**Dysregulation of the epithelial barrier by environmental and other exogenous factors**

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**Abstract**
The “epithelial barrier hypothesis” proposes that the exposure to various epithelial barrier–damaging agents linked to industrialization and urbanization underlies the increase in allergic diseases. The epithelial barrier constitutes the first line of physical, chemical, and immunological defense against environmental factors. Recent reports have shown that industrial products disrupt the epithelial barriers. Innate and adaptive immune responses play an important role in epithelial barrier damage. In addition, recent studies suggest that epithelial barrier dysfunction plays an essential role in the pathogenesis of the atopic march by allergen sensitization through the transcutaneous route. It is evident that external factors interact with the immune system, triggering a cascade of complex reactions that damage the epithelial barrier. Epigenetic and microbiome changes modulate the integrity of the epithelial barrier. Robust and simple measurements of the skin barrier dysfunction at the point-of-care are of significant value as a biomarker, as recently reported using electrical impedance spectroscopy to directly measure barrier defects. Understanding epithelial barrier dysfunction and its mechanism is key to developing novel strategies for the treatment of allergic diseases.

**Abbreviations:**
AD, atopic dermatitis; AJ, adherence junction; ALI, air-liquid interface; AR, allergic rhinitis; CRS, chronic rhinosinusitis; DEP, diesel exhaust particles; Der p1, Dermatophagoides pteronyssinus peptidase 1; EI, electrical impedance; HBEC, human bronchial epithelial cells; HDACs, histone deacetylases; HDM, house dust mite; IL, interleukin; ILC, innate lymphoid cell; NEC, nasal epithelial cell; NHEK, normal human keratinocytes; NO2, nitrogen dioxide; PAR, protease-activated receptor; PM, particulate matter; ROS, reactive oxygen species; TEWL, transepidermal water loss; TLR, Toll-like receptor; TSLP, thymic stromal lymphopoietin; VOCs, volatile organic compounds; ZO, zonula occluden.

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1 | INTRODUCTION

Since the introduction of the “epithelial barrier hypothesis,” factors that damage the skin and mucosal barriers have become a major area of interest. Epithelial barrier leakiness has been demonstrated in asthma, atopic dermatitis (AD), allergic rhinitis (AR), chronic rhinosinusitis (CRS), eosinophilic esophagitis, celiac disease, and inflammatory bowel disease. Leakage of the gut epithelium is also implicated in systemic autoimmune and metabolic conditions such as obesity, diabetes, rheumatoid arthritis, multiple sclerosis, systemic lupus erythematosus, fatty liver, autoimmune hepatitis, and ankylosing spondylitis. Although further studies are needed, microbial dysbiosis and an impaired gut barrier are suspected in Alzheimer’s disease, Parkinson’s disease, chronic depression, and autism spectrum disorders. The epithelium is a pivotal structure in host defense because it not only provides a physical barrier between the environment and the subepithelial region, but also contributes to the induction of an appropriate immune response against allergens, pathogens, and noxious stimuli that attenuate the epithelial barrier. Recent studies have shown that a defective epithelial barrier, with compromised tight junctions (TJs) and adherence junctions (AJs), is part of the underlying pathology in diseases such as AD, bronchial asthma, eosinophilic esophagitis, food allergy, CRS, and AR, which are discussed in this review. The sequential development of these diseases starting from AD in infancy followed by food allergy, asthma and rhinitis, commonly known as the atopic march, has sharply increased. The inner molecular mechanisms underlying the epithelial barrier dysfunction involve a type 2 immune response through type 2 cytokines produced by Th2 cells and type 2 innate lymphoid cells (ILC2s). It is well-known that lifestyle changes due to industrialization cause epithelial barrier dysfunction. Factors that have been recognized to damage the epithelial barrier include allergens, pathogens, commercial detergents, surfactants, emulsifiers in processed food, cigarette smoke, particulate matter, diesel exhaust, ozone, nanoparticles, and microplastics. These changes also compromise epithelial barrier function across multiple organ systems. Quantitative skin barrier assessment in vivo can be beneficial for many clinical applications, including diagnosis, follow-up, prevention, and monitoring the therapy of AD.

Supporting our “epithelial barrier hypothesis,” we discuss recent advances in our understanding of the mechanisms underlying epithelial barrier dysfunction triggered by environmental and other culprit factors. The latest technological developments to measure skin barrier dysfunction are reviewed.

1.1 | Structure of the epithelial barrier

The epithelial barrier consists of a stratified epithelial cellular sheet that forms a physical barrier on the body surface. Four main components can be identified: (a) epithelial cells; (b) structural proteins, such as filaggrin, loricrin, involucrin, and proteins involved in the formation of TJs and AJs; (c) secreted epithelial products, such as mucus, antimicrobial peptides, and a lipid-rich matrix composed of ceramides, cholesterol, and free fatty acids (FFAs); and (d) epithelial microbiota (Figure 1). The epidermis has its original structure and is composed of four main layers: the stratum corneum, stratum granulosum, stratum spinosum, and the stratum basale. The stratum corneum is the outermost layer, consisting of enucleated keratinocytes referred to as corneocytes. It is maintained by the complex interaction of the cornified envelope, intracytoplasmic moisturizing factors, and a complex lipid mixture in the extracellular space. Filaggrin is a structural protein important for the alignment of keratin filaments and the formation of the cornified envelope and natural moisturizing factor. Epidermal barrier dysfunction is not fully understood and further research is warranted.

1.2 | Culprit factors for epithelial barrier dysfunction

1.2.1 | Environmental factors

Environmental factors and lifestyle changes may be responsible for the increasing prevalence of allergic diseases. The sum of external factors that contribute to the dysregulation of epithelial barrier function.
Factors that an individual is exposed to throughout life is referred to as the exposome. The combination of multiple factors, such as cigarette smoke, air pollutants, chemicals, aeroallergens, and diet, contributes to the development and exacerbation of asthma and other allergic diseases.

**Oxidative stress and air pollution**
Cigarette smoke and its reactive oxygen species (ROS) products impair the epithelial barrier function and increase epithelial permeability by triggering the RhoA/Rho-associated protein kinase (ROCK) signaling pathway in which ROCK is activated after hyaluronan...
fragmentation via ROS, which leads to disruption of AJs through a decrease in E-cadherin gene and protein expression in human bronchial epithelial cells (HBECs). Exposure to microplastics and air pollutants, such as diesel exhaust particles (DEPs), ozone, and nitrogen dioxide, induces the production of ROS. Particulate matter 2.5 (PM$_{2.5}$), the main component of DEP, exacerbated AR through TJ disruption in a mouse model of allergic rhinitis. A population-based prospective study has shown that a 2.3 parts per billion increase in nitrogen dioxide (NO$_2$) is associated with an increased risk of prevalent and atopic eczema in male adults. Exposure to traffic-related air pollutants, PM$_{2.5}$, PM$_{10}$, and oxides of nitrogen, is associated with increased odds of incident eczema, particularly PM$_{2.5}$, and is more pronounced with nonatopic eczema in elderly women. Moreover, DEP exposure induces IL-25, IL-33, and thymic stromal lymphopoietin (TSLP) expression in the lungs, leading to severe asthma by activation of the aryl hydrocarbon receptor.

**Volatile organic compounds and ozone**

Volatile organic compounds (VOCs) are composed of carbon-based molecules such as formaldehyde, benzene, and toluene that affect the urban air quality and human health. VOCs are commonly found in cleaning products, wallpaper, furniture, and plastics, and are main contributors to indoor air pollution. VOC exposure leads to protease inactivation and protein oxidation, DNA damage, and apoptosis in keratinocytes and human skin explants. Exposure to formaldehyde for 1 hour increases transepidermal water loss (TEWL) in both healthy and AD children, supporting the role of short-term exposure to airborne formaldehyde in impairment of the skin barrier. VOCs can react with NO$_2$ in the presence of sunlight to form ozone, which causes airway hyperreactivity, airway inflammation, and bronchial epithelial barrier disruption by inducing ROS production. IL-33 plays a critical role in ozone-induced neutrophilic rapid lung inflammation and bronchial epithelial barrier injury.

**Emulsifiers in processed foods**

Emulsifiers are frequently used as additives in the food industry. There is evidence indicating that emulsifiers increase intestinal permeability, even at low concentrations. Some commonly used emulsifiers, including polysorbate 80 and carboxymethyl cellulose, significantly increased bacterial translocation in Caco-2 cells derived from a human colon carcinoma.

**High glucose-induced barrier defects**

Thais et al showed that elevated glucose concentrations lead to intestinal barrier dysfunction and enhanced dissemination of enteric infection in a mouse model of type 1 diabetes mellitus induced by administering streptozotocin. Similarly, Yu et al reported that high glucose levels disrupted the TJs by downregulation of connexin 43, which plays a critical role in maintaining the function of the airway epithelial barrier in the respiratory tract.

### 2 | ALLERGENS

The protease activity of allergens, such as house dust mites (HDMs), Aspergillus fumigatus, and pollen, has been suggested to be involved in the pathogenesis of allergic diseases by increasing the epithelial permeability and causing barrier dysfunction (previously reviewed). Proteolytically active allergens not only cleave the junction proteins but also activate epithelial cells and adaptive immune responses directly through protease-activated receptors (PARs).

HDM allergens increase the mucosal permeability of ALI-cultured nasal epithelial cells (NECs) from HDM-induced AR patients. In addition, HDM perturb N-glycosylation of Toll-like receptor (TLR) 3 and impair the interferon response, which may aggravate allergic lung inflammation. Protease allergens, such as Dermatophagoides pteronyssinus peptidase 1 (Der p 1) derived from HDM, induce type 2 inflammation, thereby promoting alarmins (IL-25, IL-33, TSLP) in
epithelial cells. These cytokines activate ILC2 and promote type 2 helper cell differentiation.\textsuperscript{39,415} Hirashii et al showed that fungal-associated proteases induce ILC3-mediated airway eosinophilia through the expression of IL-25, IL-33, and TSLP.\textsuperscript{74} Unlike other protease allergens, Der f3 from Dermatophagoides farinae (Der f) induces pro-inflammatory mediators (IL-6, IL-8, and granulocyte-macrophage colony-stimulating factor), but not IL-25, IL-33, and TSLP, and causes barrier dysfunction through PAR-1 and PAR-2.\textsuperscript{75} Allergen immunotherapy has been used for the treatment of allergic diseases.\textsuperscript{76-79} Yuan et al reported that allergen-specific immunotherapy restored airway epithelial integrity, and attenuated IL-25-induced epithelial endoplasmic reticulum stress and epithelial apoptosis in a Der f-induced airway inflammation model.\textsuperscript{80}

Pollen is also a well-known trigger of respiratory allergies and asthma. Vinhas et al found that pollen proteases damage the epithelial barrier via PARs.\textsuperscript{81} Consistently, Cleempt et al showed that pollen proteases selectively and irreversibly damage the integrity and anchorage of columnar respiratory epithelial cells. In addition, this partial loss of barrier function facilitates the invasion of alpha-herpesviruses.\textsuperscript{82}

### 3 | MICROBIOTA CHANGES

The human body is colonized by a diverse microbial flora that plays an essential role in human health and disease. As the outermost component, the skin microbiota is the first line of defense against pathogenic microorganisms. It is known that healthy skin microbiota limits pathogen colonization via competition for space and nutrients, altering skin pH, and producing antimicrobial peptides (AMPs).\textsuperscript{83} Skin injury induced by tape-stripping in mice disturbs the skin barrier and alters the skin microbiota and host genes.\textsuperscript{84} It is well-known that poor microbiome diversity is accompanied by an increase in Staphylococcus aureus (S. aureus) abundance, which is positively correlated with AD disease severity.\textsuperscript{85-87} Recently we also demonstrated that S. aureus is significantly more abundant in lesional skin compared to nonlesional and healthy skin.\textsuperscript{39} Moreover, when performing next-generation sequencing on matched lesional and nonlesional skin tissue biopsy specimens from patients with AD and healthy subjects, we identified four TJ genes (CLDN4, CLDN5, TJP1, and TJP2) that are robustly correlated to microbiome dysbiosis in patients with AD.\textsuperscript{88,89} Consistent with these results, Clausen et al reported that the microbiome alpha diversity is lower in patients with AD compared with healthy controls and is inversely correlated with disease severity, not only for lesional skin but also nonlesional skin. Filaggrin gene mutations were associated with microbiome composition in the nonlesional skin of patients with AD.\textsuperscript{89} Of interest, we found that S. aureus and Staphylococcus epidermidis enhance the expression of TJs in healthy nasal tissue, but not in nasal polyps.\textsuperscript{88,89} The microbiome may have a protective role as observed in healthy epithelial cells. S. aureus–secreted proteins may be contributing to the initiation and acute exacerbations of human asthma and CRS with nasal polyps.\textsuperscript{90} Recent reports suggest that early life bacterial supplementation may prevent the onset and progression of allergic diseases.\textsuperscript{91} On the other hand, Roßberg et al reported that applying bacterial lysates of heat-killed gram-negative Escherichia coli and gram-positive Enterococcus faecalis in early infancy does not influence the development of AD, AR, asthma, and sensitization at school age.\textsuperscript{92}

It is widely accepted that the epithelial barrier is armed with its own protective mechanisms. Epithelial cells sense pathogen-associated molecular patterns by expressing pattern-recognition receptors, including TLR and PAR. It is known that TLR2 is essential for maintaining epithelial barrier function.\textsuperscript{93,94} In line with these studies, Ruffner et al found that TLR2 stimulation induces claudin-1 and ZO-1 production in esophageal epithelial cells and increases histone deacetylation in claudin-1 gene enhancer and promoter.\textsuperscript{95} Decreased expression of TLR2 on Langerhans cells in AD skin impairs S. aureus–derived signals and contributes to the immune deviation from S. aureus clearance.\textsuperscript{96} Microbial DNA sequences containing unmethylated CpG dinucleotides activate TLR9, restoring epithelial barrier integrity by modulating TJ expression.\textsuperscript{97} Furthermore, probiotic bacteria, mostly lactobacilli, interact with the epithelial barrier and immune cells through pattern recognition receptors and promote the expression of TJs and AJs, restoring the epithelial barrier integrity.\textsuperscript{98}

S. aureus induces proinflammatory cytokines, such as tumor necrosis factor α (TNF-α) in keratinocytes. We showed that TNF-α and TNF-like weak inducer of apoptosis (TWEAK) cooperate in the induction of apoptosis in primary keratinocytes and that a high TWEAK expression is observed in lesional AD skin.\textsuperscript{99}

### 3.1 | Mechanism of barrier dysfunction

#### 3.1.1 | Cytokines and hormonal factors

It is well-established that signature type 2 cytokines, such as IL-4 and IL-13, impair the epithelial barrier function, reducing the expression of TJs proteins and filaggrin.\textsuperscript{7,88,100} For example, IL-4 and IL-13 downregulate claudin-4, ZO-1, and occludin in HBECs, which results in increased paracellular leakiness and respiratory hyper-responsive-ness.\textsuperscript{101} On the other hand, Sweerus et al reported that IL-13 downregulates the expression of claudin-18 but not of claudin-1, -4, and -7.\textsuperscript{102} A recent systematic review showed that anti–IL-4 and IL-13 receptor monoclonal antibodies (dupilumab), anti–IL-5 monoclonal antibodies (mepolizumab and reslizumab), and anti–IL-5 receptor alpha monoclonal antibodies (benralizumab) are effective treatments for severe asthma and AD.\textsuperscript{103-109} Type 2 cytokines can cause barrier dysfunction by downregulating filaggrin gene expression. Mitamura et al reported that IL-24, a member of the IL-20 family, mediates the IL-13–induced downregulation of filaggrin gene expression.\textsuperscript{110} Single-cell analysis of biopsy samples and blisters showed that the frequencies of type 2 (IL13+)/type 22 (IL22+) T cells are higher than those of type 1 (IFN-γ+) in lesional AD, whereas this ratio is slightly reduced in nonlesional AD.\textsuperscript{111-113}

Epithelium-derived alarmins, IL-25, IL-33, and TSLP, lead to systemic inflammation characterized by activation of ILC2, exacerbated...
eosinophilia and IgE/IgG1 production and induce an immune response toward inhaled noxious agents and allergens.\textsuperscript{114,115} Xiong et al found that leukotriene B4 induces IL-33 expression and ILC2 activation in the lungs via engagement of its receptor 1 (BLT1) in a papain-induced lung inflammation mouse model.\textsuperscript{116} ILC2s also play an essential role in disrupting the epithelial barrier. We demonstrated that IL-13 produced by ILC2s induces keratinocyte and bronchial epithelial barrier disruption via downregulation of the expression of TJ components.\textsuperscript{8,117}

The common inflammatory cascade in allergic diseases is initiated by an IgE-dependent mast cell degranulation with the release of histamine, among other mediators, and is further orchestrated by type 2 cytokines.\textsuperscript{118,119} Geschwandtner et al first demonstrated that histamine aggravates the severity of AD and that anti-histamines may have potential therapeutic value to restore skin barrier function in these patients.\textsuperscript{119} Of interest, histamine directly inhibits the expression of filaggrin, loricrin, claudin-1, claudin-4, and occludin in keratinocytes.\textsuperscript{119} Histamine and Th2 cells are critical factors in initiating and maintaining a leaky barrier in patients via histamine receptor 1 with an early phase allergic airway response.\textsuperscript{120} Leukotriene E4, an arachidonic acid-derived bioactive molecule, mediates eosinophilic airway inflammation by decreasing the level of surfactant protein D.\textsuperscript{121} On the other hand, prostaglandin D2, which is also a potent pro-inflammatory lipid mediator, has been reported to have protective effects in acute lung injury\textsuperscript{122} and later phase skin and airway inflammation.\textsuperscript{123} Chymases are a family of serine proteases found primarily in mast cells. Zhou et al reported that chymase suppresses the expressions of occludin, claudin-4, ZO-1, E-cadherin, focal adhesion kinase, and cytokeratin, resulting in dysfunction of the airway wall in the pathogenesis of asthma.\textsuperscript{124} Moreover, an impaired epithelial barrier facilitates allergen passage and mast cell degranulation even in the absence of allergic inflammation.\textsuperscript{125}

4 | GENETICS AND EPIGENETICS OF EPITHELIAL BARRIER LEAKINESS

Recent studies have shown that epigenetic mechanisms mediate the effect of environmental and inflammatory triggers associated with allergic diseases.\textsuperscript{126,127} Histone acetylation induced by histone acetyltransferases is associated with gene transcription. On the other hand, histone deacetylases (HDACs) suppress gene transcription. Of interest, Nicodemus-Johnson et al showed that exposure of HBEC to IL-13 changes global DNA methylation patterns and results in long-lasting epigenetic changes near asthma-associated genes.\textsuperscript{128} Moreover, we found that IL-4 and IL-13 increase HDAC activity, inducing barrier leakiness in HBECs from patients with allergic asthma.\textsuperscript{100} Kaneko et al reported that HDAC inhibitors induce the expression of claudin-1 and -4 and ciliogenesis via p63 in normal and diseased nasal epithelium tissues.\textsuperscript{129} The role of HDAC in barrier dysfunction and potential treatments using HDAC inhibitors are yet to be elucidated.

CpG sites are regions of DNA consisting of guanine and cytosine. The methylation of CpG sites plays an important role in the regulation of gene expression. We recently reported that an increased global methylation level in HBEC from asthmatic individuals. Interestingly, the inhibition of CpG methylation restores leakiness that was shown in the asthmatic epithelium.\textsuperscript{130}

Filaggrin loss-of-function mutations are associated with higher total IgE levels, more sensitizations, and a more severe course of AD.\textsuperscript{131,132} In humans, individuals with reduced filaggrin gene expression levels exhibit early onset AD that is closely associated with asthma and food allergy, compared to subjects with normal filaggrin gene expression levels.\textsuperscript{133,134} Renert-Yuval et al showed comparative skin biopsy profiles of AD across different age groups and found that only adults had a significant reduction in filaggrin expression.\textsuperscript{135} The human filaggrin gene (FLG) is polymorphic with an intragenic copy number variation. Specifically, 10, 11, or 12 nearly identical tandem repeats can be present in exon 3. Not only loss-of-function mutation, but also low copy numbers of filaggrin affect AD risk.\textsuperscript{136}

4.1 | Detection of skin barrier dysfunction

Quantitative skin barrier assessment in vivo has potential value in many clinical applications, including diagnosis, follow-up, prevention, and therapy evaluation. Several invasive and non-invasive methods have been developed to study the barrier function. The measurement of skin hydration, colorimetry, skin surface pH, and sebometry are all examples of non-invasive methods. However, these methods provide only limited information on different skin characteristics and conditions and do not directly measure the skin barrier function.\textsuperscript{137} TEWL is the amount of water that evaporates passively from the surface of the skin and its measurement allows for quantification of skin barrier dysfunction.\textsuperscript{138} However, TEWL can be affected by several environmental factors. Indeed, its accuracy is dependent on humidity, temperature, and skin hydration level. In diseased skin, TEWL is higher due to damage in the skin barrier and/or alterations in keratinization.\textsuperscript{138,139}

Confocal Raman spectroscopy is another non-invasive method to characterize the molecular composition of the skin in vivo by irradiating the sample with low-power monochromatic laser light. After the incident light excites the molecules within the tissue, the light is reflected in a wavelength characteristic of each skin component. The scattered light is then captured and analyzed, thus allowing non-invasive in vivo measurements at different depths within the tissue.\textsuperscript{140} Several studies have suggested that the confocal Raman spectroscopy is useful for the detection of FLG-related AD skin barrier by assessing the reduction of natural moisturizing factors, which are driven from the breakdown of FLGs.\textsuperscript{141-143} A recent study used confocal Raman spectroscopy to quantify the amount of water, ceramide, and urocanic acid in the skin, and found reduced levels of these components in atopic skin and a decreased lipid-to-protein ratio, suggesting the potential use of this technique for the stratification of AD patients.\textsuperscript{144}

A promising non-invasive tool for detecting skin barrier function in vivo is represented by electrical impedance spectroscopy (EIS). The electrical impedance of a tissue measured at various frequencies provides information about its structure and integrity, reflecting its pathophysiological status because normal and pathologic tissues differ
Current EIS applications include the diagnosis of malignant tissues in melanoma, breast tissue, prostate, and skin, and the characterization of tissue changes after ischemia. Recently, Rinaldi et al demonstrated EIS as a tool for the characterization of the epithelial barrier function in vivo. In the first group of studies in mice, EIS appeared to be a useful and reliable tool for detecting skin barrier defects. After experimentally damaging the skin barrier by tape stripping and epicutaneous application of proteases, such as papain, trypsin, and cholera toxin, a significant reduction in skin electrical impedance was observed. The findings were inversely correlated with TEWL. In a clinical study of AD patients, EIS was used to measure the skin barrier status with good specificity and sensitivity between controls, non-lesional skin of AD, and lesional skin of AD patients. EIS was also useful in assessing skin lesion healing in response to treatment, correlating with the disease score SCORAD and pruritus score, confirming that EIS has clinical potential for objective disease assessment and lesion follow-up in AD. Furthermore, EIS measurements on the non-lesional skin of AD patients correlated with the number of tandem repeats in the FLG gene. EIS has many potential clinical applications (Figure 3). We consider that it may be useful for identifying infants with a high risk of developing AD by measuring the integrity of the epithelial barrier. EIS can be a valuable tool for precision medicine to prevent the atopic march, exacerbation, and relapse of AD.

**CONCLUSION**

A dysfunctional epithelial barrier might facilitate the uptake of allergens and exogenous particles, leading to lesional inflammation. Allergen entry through a leaky epithelial barrier may cause systemic atopic responses that contribute to the atopic march. Understanding the underlying mechanisms involved in epithelial dysfunction is essential for developing novel strategies for the prevention and treatment of allergic diseases.

There is a pressing need to improve our understanding of the factors and molecular mechanisms associated with “leaky epithelial barriers.” Experimental models and skin organoids should be developed to study the passage of allergens across a leaky epithelial barrier. There is strong evidence linking barrier leakiness and inflammatory skin diseases, which needs to be considered when developing novel strategies for its prevention, early intervention, and diagnosis. Numerous strategies target the epithelial barrier including avoidance and dose control of hazardous products together with the development of safer alternatives, clinical application of EIS for the identification of individuals with a leaky barrier, development of therapeutic approaches for restoring the...
epithelial barrier integrity, and interventions through diet and microbiome.

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AUTHOR CONTRIBUTIONS

Yasutaka Mitamura: Conceptualization, methodology, visualization, writing – original draft (equal); writing – review and editing (equal).

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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