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The impact of airborne pollution on atopic dermatitis: a literature review*

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Summary

The increasing prevalence of atopic dermatitis (AD) parallels a global rise in industrialization and urban living over recent decades. This shift in lifestyle is accompanied by greater cutaneous exposure to environmental pollutants during the course of daily activities. The objectives of this review are to highlight the effects of airborne pollution on epidermal barrier function, examine evidence on the relationship between pollutants and AD, synthesize a proposed mechanism for pollution-induced exacerbation of AD, and identify potential methods for the reduction and prevention of pollutant-induced skin damage. The literature review was done by searching the PubMed, Embase and Google Scholar databases. Inclusion criteria were *in vitro* and animal studies, clinical trials and case series. Non-English-language publications, review articles and case reports were excluded. Pollutants induce cutaneous oxidative stress and have been shown to damage skin barrier integrity by altering transepidermal water loss, inflammatory signalling, stratum corneum pH and the skin microbiome. AD represents a state of inherent barrier dysfunction, and both long- and short-term pollutant exposure have been linked to exacerbation of AD symptoms and increased AD rates in population studies. Airborne pollutants have a detrimental effect on skin barrier integrity and AD symptoms, and appear to pose a multifaceted threat in AD through several parallel mechanisms, including oxidative damage, barrier dysfunction, immune stimulation and propagation of the itch–scratch cycle. Future research is needed to elucidate specific mechanisms of pollution-induced epidermal barrier dysfunction and to identify efficacious methods of skin barrier repair and protection against pollutant-driven damage.

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While the number of children with atopic dermatitis (AD) continues to increase globally, developed countries such as New Zealand and the U.K., which previously reported high rates of AD, have experienced a plateau at around 10–15%.[1,2] However, the prevalence of AD is growing in developing nations, with rates higher than 15% and up to 24·6% reported in countries of Southeast Asia, Africa and Latin America.[1,2] For example, during its rapid industrial growth over the last two decades, China has experienced a dramatic rise in the prevalence of childhood AD, reported to be 2·8% in 1995 vs. 15·8% in 2012.[3,4] The rising prevalence of AD coincides with increased urbanization and industrialization worldwide, and investigation of the role of airborne pollution in the pathogenesis of AD and barrier dysfunction has become increasingly relevant. Environmental pollutants impart a significant and widespread disease burden, with 3 million deaths annually worldwide attributable to outdoor air pollution, according to the World Health Organization.[5] Developing nations in Asia, Africa and the Middle East experience elevated levels of airborne pollution compared with other parts of the world, further underscoring the global impact and urgency of this issue.[5]

AD represents a chronic cycle of intrinsic barrier disruption and entry of extrinsic pathogens and immunogens.[6] *Staphylococcus aureus* colonization is a prominent component of AD pathogenesis, as skin microbial dysbiosis and digestion of the epidermal barrier by *S. aureus* protease contribute to impaired barrier function. Skin barrier dysfunction manifests as increased transepidermal water loss (TEWL), decreased stratum corneum hydration and increased stratum corneum pH.[7] Barrier disruption facilitates the entry of environmental irritants,

allergens and pathogens, inducing an inflammatory response.[7–9] Resulting pruritus and excoriation further damage the barrier to fuel a vicious itch–scratch cycle.[7,10] Airborne pollution is of significant concern in patients with AD, as existing deficits in skin barrier function and oxidative defence and repair result in increased permeability to pollutants and an exaggerated inflammatory response. The goal of this review was to explore the impact of airborne pollutants on skin barrier integrity, to examine the relationship between urbanization and AD, to analyse the mechanistic roles of pollutants in AD and to discuss potential strategies to combat pollution-induced exacerbation of barrier dysfunction.

Types of pollution

Major constituents of airborne pollution include particulate matter (PM), volatile organic compounds (VOCs), traffic-related air pollution (TRAP) and cigarette smoke. PM describes liquid or solid particles in gas suspension and is classified by aerodynamic diameter.[11,12] Fine PM ($PM_{2·5}$; $\leq$ 2·5μm in diameter) is generated from open fires, power plants and car exhaust. Coarse PM (PM_{10}, 2·5-10μm) originates from soil, dust, pollen and industrial emissions.[11,12] VOCs are carbon-based substances that readily vaporize at ambient air pressure and contribute to indoor air pollution, and are primarily organic solvents such as benzene, toluene, xylene and formaldehyde.[13] TRAP includes PM, VOCs and gaseous components such as nitrogen oxides (NO, NO_2, N_2O), sulfur dioxide (SO_2), carbon monoxide (CO) and ozone (O_3) generated from gasoline and diesel-powered engines.[11] Cigarette smoke from burning tobacco contains antigenic and carcinogenic compounds such as nicotine, polycyclic aromatic hydrocarbons and metal residues.[14]

Methods

In November 2018, two research personnel conducted a literature review using the PubMed, Embase and Google Scholar databases. Search terms included combinations of "pollution", "particulate matter", "traffic-related air pollution", "volatile organic compounds", "cigarette smoke", "atopic dermatitis" and "skin barrier". Inclusion criteria were *in vitro* and animal studies, clinical trials and case series. Non-English-language publications, review articles and case reports were excluded. Following these inclusion and exclusion criteria, a total of 21 publications were selected for evaluation in this review.[7–10,13,15–30]

Results

Particulate matter

PM has been demonstrated to induce skin barrier dysfunction *in vivo*. In pig models, dorsal skin treated with solubilized PM exhibited a twofold increase in TEWL vs. vehicle control.[15] Histologically, PM treatment resulted in loss of stratum corneum structural proteins, including cytokeratin and filaggrin, as well as decreased E-cadherin, a component of epidermal tight junctions.[15] PM stimulates keratinocyte production of matrix metalloproteinases and the inflammatory cytokines tumour necrosis factor (TNF)-α, interleukin (IL)-1α, IL-1β and IL-8,[16,17] and has also been shown to have dose- and time-dependent cytotoxic effects on cultured keratinocytes.[8,16] PM drives cutaneous inflammation through activation of nuclear factor kappa B (NFκB) signalling and increased expression of IL-1α.[8] NFκB activation has been implicated in the pathogenesis of AD through augmentation of the inflammatory response, and NFκB decoys have been evaluated as potential therapeutic approaches for decreasing chronic skin inflammation in AD.[31]

PM can penetrate barrier-disrupted skin and incite an inflammatory response in mice.[16] Jin *et al.* evaluated intact and tape-stripped dorsal skin to compare the effects and localization of PM. PM was identified not only in the hair follicles of both intact and tape-stripped skin, but was also present intercellularly in samples of barrier-disrupted epidermis. Furthermore, repeated topical application of PM with subsequent occlusive dressing led to neutrophil-predominant dermal inflammation in both intact and barrier-disrupted mouse skin.[16] Han *et al.* used a rat model of capsaicin-induced AD to study the effects of vaporized glyoxal, a major source of PM production. Exposure to 40% glyoxal vapour for 2 h daily over 5 weeks led to increased pruritus and dermatitis in rats with existing AD but did not induce AD symptoms in healthy animals,[9] indicating that intrinsic barrier disruption is required for PM to exacerbate AD. Increased skin *S. aureus* colonization was observed in both AD and healthy animals after glyoxal exposure.[9] *Staphylococcus aureus* is more prevalent on AD skin than on healthy skin, and colonization is a major driving factor in the disease cycle. These studies demonstrate the detrimental effects of PM in both healthy and AD skin, and suggest an increased susceptibility to PM-induced damage in the barrier-disrupted state of AD.

Following alarming correlations between PM and AD in rodent models, a study of 21 Korean paediatric patients with AD living in an urban area over two 6-month periods found a positive correlation between PM exposure and exacerbation of AD, with temporal association between elevated PM levels and increase in reported AD symptoms.[18] $PM_{2·5}$ levels had a stronger positive correlation with AD symptoms than PM_{10}, with respective odds ratios (ORs) of 1·399 and 1·215 per 10 $\mu g/m^3$ increase in PM exposure.[18] A population-based cross-sectional study of > 5000 Taiwanese adults identified a modest association between frequent $PM_{2·5}$ exposure and development of AD [adjusted OR (aOR) 1·05].[19] Based on these findings, it appears that fine PM may be most detrimental, as it is capable of penetrating the epidermal barrier of tape-stripped skin,[16] and may inflict greater damage with high PM concentrations or prolonged exposure time.

Traffic-related air pollution

TRAP includes PM, as well as the gaseous pollutants NO_2, SO_2 and O_3. Silverberg *et al.* evaluated the association between

climatic and environmental factors and childhood AD using data from the 2007 National Survey of Children's Health. Children exposed to the highest quartile of stratospheric O_3 levels demonstrated higher rates of AD (aOR 1·28; $P < 0·001$) than the lowest quartile of O_3 exposure.[30] He *et al.* found that exposure of human skin to 0·8 ppm O_3 for 2 h led to a nearly 50% reduction in colony-forming units of resident microflora vs. air exposure alone.[20] This effect is of particular interest in relation to dysbiosis in AD, where alteration of resident skin flora and predisposition to *S. aureus* colonization are widely observed, although a direct link between TRAP exposure and *S. aureus* colonization has not been established.

TRAP exposure is of heightened relevance as cities become increasingly urbanized. In an effort to evaluate the health effects of this trend, the Study on the Influence of Air pollution, Lung function, Inflammation and Aging was initiated in 1985, and has followed a cohort of healthy German women over the age of 55 years living in urban and rural areas.[21] Longitudinal follow-up during the period 2008–09 included 834 women and identified a 7·9% incidence of AD symptoms after 55 years of age. A significant positive association was reported between incidence of AD symptoms and exposure to TRAP, with TRAP exposure determined by measuring levels of PM and nitrogen oxides in 2008–09 and back-extrapolation to baseline levels.[21] Furthermore, a subset of the women who carry a minor allele single nucleotide polymorphism in the aryl hydrocarbon receptor (AhR) gene were coincidentally more likely to develop TRAP-induced AD symptoms than those homozygous for the AhR major allele.[21] These findings suggest involvement of AhR signalling in development of TRAP-induced eczematous symptoms.

During the prenatal and infancy periods, TRAP exposure increases the risk of AD. A prospective cohort of Japanese mother–child pairs was followed from pregnancy to an infant age of 16–24 months and assessed for development of asthma and AD. After controlling for parental atopic history, the risk for development of allergic disorders was assessed in relation to proximity of the child's residence to the nearest main road.[22] Within this cohort of 756 children, 8·9% developed physician-diagnosed AD by 16–24 months of age. Compared with children living > 200 m from the nearest main road, those living within 50 m had a significantly higher risk of physician-diagnosed AD (aOR 2·26; $P = 0·03$).[22] These results align with findings in studies of perinatal TRAP exposure in China. Lu *et al.* identified an increased risk of AD in preschool children whose mothers experienced high levels of NO_2 exposure in the 3 months prior to conception (OR 1·19) and throughout pregnancy (OR 1·21; $P < 0·05$).[23] A similar investigation of TRAP exposure in Shanghai identified a significant association between elevated gestational and lifetime NO_2 exposure and childhood AD (aORs 1·80 and 2·00, respectively), indicating a possible epigenetic influence of airborne pollutant exposure in AD development.[24]

These findings indicate a role of TRAP (specifically NO_2) in the childhood development of AD and suggest a possible contribution to the rising prevalence of AD in industrialized and developing countries over recent decades. Direct effects of TRAP on the skin barrier have not been investigated.

Volatile organic compounds

VOCs comprise carbon-based molecules such as benzene, toluene and formaldehyde, which are released from common household materials, including cleaning supplies, wallpaper, new furniture, plastics and plywood.[13] VOCs are important contributors to indoor air pollution and have been demonstrated to induce skin barrier dysfunction. Huss-Marp *et al.* evaluated 12 patients with AD and 12 healthy participants exposed to dust mite allergen and subsequently to a mixture of 22 VOCs at 5 mg m^{-3} for 4 h in a total body chamber. Compared with a purified air control, a mean 34% increase in TEWL was observed at 48 h post-VOC exposure in both healthy participants and those with AD, without significant difference between the two groups.[25] Furthermore, six of seven patients with AD patch tested with house-dust mite allergen exhibited an enhanced skin reaction after VOC exposure, demonstrating that VOCs can exacerbate the atopic response to allergens.[25] Kim *et al.* found that exposure to airborne formaldehyde caused an increase in TEWL and skin pH in both healthy participants and those with AD. The median difference in TEWL was 2·5 g m^{-2} h^{-1} and 1·4 g m^{-2} h^{-1} in AD and healthy skin, respectively.[7] A more pronounced increase in skin pH was also observed in AD than in healthy skin (0·11 vs. 0·04 pH units), indicating that individuals with existing AD are more susceptible to VOC-induced barrier damage. These findings are in agreement with animal studies conducted by Han *et al.*,[10] which found that formaldehyde fume exposure exacerbated pruritus and dermatitis in a rat model of AD. Symptom exacerbation from VOC exposure was associated with significantly increased serum IgE and T helper (Th)1 cytokines (TNF-α, IL-1β) in the AD model compared with control.[10] Although the initial pathogenesis of AD involves a Th2 response, environmental triggers have been shown to stimulate a mixed Th1/Th17 inflammatory response later in the disease course.[10]

While exposure studies constitute a basis for the negative effects of VOCs on skin barrier function, it is useful to consider the impact of VOC indoor air pollution in real-world settings. A cross-sectional study conducted by Lee *et al.* examined the association between home remodelling and AD in > 4000 Korean schoolchildren. Children living in homes that had been remodelled within the preceding 12 months had more than a threefold greater risk of AD than those who did not live in areas of remodelling.[26] A combination of recent remodelling and food allergy synergistically increased the risk of AD in children by sevenfold.[26] Kim *et al.* studied the effects of plant-based wallpaper vs. polyvinylchloride-based wallpaper, and reported that AD children living in apartments with higher formaldehyde and VOC levels had significantly higher SCOring Atopic Dermatitis indices.[13] Furthermore, the authors found that eco-friendly wallpapering was associated with an increase in natural VOCs (also known as phytoncides) that are given

off by trees and plants. Higher levels of natural VOCs correlated with improvement in AD symptoms, suggesting that plant-based VOCs may have positive effects on barrier integrity.[13]

Cigarette smoke

Cigarette smoking has been associated with increased TEWL, an indicator of impaired skin barrier integrity. Muizzuddin *et al.* evaluated barrier function in a cohort of 100 patients, comprising 45 active heavy smokers (> 1 pack per day for > 5 years), 30 passive smokers (nonsmoking individuals living with active smokers for 20 years) and 25 nonsmokers. TEWL was averaged for each subset and was not significantly different between active and passive smokers at approximately 16 g m^{-2} h^{-1} for both groups. Nonsmokers demonstrated significantly lower TEWL at 11 g m^{-2} h^{-1} compared with both active and passive smoking groups ($P < 0{\cdot}001$).[27] This work suggests that environmental exposure to cigarette smoke is associated with damage to the barrier capacity of the epidermis.

Cigarette smoke has been implicated as an exacerbating factor in AD. In a cross-sectional study of > 7000 Korean schoolchildren, exposure to environmental tobacco smoke was significantly linked to development of AD, with exposure during the mother's pregnancy and children's infancy associated with a twofold greater risk.[28] In a large survey-based study of > 145 000 Korean adolescents, > 10 000 respondents reported AD symptoms within the last 12 months. Among this subset, both active and passive cigarette smoking were significantly associated with AD.[29] The strongest association was observed in those who actively smoked > 20 days per month (OR 1·18). Increased risk of AD was observed even in the subsets of lighter smoking (OR 1·11) or less frequent exposure to second-hand smoke (OR 1·08).[29]

While increased TEWL and higher prevalence of AD symptoms have been demonstrated in association with smoking, additional details remain to be established in the direct relationship between cigarette pollution and exacerbation of AD. Nevertheless, substantial evidence exists to support efforts in smoking cessation for dermatological, as well as general health.

A summary of the effects of specific pollutants on skin barrier function and AD is presented in Table 1.

Proposed mechanism of pollution-induced skin barrier dysfunction

General mechanisms of pollution-induced barrier dysfunction involve increased oxidative stress and induction of proinflammatory signalling cascades. Airborne pollution stimulates formation of reactive oxygen species (ROS), and overabundant ROS deplete the skin's antioxidant capacity.[16] This imbalance between pro-oxidant and antioxidant mechanisms leads to oxidative damage to keratinocytes,[8] decreased cell–cell adhesion and increased barrier dysfunction. Signalling cascades implicated in pollutant-induced skin barrier damage include the NFκB inflammatory pathway and AhR.[8,11,21] Airborne pollutants have been found to increase NFκB signalling, leading to enhanced expression of proinflammatory cytokines, including TNF-α, IL-1α, IL-1β, IL-6 and IL-8.[9,16,17,32,33] These cytokines mediate epidermal inflammation, leading to skin erythema, oedema, itch and pain. AhR acts as a chemical sensor in keratinocytes and is activated by polycyclic aromatic hydrocarbons and certain VOCs, leading to downstream activation of inflammation and itch mediators. One of these mediators is artemin, a neurotrophic factor that induces epidermal hyperinnervation and contributes to pruritus, and is upregulated in AD skin.[34] AhR also regulates the expression of nuclear factor erythroid 2-related factor, which, in turn, stimulates epidermal antioxidant defence, inflammation and barrier repair, all of which protect the skin against airborne pollutants.[35]

The impact of environmental pollutants in AD appears to be multifactorial, driven by the parallel effects of several mechanisms, including oxidative damage, barrier disruption, inflammation and dysbiosis. O_3 primarily exacerbates AD via generation of free radicals that result in cumulative oxidative damage. Exposure to O_3 causes dose-dependent depletion of cutaneous antioxidants such as glutathione and vitamins C and E, and is measurable via formation of malondialdehyde, a marker of lipid peroxidation.[36,37] Peroxidation disrupts lipid organization, compromising a critical building block of skin barrier integrity. Barrier disruption also results from decreased expression of structural proteins (cytokeratins, filaggrin, E-cadherin)[15] and increased expression of matrix metalloproteinases.[16,17] TRAP and PM exert proapoptotic effects on keratinocytes in the upper epidermis via induction of caspase-14,[38] impairing the hydration and barrier capacity of the stratum corneum. Pollution-induced inflammation involves IL-1α, IL-1β, IL-6 and IL-8, which stimulate granulocyte chemotaxis and phagocytosis, and result in cutaneous inflammation. Pollutants contribute to dysbiosis through bactericidal effects of O_3 that diminish commensal species,[20] as well as PM-induced increase in *S. aureus* colonization that contributes to AD flares.[9,39]

The cascading and interrelated effects of oxidative damage, barrier defects, inflammation and dysbiosis pose a complex and multifaceted threat to skin homeostasis, with an exaggerated impact in the inherently barrier-impaired state of AD. The cutaneous effects of airborne pollution on the skin barrier may be viewed as analogous to the classic itch–scratch cycle of AD, wherein barrier disruption leads to irritation that promotes scratching, which further damages the skin barrier. Pollutants can more effectively penetrate a disrupted skin barrier leading to a greater magnitude of proinflammatory and oxidative changes, which, in turn, lead to further compromise of skin barrier integrity and greater susceptibility to airborne pollutants and pathogens that exacerbate AD. The proposed mechanisms of pollution in AD are shown in Figure 1.

Where do we go from here?

The growing prevalence of AD coincides with increased urbanization worldwide over recent decades. These trends

Table 1 Summary: effects of specific pollutants on skin barrier function and atopic dermatitis (AD)

Pollutant	Associated effects
PM	• Twofold increase in TEWL in pig skin treated with solubilized PM vs. control[15] • Loss of epidermal structural proteins (cytokeratin, filaggrin, E-cadherin)[15] • Stimulates production of MMPs, inflammatory cytokines TNF-α, IL-1α, IL-1β and IL-8 by keratinocytes[16,17] • Dose- and time-dependent cytotoxicity to cultured keratinocytes; activation of NFκB signalling and IL-1α production[8] • Penetrates epidermal barrier of tape-stripped mouse skin and incites neutrophilic dermal inflammatory response in intact and barrier disrupted skin[16] • Exacerbation of itch and dermatitis in rats with existing AD[9] • Increased *Staphylococcus aureus* colonization in both AD and healthy rats[9] • Temporal association of elevated PM levels and exacerbation of AD symptoms in Korean children[18] • Association of PM exposure with development of AD in Taiwanese adults[19]
TRAP	• Children exposed to highest quartile of stratospheric O_3 levels demonstrated higher rates of AD (aOR 1·28; $P < 0·001$) than the lowest quartile of O_3 exposure[30] • Reduction in resident skin flora by 50% after exposure to O_3 vs. air alone[20] • Positive correlation between TRAP exposure and development of AD after 55 years of age in German women, with increased likelihood of AD in those carrying AhR SNP[21] • Greater than twofold increased risk of AD in children living within 50 m of the nearest main road vs. those living > 200 m from nearest main road[22] • Increased risk of AD in preschool children whose mothers experienced high levels of NO_2 exposure during 3 months prior to conception and throughout pregnancy[23] • Positive correlation between elevated gestational and lifetime NO_2 exposure and childhood AD in Shanghai preschool children[24]
VOCs	• 34% increase in TEWL in healthy and AD skin 48 h after exposure to VOC mixture[25] • Enhanced reaction to house-dust mite patch testing in patients with AD exposed to aerosolized VOCs[25] • Increased TEWL and stratum corneum pH in healthy and AD skin in response to formaldehyde[7] • Exacerbation of pruritus and dermatitis in rat model of AD, with increase in serum levels of IgE and Th1 cytokines after exposure to formaldehyde fumes[10] • Greater than threefold higher risk of AD in children living in homes remodelled in the previous year vs. those living in nonremodelled residences[26] • Higher SCORAD indexes in children living in apartments with PVC-based wallpaper and elevated indoor levels of VOCs, and improvement of AD symptoms associated with plant-source wallpaper[13]
Cigarette smoke	• Increased TEWL in active and passive smokers vs. nonsmokers[27] • Twofold increased risk of AD in children exposed to environmental tobacco smoke during mothers' pregnancies and the children's infancies[28] • Association of both active and passive smoking with AD symptoms in Korean adolescents in the previous 12 months[29]

PM, particulate matter; TEWL, transepidermal water loss; MMP, matrix metalloproteinase; TNF, tumour necrosis factor; IL, interleukin; NFκB, nuclear factor kappa B; TRAP, traffic-related air pollution; O_3, ozone; aOR, adjusted odds ratio; AhR, aryl hydrocarbon receptor; SNP, single nucleotide polymorphism; VOC, volatile organic compound; Th1, T helper 1; SCORAD, SCOring Atopic Dermatitis; PVC, polyvinylchloride.

suggest that environmental pollution secondary to changes in construction, transportation and manufacturing techniques may impact the skin barrier at the body's interface with the outside world. Airborne pollution has been demonstrated to affect TEWL, skin pH, expression of inflammatory cytokines and the cutaneous microbiome.[7,9,10,15–17,27,32,33] Investigation of these effects allows us to begin to understand the interaction between environmental pollutants and skin homeostasis, and to form hypotheses regarding the role of pollution in the pathogenesis and exacerbation of AD.

Knowledge gaps and investigative directions

While some specific dermatological effects of environmental air pollutants have been identified, the picture becomes more complex when considering the mixture of substances to which skin is exposed on a daily basis. The combined impact of individual pollutants may lead to different effects than those elicited by a single component. Additionally, environmental factors, including temperature, humidity and ultraviolet light, likely interact with airborne pollutants, and fluctuations in these parameters may either mitigate or aggravate the cutaneous effects of pollutants. The practical nature of airborne pollution exposure is difficult to replicate in a research setting owing to the variable composition and exposure time of actual air pollutants. The generalized population effects are also difficult to quantify considering varying location and activity patterns between individuals.

Owing, in part, to these challenges, knowledge gaps remain regarding the role of airborne pollutants in AD, as it is unclear whether pollution is capable of inducing skin barrier dysfunction in naive individuals or rather exacerbates underlying barrier abnormalities intrinsic to AD. While current evidence is insufficient to make this distinction, population-based

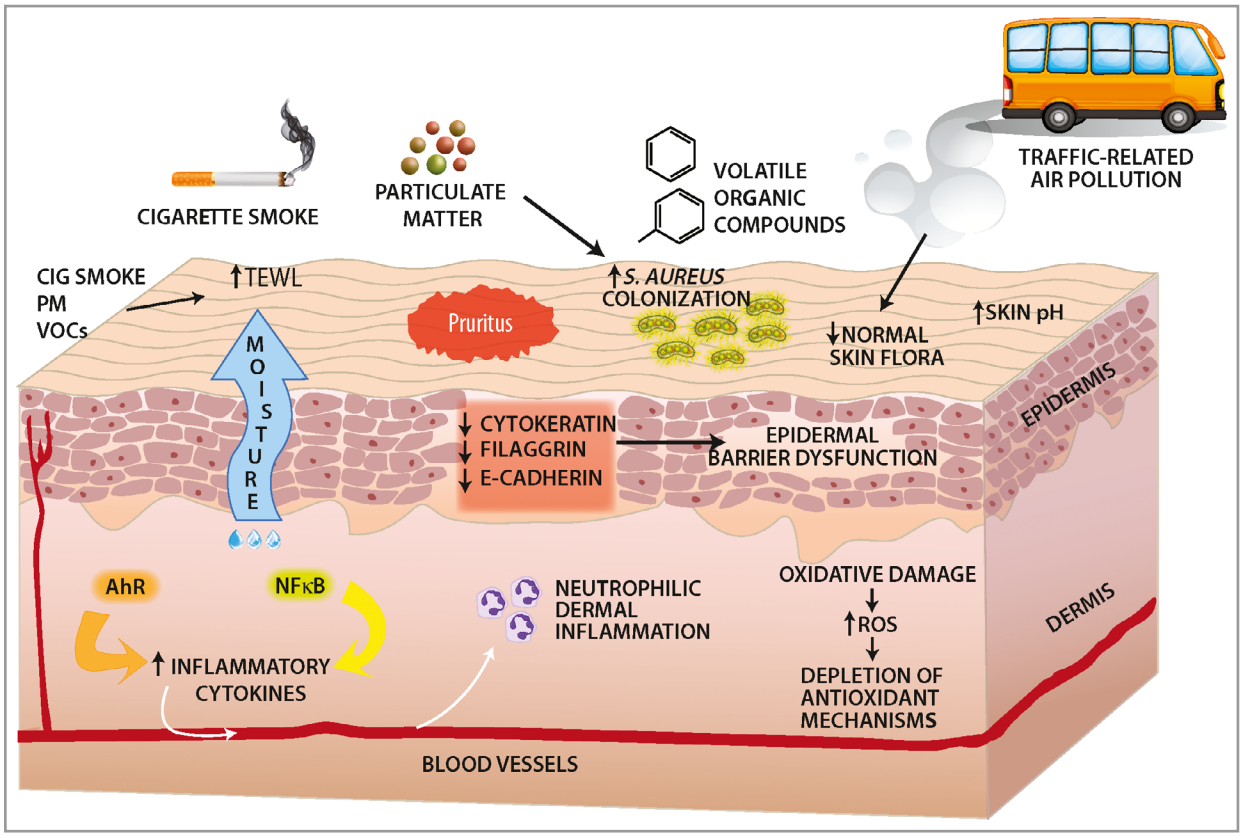

Fig 1. Proposed influence of pollutants in atopic dermatitis (AD). AD is caused by a constellation of aetiological factors that include skin barrier dysfunction, inflammatory dysregulation, microbiome alteration and oxidative damage. Pollutants, including particulate matter (PM), traffic-related air pollution (TRAP), volatile organic compounds (VOCs) and cigarette smoke, cause damage to the epidermal barrier, partly by decreasing the expression of barrier proteins (cytokeratins, filaggrin and E-cadherin). Cigarette smoke, PM and VOCs have been demonstrated to increased transepidermal water loss (TEWL). Expression of inflammatory cytokines through aberrant aryl hydrocarbon receptor (AhR) and nuclear factor kappa B (NFκB) signalling contributes to increased pruritus, inflammation and exacerbation of AD. Pollution-induced changes in the skin microbiome include decreased normal skin flora and increased *Staphylococcus aureus* colonization. Oxidative damage from all forms of pollution leads to increased reactive oxygen species (ROS) and exhaustion of the skin's antioxidant mechanisms.

longitudinal studies have identified a correlation between higher pollution exposure and AD prevalence, suggesting that exposure to certain pollutants or exposure surpassing a certain threshold may contribute to development of AD. Timely research is needed to further characterize critical pollutant exposures and levels. Additional investigation addressing skin microbiome modulation in response to pollutants and protective measures may lead to better understanding of the interplay between pollution and AD symptoms. The genetic effects of air pollution on AD also deserve further exploration. Long-term exposure to metals in PM has been linked to DNA damage and skin cell apoptosis through mitochondria-regulated pathways.[40,41] Gene–environment interaction studies have highlighted the important association between AD and air pollution.[42] Emerging evidence suggests that epigenetic phenomena play a central role in linking environmental pollutants, transcutaneous sensitization and the development of allergic diseases in children.[43] Future research is warranted to elucidate these mechanisms and to identify possible methods for reversal and prevention of pollutant-related barrier dysfunction.

Pollution protection and solutions

Looking toward a future of continued urbanization and industrial growth, preventive and protective strategies are necessary to combat the health effects of airborne pollution. In the context of AD, three main arms for intervention should be considered: (i) avoidance of pollutant exposure and decreasing skin barrier damage through selection of nonirritating materials; (ii) thorough, regular cleansing to remove pollutants from the skin surface; (iii) protection of the skin barrier against pollutant entry. Patients should be encouraged to wash daily (preferably at the end of the day following exposure to ambient pollution), with subsequent emollient application for skin barrier repair. Further research is needed to identify efficacious barrier repair formulations, as ideal ingredients and formulas for repair may be pollutant-specific. The potential role of topical antioxidants and anti-inflammatory compounds as adjuvant therapy is an additional area of future investigation, as NFκB inhibitors and vitamin and trace mineral formulations may bolster the skin's capacity to protect against oxidative damage and

resulting inflammation.[31,44] Topical formulations that have shown efficacy in reducing pollutant-induced cutaneous oxidative damage include antioxidants vitamin C and vitamin E,[45–47] and formulas that create a physical barrier such as a mixture of Dead Sea mineral water and anionic polysaccharide.[48]

While emollients and antioxidants may prove helpful in reducing pollutant-induced skin barrier dysfunction, larger-scale lifestyle and industrial modifications may yield promising findings in minimizing or preventing barrier dysfunction. In developing countries, major sources of indoor air pollutants originate from domestic practices such as burning solid fuels (coal, dung, wood, biomass) for cooking, lighting and heating. Women and children are most frequently exposed to high levels of indoor air pollutants, constituting a public health concern due to adverse respiratory, ophthalmological and dermatological effects.[49,50] Clean-cooking campaigns are being implemented in developing regions around the world in an effort to reduce indoor air pollutant exposure. These initiatives have led to improved household air ventilation via installation of chimneys, outdoor kitchens and modern stoves that use safer fuels to decrease the health burden of indoor pollution.[51] In urban settings with small and crowded living quarters, indoor pollutants such as cigarette smoke, dust mites, PM and CO can act as major contributors to the exacerbation of AD and skin barrier dysfunction. In addition to limiting these exposures, selection of construction materials that do not contain VOCs may lead to lower levels of indoor air pollution and decreased incidence of inflammatory dermatoses. Similarly, urban planning to incorporate greenspace in residential neighbourhoods may reduce exposure to outdoor air pollution. These large-scale adjustments will require combined efforts of the healthcare, public health, construction development and mechanical engineering industries to inform the public of the health impact of environmental pollution and encourage more thoughtful selection of materials used in buildings, factories and vehicles in our increasingly urban society. As these adjustments require significant time for implementation, additional research on methods of reversing pollutant-induced skin barrier damage will be critical in the coming years.

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