs 1 and 2). The most pertinent observations are listed in Table I.* This hypothesis

offers a separate but not competing partial explanation, which should be viewed as not discounting the role of the etiopathogenic factors that also could influence the prevalence of atopic disorders.

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