



## REVIEW ARTICLE

# The epithelial barrier theory and its associated diseases

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## Abstract

The prevalence of many chronic noncommunicable diseases has been steadily rising over the past six decades. During this time, over 350,000 new chemical substances have been introduced to the lives of humans. In recent years, the epithelial barrier theory came to light explaining the growing prevalence and exacerbations of these diseases worldwide. It attributes their onset to a functionally impaired epithelial barrier triggered by the toxicity of the exposed substances, associated with microbial dysbiosis, immune system activation, and inflammation. Diseases encompassed by the epithelial barrier theory share common features such as an increased prevalence after the 1960s or 2000s that cannot (solely) be accounted for by the emergence of improved diagnostic methods. Other common traits include epithelial barrier defects, microbial dysbiosis with loss of commensals and colonization of opportunistic pathogens, and circulating inflammatory cells and cytokines. In addition, practically unrelated diseases that fulfill these criteria have started to emerge as multimorbidities during the last decades. Here, we provide a comprehensive overview of diseases encompassed by the epithelial barrier theory and discuss evidence and similarities

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For affiliations refer to page 3220.

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for their epidemiology, genetic susceptibility, epithelial barrier dysfunction, microbial dysbiosis, and tissue inflammation.

#### KEYWORDS

epidemiology, epithelial barrier, epithelial barrier dysfunction, inflammation, microbial dysbiosis

## 1 | INTRODUCTION

During the last 60 years, the prevalence of many chronic noncommunicable diseases has been rising and they are now a major health concern, currently impacting more than 25% of the global population.<sup>1–5</sup> During this time, over 350,000 new substances have been introduced into the lives of humans and domestic animals.<sup>6</sup> A second epidemic rise in allergic diseases began after the 2000s, with a significant increase in the prevalence of food allergy, eosinophilic esophagitis, and drug-induced anaphylaxis.<sup>1</sup> This period coincides with a continuous exposure to environmental factors present in our modern lifestyle, such as detergents, food additives, microplastics, and nanoplastics.<sup>4,5</sup> The exploration of epithelial barriers started in 2000s, focusing on elucidating the mechanisms underlying type 2 diseases such as eczema, asthma, and chronic rhinosinusitis. This research revealed that the death of epithelial cells leads to chronic defects in the epithelial barrier, accompanied by periepithelial inflammation triggered by innate and adaptive immune responses.<sup>7–9</sup>

Initially, the understanding of epithelial barrier functions in relation to type 2 diseases centered around the concept of preventing allergens, toxins, pollutants, and microbes from breaching the barrier. This involved processes such as “washing away” inflammatory cells and cytokines through the opening of epithelial barriers, as well as “suppression” mediated by regulatory cytokines released by T cells and other cells on barrier surfaces during type 2 inflammation and exposure to high allergen doses in healthy individuals.<sup>10,11</sup>

Recent studies identified epithelial barrier defects in conditions like asthma, atopic dermatitis, and chronic rhinosinusitis, attributing them to genetic factors, exposure to toxic substances affecting the epithelial barrier, and the influence of immune cells and cytokines associated with type 2 responses, particularly IL-4 and IL-13.<sup>12,13</sup> Certain lifestyle-related or environmentally encountered substances, such as detergents, food emulsifiers, and air pollution, were found to damage the epithelial barrier, trigger alarmin release, and induce tissue inflammation.<sup>14–24</sup>

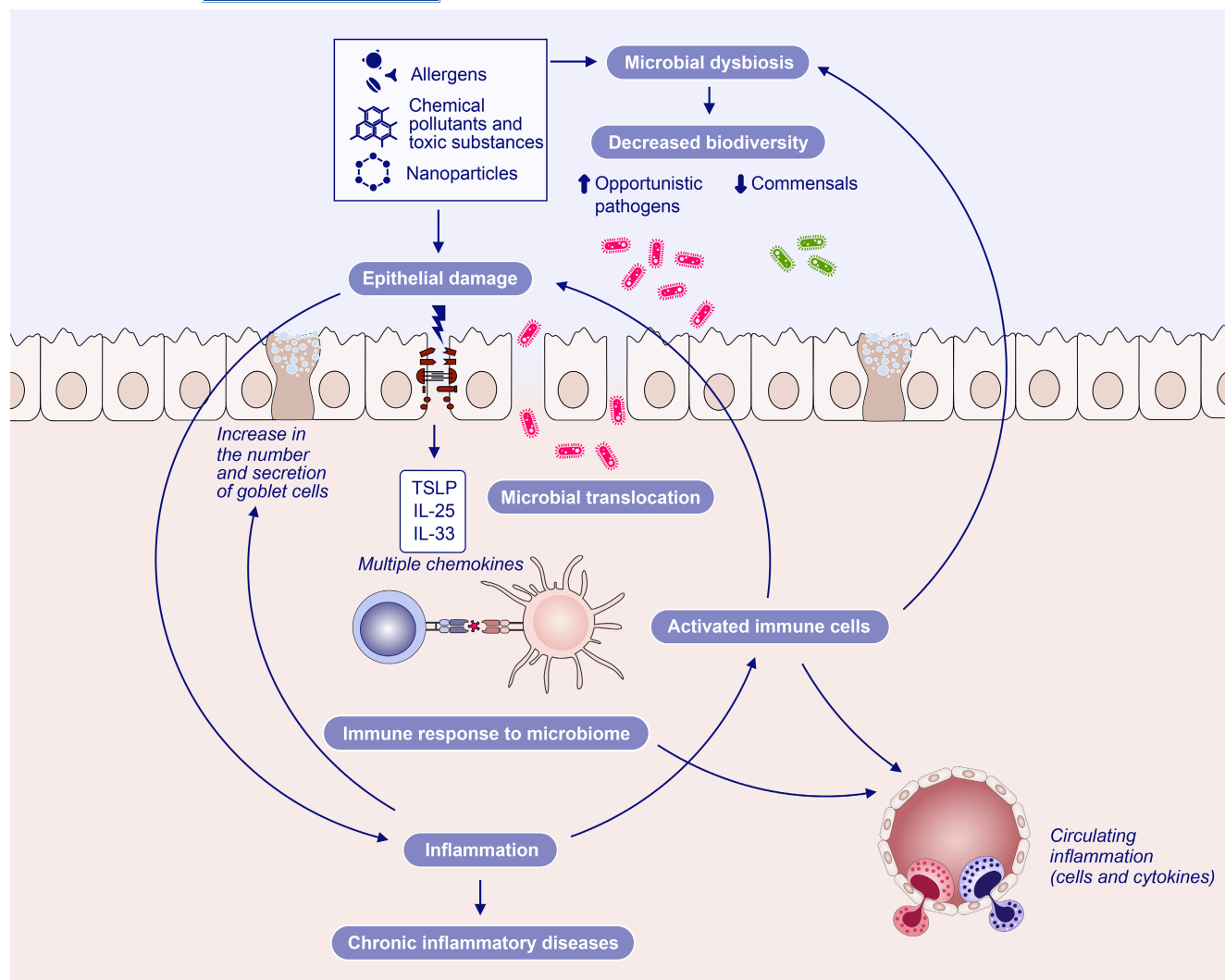
This research culminated in the development of the comprehensive “Epithelial Barrier Theory”<sup>1,3</sup> was proposed by Akdis to explain the growing prevalence of many chronic noncommunicable diseases observed over the last 60 years. It attributes the onset of these diseases to a damaged epithelial barrier triggered by hazardous substances originating from industrialization, urbanization, and westernized lifestyles, such as air pollution, cigarette smoke, particulate matter, ozone, microplastics, nanoplastics, several surfactant formulations in detergents, household cleaners, dishwashers,

hand sanitizers, disinfectants, toothpastes, and processed food emulsifiers and additives.<sup>25,26</sup> An impaired epithelial barrier can initiate a chronic vicious cycle of pathological events, including opportunistic pathogen colonization, bacterial translocation to subepithelial areas, immune response to pathogens, microbial dysbiosis, periepithelial chronic inflammation, and defective epithelial barrier healing (Figure 1).<sup>3</sup>

Epithelial barrier-related diseases are triggered by the barrier disruption, chronic inflammation, and microbial dysbiosis that occurs in organs or tissues such as skin, respiratory tract, digestive tract, and ocular surface. These diseases include atopic dermatitis, psoriasis, asthma, allergic rhinitis, eosinophilic esophagitis, food allergy, irritable bowel syndrome, ocular allergy, and dry eye.<sup>1</sup> Another group of epithelial barrier-related diseases mainly constitutes autoimmune, autoinflammatory, metabolic, and neuropsychiatric diseases associated with intestinal barrier dysfunction and microbial dysbiosis.<sup>1</sup> These are triggered through the gut–thyroid axis, gut–joint axis, gut–liver axis, or gut–brain axis such as in Hashimoto's thyroiditis, Graves' disease, osteoarthritis, obesity, diabetes, and cirrhosis. These diseases share common characteristics with an increased prevalence after the 1960s or 2000s, and similar pathophysiology involving defects in the epithelial barrier, microbial dysbiosis, and circulating microinflammation. Herein, we provide a comprehensive overview of diseases encompassed by the epithelial barrier theory and discuss their epidemiology, genetic predisposition, epithelial barrier disruption, microbial dysbiosis and tissue, and circulating inflammation.

## 2 | CROSSTALK BETWEEN THE EPITHELIAL BARRIER, MICROBIOTA, AND THE IMMUNE SYSTEM

The external surfaces of the body, such as the skin, the respiratory and digestive tracts, and the ocular surface, serve as a vital line of defense against the invasion of a variety of exogenous factors, such as allergens, microbes, and environmental substances, while at the same time, “trespassing” and exchange of particles is required to be facilitated.<sup>1,25</sup> Epithelial cells are key players in the innate defense of the mucosal surface. Epithelial cells not only form a physical barrier based on tight junctions (TJs) and adherens junctions (AJs), but also constitute complex chemical and biological barriers.<sup>27–29</sup> Under normal physiological conditions, epithelial cells separate immune cells and commensal microbiota to control and prevent excessive immune responses, thus maintaining homeostasis. In addition, the

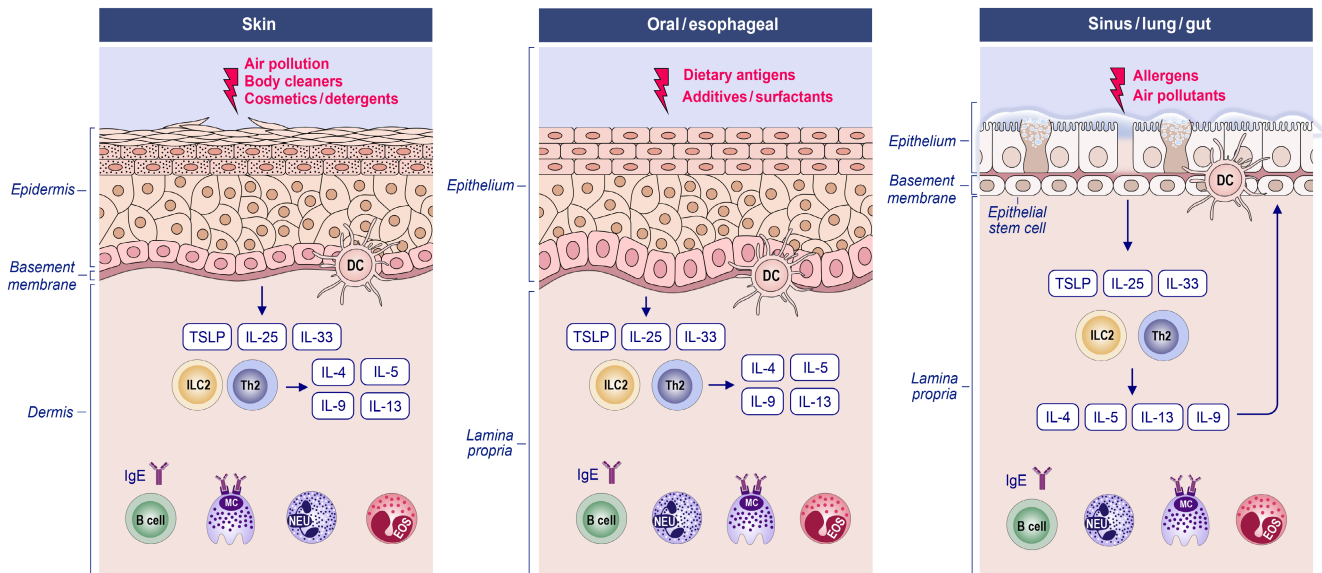


**FIGURE 1** Exposure to allergens, chemical pollutants, toxic substances, and nanoparticles causes epithelial damage, microbial dysbiosis, and inflammation. The resulting epithelial damage and microbial translocation across epithelial barriers increase the production of alarmins and multiple chemokines, altering the activation thresholds of resident immune cells and leading to cell migration. This cascade results in an inflammatory state, contributing to chronic inflammatory diseases.

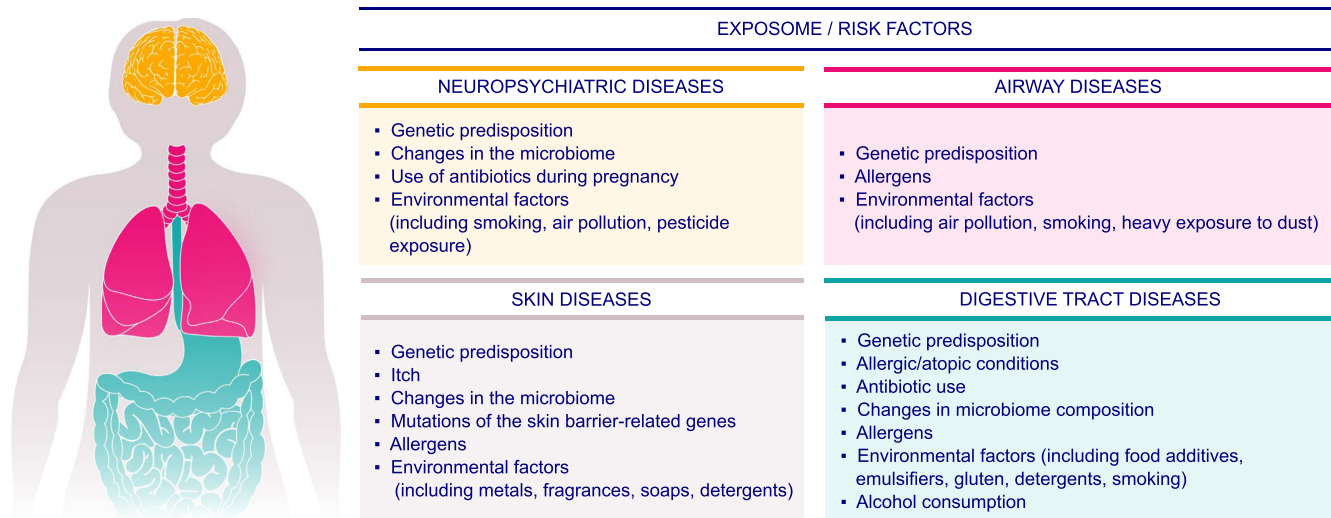
commensal microbiota and its metabolites can enhance the defense mechanisms of the epithelium and ameliorate the intestinal permeability, as part of the mucosal barrier.<sup>30</sup> Commensal segmented filamentous bacteria (SFBs) adhering to the luminal surface of Peyer's patches in the gut have been shown to induce T helper 17 (Th17) cell differentiation and prevent pathogen colonization.<sup>31,32</sup> Short-chain fatty acids (SCFAs) produced as end metabolites by the gut microbiota also play an essential role in maintaining the integrity of the intestinal barrier and mitigating local inflammation.<sup>33,34</sup> However, many different exogenous factors can impact epithelial cells and cause the loss of junctional proteins and mucosa, resulting in a leaky epithelial barrier that allows the translocation of microbiota to sub-epithelial areas.<sup>25</sup> Many viruses cause a transient damage in the epithelial barrier,<sup>35</sup> which is further impaired in chronic inflammatory diseases, such as asthma.<sup>36</sup> Epithelial cells, infected with respiratory viruses and exposed to inhaled allergens, are partly damaged and release many pro-inflammatory cytokines, including IL-1 family

molecules and alarmins, which further delay antiviral response and enhance problems with epithelial repair.<sup>37</sup> During chronic subepithelial inflammation, the distribution of many epithelial receptors is changing, including angiotensin-converting enzyme 2 for SARS-CoV-2, which might facilitate epithelial barrier damage upon infection.<sup>38</sup> Recent studies have suggested that cigarette smoke or ozone can alter lung microbial composition and function, reduce epithelial integrity, and increase susceptibility to respiratory pathogens, including COVID-19.<sup>20,39-41</sup>

Defects in the epithelial barrier function trigger immune responses, which vary depending on the location (e.g., skin, airway, esophagus, gut, and ocular surface) (Figure 2). Epithelial cells release inflammatory cytokines, including thymic stromal lymphopoietin (TSLP), interleukin (IL)-25, and IL-33, alarmins, and several chemokines that activate epithelial cells, mast cells, macrophages and attract and activate dendritic cells (DCs), eosinophils, neutrophils, T and B cells and innate lymphoid cells (ILCs).<sup>42,43</sup> A damaged epithelial



**FIGURE 2** Defects in epithelial barrier function with different allergens and environmental toxic substances are required to initiate epithelial immune responses. The secretion of alarmins IL-25, IL-33, and TSLP leads to the development of type 2 inflammation, which is characterized by the presence of ILC2s, Th2 cells, B cells, eosinophils (EOS), neutrophils, and mast cells (MC). ILC2s and Th2 cells secrete IL-4, IL-5, IL-9, and IL-13 that induce an inflammatory immune response.



**FIGURE 3** Exposome and/or risk factors in contact with neuropsychiatric diseases, airway diseases, skin diseases, and digestive tract diseases.

barrier function along with the activation of DCs, Th2 cells, and ILCs form a single immunopathological unit has been demonstrated to initiate type 2 immune and inflammatory responses,<sup>27</sup> which are persistently abnormal in allergic patients.<sup>44</sup>

A compromised skin epithelial barrier triggered by environmental factors such as mechanical trauma, repeated scratching, exposure to exogenous proteases, detergents, and air pollution can activate the innate immune system (Figure 3), inducing keratinocytes to release pro-inflammatory cytokines and chemokines and enhancing the antigen presentation by intradermal Langerhans cells (LCs) and dermal DCs.<sup>45,46</sup> Simultaneously, antigen binding promotes the secretion of Th2-promoting cytokines (IL-25, IL-33,

and TSLP), which drives immunoglobulin (Ig)E-bearing LCs and DCs to migrate to regional lymph nodes to initiate Th2 differentiation. In turn, memory T cells cycle back to infiltrate the skin or distribute in the periphery to other end organs, triggering various skin diseases.<sup>47</sup>

Inhalation of air pollutants, infectious agents, or aeroallergens leads to airway epithelial dysfunction and causes the release of mediators, including the pro-inflammatory cytokines, alarmins, and chemokines C-C motif chemokine ligand 2 (CCL2) and CCL20.<sup>48</sup> These cytokines trigger the massive secretion of IL-5 and IL-13 from ILC2s adjacent to the airway epithelium, leading to eosinophilic infiltration and goblet cell formation in the airways.<sup>49,50</sup> In addition, DCs

activated by these cytokines migrate to regional lymph nodes where they trigger the differentiation of naïve T cells into Th2 cells.<sup>51</sup> Th2 cells secrete IL-4 and IL-13, which induce airway inflammation and the onset of respiratory inflammatory diseases.

A disrupted esophageal epithelial barrier allows dietary antigens, bacteria, and bacterial metabolites to penetrate the esophageal mucosa (Figure 3). Recent studies have shown that biofilm formation following microbial dysbiosis, particularly by *Campylobacter* species on the esophageal mucosa, can exacerbate inflammation and further contribute to barrier damage.<sup>52</sup> CD1<sup>+</sup> LCs and DCs in the esophageal epithelium take up antigens directly from the lumen<sup>53</sup> as the esophagus, unlike the small and large intestines, lacks secondary lymphoid tissues with follicle-associated epithelium.<sup>54</sup> DCs migrate to draining lymph nodes to present antigens to T cells, which primes naïve T cells or activates effector T cells to produce Th2 cytokines and induce the expression of chemokines in the lamina propria, aggravating inflammatory esophageal diseases.<sup>54</sup>

The intestine is the largest compartment of the immune system, and it is constantly exposed to dietary antigens and commensal microbiota. Intestinal epithelial cells (IECs), consisting of several specialized cell types (enterocytes, Paneth cells, microfold cells (M cells), goblet cells, tuft cells, and enteroendocrine cells), construct an important defensive barrier system against exogenous factors (Figure 3).<sup>55</sup> Once the intestinal epithelial barrier is impaired, antigens and pathogenic bacteria can be taken up by M cells in the follicle-associated epithelium of Peyer's patches and isolated lymphoid follicles and transported to DCs in the subepithelial areas.<sup>56</sup> In addition, goblet cells can transport soluble luminal antigens to subepithelial CD103<sup>+</sup> DCs.<sup>57</sup> In response to antigens and pathogenic bacteria, IECs express and release more TSLP that acts directly on DCs to instruct naïve T cells to differentiate into Th2 cells to produce cytokines such as IL-4, IL-5, IL-10, and IL-13.<sup>58,59</sup> Similar to TSLP, the epithelial cytokines IL-25 and IL-33, released by damaged IECs during parasitic infection and allergen stimulation, can also promote type 2 immune responses by activating ILC2 to produce IL-5 and IL-13.<sup>60-62</sup> These immune responses further contribute to the development of intestinal inflammation and the onset of intestinal disorders. Similar to sweeteners it is suggested that in both CD and UC it may be prudent to reduce the intake of processed foods that contain carrageenan, carboxymethylcellulose, and polysorbate-80, all of which are food additives from the group of emulsifiers and thickeners. The health effects of carrageenan were studied in many animal models including rats, mice, guinea pigs, rhesus monkeys, and rabbits.<sup>63</sup> In the animal studies, intestinal lesions, neoplasia, ulcerations, accumulation in intestinal lymph nodes, stricture formation, and UC-like inflammatory changes were reported.<sup>63</sup> Emulsifiers also have been reported to aggravate intestinal inflammation in mouse models.<sup>64</sup> Interestingly, at least some of the adverse effects of these emulsifiers on promoting colitis or obesity might be driven by the induction of intestinal microbial alterations in conjunction with immune activation and can be transmitted via the transfer of fecal material.<sup>64</sup>

Environmental allergens in contact with the ocular surface epithelium can interact with epithelial cells or cross the epithelial

layer and enter the subepithelial layer where they encounter DCs. DCs sample and process the allergens, then migrate to the regional lymph node and present them to naïve CD4<sup>+</sup> T cells, which triggers the activation, proliferation, and differentiation of CD4<sup>+</sup> T cells into allergen-specific Th2 cells, resulting in allergic inflammation.<sup>65</sup> Moreover, damaged conjunctival epithelial cells induced by allergens can release pro-type 2 cytokines, particularly TSLP and IL-33,<sup>66</sup> the epithelial-derived IL-33 is involved in conjunctival epithelium barrier disruption and exacerbation of allergic inflammation via the IL-33/ST2/IL-9/IL-9R signaling pathway.<sup>67</sup> TSLP activates resident DCs in the conjunctiva by interacting with TSLP receptors on conjunctival DCs. Activated DCs expressing OX40 ligands migrate to regional lymph nodes and promote Th2 differentiation through the OX40 ligand and OX40 interactions.<sup>68,69</sup>

### 3 | EVIDENCE FOR EPITHELIAL BARRIER THEORY-ASSOCIATED DISEASES

The selection criteria for epithelial barrier theory-associated diseases (see Box 1) are diseases that fit at least two of the five criteria are included.

#### 3.1 | Skin diseases

Studies have shown that the skin microbiome contributes to host immunity by maintaining the epithelial barrier function of the skin.<sup>70,71</sup> As such, disruption of the skin epithelial barrier has been linked to an altered microbiome. Several studies have demonstrated epithelial barrier disruption, microbial dysbiosis, and microinflammation present in lesional skin from a broad range of dermatological diseases (Table 1), such as atopic dermatitis, allergic contact dermatitis, chronic spontaneous urticaria, psoriasis, bullous pemphigoid, alopecia areata, and hidradenitis suppurativa.

#### BOX 1 Selection criteria for diseases encompassed by the epithelial barrier theory

- Increased prevalence after 1960s or 2000s that cannot (solely) be accounted for by novel diagnostic methods.
- Epithelial barrier defects and epithelitis (IL-1, IL-25, IL-33, and TSLP).
- Microbial dysbiosis with loss of biodiversity, loss of commensals, and colonization of opportunistic pathogens.
- Circulating inflammation as evidenced by elevated inflammatory cells, cytokines, or chemokines in the blood.
- Different and practically non-related diseases that fulfill these criteria appear as multimorbidities.

TABLE 1 Skin diseases in the context of the epithelial barrier theory.

Skin disease	Epidemiological evidence	Evidence for epithelial barrier disruption, microbial dysbiosis, and microinflammation
Atopic dermatitis	Epidemiological studies suggest that the prevalence of atopic dermatitis among children aged 0–7 years tripled in Denmark, from 3% in 1960–1964 to 10% in 1970–1974. <sup>77</sup> The prevalence of atopic dermatitis in young Finnish men increased from 0.15% to 2.90% during the period 1966–2017. <sup>78</sup>	Patients with atopic dermatitis exhibited increased transepidermal water loss, altered bioelectric properties in the epidermis, and reduced expression of tight junction proteins. <sup>83,84</sup> The expression of 4 tight junction genes (CLDN4, CLDN5, TJP1, and TJP2) was closely associated with microbial dysbiosis in the lesional skin of atopic dermatitis patients. <sup>17</sup> Serum from atopic dermatitis patients showed upregulation of inflammatory and cardiovascular risk proteins. <sup>87</sup>
Alopecia areata	The prevalence of alopecia areata in Japan has gradually increased from 0.16% in 2012 to 0.27% in 2019. <sup>509</sup>	The keratins KRT35, KRT83, and KRT81 were significantly downregulated in lesional tissue of individuals with alopecia areata relative to healthy controls. <sup>510</sup> Th1/Th2-related indicators were strongly linked with the clinical severity of alopecia areata. <sup>510,511</sup> Alopecia areata subjects showed over-colonization of <i>Propionibacterium acnes</i> along with a decreased relative abundance of <i>Staphylococcus epidermidis</i> compared with healthy controls. <sup>512</sup>
Allergic contact dermatitis	The reported clinical prevalence trends from Europe and North America show a notable rise in allergic contact dermatitis from the late 1960s to the mid-1970s. <sup>98,99</sup>	Skin biopsy specimens from patients with p-phenylenediamine (PPD)-related allergic contact dermatitis demonstrated downregulation of tight junction mRNAs and proteins after PPD exposure. <sup>103</sup> Despite a lack of direct data on changes in the skin microbiome, dysbiosis in allergic contact dermatitis is possible as also evidenced in studies of the skin microbiome in mouse models. <sup>513</sup>
Irritant contact dermatitis	One study from UK on healthcare workers showed that campaign to increase hand hygiene with increased hand washing increased irritant contact dermatitis. However, little other longitudinal epidemiological data is available. <sup>70</sup>	Atopic skin and filaggrin defects are major risk factors. <sup>68</sup> Pathogenesis starts with keratinocyte damage, followed by inflammatory cascade of neutrophils and T cells. <sup>69</sup>
Chronic spontaneous urticaria	Epidemiological data from the Italian Health Search IMS Health Longitudinal Patient Database showed that the annual prevalence of chronic spontaneous urticaria increased from 0.02% in 2002 to 0.38% in 2013. <sup>110</sup>	Urticaria patients exhibit elevated plasma levels of IL-17, IL-31, and IL-33 compared with healthy individuals. <sup>114</sup> Moreover, alterations in the gut microbiome and high levels of IL-31 and IL-33 were found in the serum of chronic urticaria patients. <sup>116</sup>
Psoriasis	The overall age- and sex-adjusted annual incidence of psoriasis in the United States has nearly doubled from 50.8 in the period 1970–1974 to 100.5 per 100,000 in the 1995–1999 time period. <sup>121</sup> The age- and sex-standardized cumulative prevalence of psoriasis in Ontario, Canada increased from 1.74% in 2000 to 2.32% in 2015. <sup>122</sup>	Psoriatic skin in humans presented a defective barrier function, an inflammatory state, and dysbiosis in the microbial composition. <sup>132,133</sup>
Rosacea	The epidemiological data on rosacea is very heterogeneous. The prevalence statistics published in Europe and the United States vary widely, ranging from less than 1% to more than 20% of the adult population. <sup>514</sup> Currently, there is little longitudinal data on the prevalence of rosacea	The lesional skin of rosacea patients showed significant alterations in barrier components. <sup>515,516</sup> Moreover, patients with rosacea showed significant differences in the skin microbiota from healthy controls. <sup>517</sup>
Pemphigus vulgaris	Annual incidence of pemphigus vulgaris in the northeast region of the state of Sao Paulo in Brazil increased from 1 case/year in 1988 to 7 cases/year in 2008. <sup>518</sup>	Patients with pemphigus vulgaris showed intercellular edema in epithelial cells, dissolution of intercellular bridges, higher levels of inflammatory Th1/Th17 cytokines (IFN- $\gamma$ , IL-17, and IL-23), and an imbalance in microbial composition. <sup>519–522</sup>
Bullous pemphigoid	Incidence of bullous pemphigoid in Minnesota (United States) showed an increase from 0.9/100,000 person-years in 1960–1969 to 4.2/100,000 in 1990–1999. <sup>142</sup> Incidence of bullous pemphigoid in France was 21.7 cases per million persons per year during the 2000–2005 period, which is approximately threefold higher than the incidence that was estimated 15 years ago. <sup>143</sup>	Blister fluids and skin lesions of bullous pemphigoid demonstrated a significant increase in thymic stromal lymphopoietin (TSLP) levels when compared to healthy controls. <sup>145</sup> Cutaneous microbial dysbiosis was found in patients with bullous pemphigoid compared with healthy controls. <sup>146</sup>

(Continues)

TABLE 1 (Continued)

Skin disease	Epidemiological evidence	Evidence for epithelial barrier disruption, microbial dysbiosis, and microinflammation
Hidradenitis suppurativa	Incidence of hidradenitis suppurativa in the United States showed an increase from 4.3 per 100,000 person-years in 1970–1979 to 9.6 per 100,000 person-years in 2000–2008. <sup>153</sup>	Lesioned skin of hidradenitis suppurativa showed upregulated inflammation (PI3, TNF- $\alpha$ , IL-1 $\beta$ , and IFN- $\gamma$ ), altered epithelial organization, and dysregulated metabolic signaling. <sup>148</sup> Multiple studies in humans support a dysbiotic skin microbiome in HS patients. <sup>149</sup>

### 3.1.1 | Atopic dermatitis

Atopic dermatitis (AD), also known as atopic eczema, is the most common chronic inflammatory skin disease worldwide. It presents with clinical features such as pruritus and eczematous changes.<sup>72</sup> AD often usually begins in early childhood and may persist into adulthood,<sup>73</sup> and AD is associated with an increased risk of developing allergic rhinitis, asthma, and chronic diseases at later stages.<sup>74–76</sup> Numerous epidemiological studies revealed an increasing prevalence of AD in industrialized countries since the 1960s. AD now affects up to 20% of the general population. The prevalence of AD among children aged 0–7 years tripled in Denmark, from 3% in 1960–1964 to 10% in 1970–1974.<sup>77</sup> The prevalence of AD in young Finnish men increased from 0.15% to 2.90% during the period 1966–2017.<sup>78</sup> Moreover, AD is more prevalent in urban areas compared with rural areas, suggesting that exposure to antigenic contaminants and limited exposure to infectious agents or other antigenic triggers may contribute to the development of AD.<sup>72</sup>

Genetic and/or acquired epidermal barrier dysfunction plays a crucial role in the pathogenesis of AD, as it facilitates penetration of allergens into the skin and promotes allergic sensitization.<sup>79</sup> Loss-of-function mutations in the filaggrin (FLG) gene represent the most significant genetic risk factor for atopic dermatitis (AD).<sup>80</sup> Individuals with FLG mutations have a more than threefold increased risk of developing AD compared with the general population.<sup>81</sup> Filaggrin (FLG) ensures the alignment of keratin filaments in the corneocytes and hydrates the stratum corneum, and is thereby crucial for maintaining skin barrier functions. FLG is synthesized as the polymer proflaggrin and resides in the outer nucleated layers of the epidermis. Two independent loss-of-function genetic variants (R510X and 2282del4) in FLG genes have been identified as extremely potent predisposing factors for AD and approximately 9% of Europeans carry these variants.<sup>82</sup> These variants have also been shown to have a highly significant association with asthma occurring on the basis of AD.<sup>82</sup> In addition, epidermal barrier defects triggered by environmental factors have been shown in patients with AD, as evidenced by increased transepidermal water loss (TEWL), defective bioelectric impedance of the epidermis, and ameliorated expression of TJ proteins.<sup>83,84</sup> The expression of four TJ genes (CLDN4, CLDN5, TJP1, and TJP2) was closely associated with microbial dysbiosis in the lesional skin of AD patients, in which *Staphylococcus aureus* showed a negative correlation and *S epidermidis*, *S hominis*, and *S haemolyticus* displayed a positive correlation.<sup>17,85</sup>

Mounting evidence indicates that AD patients are at increased risk of developing “allergic”/atopic comorbidities (e.g., asthma, rhinitis, and food allergies) and chronic diseases (e.g., cardiovascular disease and ischemic stroke),<sup>75,76,86</sup> which were attributed to microinflammation. Serum of AD patients exhibits significant upregulation of Th1, Th2, and Th1/Th17/Th22-associated proteins, as well as a broad array of proteins involved in atherosclerosis, tissue remodelling, and angiogenesis.<sup>87</sup> Recently, an increased rate of alopecia areata has also been associated with having one or more atopic comorbidities.<sup>88</sup>

### 3.1.2 | Alopecia areata

Alopecia areata (AA) has been increasingly associated with allergic or atopic conditions.<sup>89</sup> Studies showed that with each atopic comorbidity the risk of developing AA increases, and IL-13 has been a strong link to AA in GWAS studies.<sup>90</sup> Further, anti-Th2 treatment with dupilumab has been shown to regrow hair in AA patients with atopy and/or high IgE, and antihistamines were shown to have an adjuvant effect in AA treatment.<sup>91</sup> Similar to other atopic diseases such as AD, AA was also suggested to have a barrier defect with significant inhibition of hair keratins, with the decreased hair keratin expression likely due to increases in Th1, Th2, and other cytokines.<sup>92</sup>

### 3.1.3 | Allergic contact dermatitis

Allergic contact dermatitis (ACD) is a common inflammatory skin disease. It is caused by type IVa T1 delayed-type hypersensitivity responses to low molecular weight haptens that come into contact with the skin.<sup>93,94</sup> ACD presents with a wide range of symptoms, such as intensely pruritic erythema, edema, oozing, and even spongiotic vesicles.<sup>93</sup> Contact allergens or haptens are mainly reactive organic compounds or metal ions that bind to proteins and other biomolecules to trigger skin immune responses.<sup>95</sup> Around 4000 chemicals have been reported as potential triggers for ACD in humans,<sup>96</sup> presenting a wide range of symptoms, such as intensely pruritic erythema, edema, oozing, and even spongiotic vesicles.<sup>93</sup> The most common contact allergies are triggered by exposure to nickel, chromium, fragrances, and preservatives. Recently, it has been reported that diphenylprone induces the strongest immune response and barrier defects characteristic of ACD.<sup>97</sup> ACD has increased in

prevalence after the 1960s and currently affects up to 15%–20% of the general population.<sup>96</sup> The reported clinical prevalence trends of chromium-allergic contact dermatitis from Europe and North America show a notable increase in ACD from the late 1960s to the mid-1970s.<sup>98</sup> Similarly, the incidence of positive patch test reactions to nickel has significantly increased in most countries, for example, in Malmo, Sweden, female patients increased from 7% to 29% in 1962 and 1997, respectively.<sup>99</sup>

As the first line of defense, impaired skin barrier function facilitates the penetration of contact allergens into the epidermal layer to interact with cutaneous DCs, which can promote allergic sensitization.<sup>100</sup> Disruption of the epithelial barrier by dysregulated filaggrin is now known to be one of the underlying causes of ACD.<sup>101</sup> The association between loss-of-function mutations in FLG and ACD to nickel has been reported.<sup>100</sup> An increased risk of contact sensitization to substances other than nickel was further observed in FLG mutation carriers with self-reported dermatitis.<sup>102</sup> Moreover, dysregulation of TJ proteins is also involved in the development of ACD. Skin biopsy specimens from patients with p-phenylenediamine (PPD)-related ACD demonstrated downregulation of TJ proteins after PPD exposure.<sup>103</sup>

Despite limited data on microbial alterations in ACD skin, dysbiosis in ACD is possible as demonstrated in studies of the skin microbiome in animal models. An ACD mouse model showed that inflammatory responses and skin inflammation created a favorable environment for the colonization of the opportunistic bacteria *Faecalibaculum* and *Muribacter muris*, and can promote the depletion of native skin bacteria such as *Streptococcus*.<sup>104</sup>

### 3.1.4 | Irritant contact dermatitis

While the pathogenesis and epidemiology of AD and ACD are well-reported, studies on irritant contact dermatitis (ICD) are sparse. ICD is one of the most common diseases overall, with most of the population having mild irritant hand dermatitis. The most common irritant arises from wet work with direct contact to water for more than 2h per day, use of protective gloves over 2h per day, and/or washing hands more than 20 times per day. Other major irritants include soaps, detergents, disinfectants, solvents, and oils. ICD is more common in women than in men and the incidence seems to decrease with age. Atopic skin and FLG deficiency are major risk factors. Diagnosis is based on clinical features and includes the exclusion of ACD by patch tests.<sup>105</sup> In contrast to ACD, ICD is characterized by a non-specific inflammation. Danger signals damage and are sensed by keratinocytes, which start an inflammatory cascade involving T cells and neutrophils.<sup>106</sup>

A study based on the EPIDERM registry in the UK reported the change in the occurrence of ICD over time from 1996 to 2012. The findings showed that overall ICD was decreasing or remaining the same in most of the population except for healthcare workers. During the study period, there was a campaign to mitigate

transmission of infections by raising awareness of the importance of hand washing and antiseptic use. Healthcare workers developed significantly higher ICDs by the end of 2012.<sup>107</sup> Unfortunately, there is no longitudinal population data available yet on the impact of similar hygiene practices on COVID-19.

### 3.1.5 | Chronic spontaneous urticaria

Chronic spontaneous urticaria (CSU), classically known as chronic idiopathic urticaria (CIU), is a systemic immune-mediated disease. It presents with recurrent itchy wheals, sometimes with, which persist for more than 6 weeks without inducible causes.<sup>108</sup> These symptoms result from pathogenic activation of skin mast cells and basophils with the release of pre-formed vasoactive mediators (i.e., histamine, tryptase, and leukotrienes) and their delayed generation of cytokines.<sup>109</sup> Longitudinal epidemiological data revealed an increased prevalence of CSU after the 2000s. The annual prevalence of CSU in Italy based on data from the Health Search IMS Health Longitudinal Patient Database increased from 0.02% to 0.38% in 2002–2013 and the incidence rates ranged from 0.10 to 1.50 per 1000 person-years, with a trend toward a continuous increase.<sup>110</sup> The risk of CSU was significantly higher in subjects who suffered from obesity, anxiety, dissociative and somatoform disorders, or malignancies.<sup>110</sup>

Even though CSU is not a priori epidermal disorder, an overexpression of genes involved in terminal epidermal differentiation and barrier function was observed in CSU skin when compared to healthy control skin.<sup>111</sup> For example, filaggrin overexpression was observed in nonlesional CSU skin vs skin from healthy controls. Another study conducted in patients with CSU/CIU showed overexpressed filaggrin, and elevated filaggrin expression was positively correlated with urticaria severity in CSU/CIU.<sup>112</sup> An increased expression of filaggrin was suggested to promote histamine production, decreasing skin barrier formation by activation of the histamine receptor 1.<sup>113</sup>

Several independent studies have demonstrated elevated levels of pro-inflammatory cytokines in patients with CSU. A study conducted in 51 CSU patients and 20 healthy controls showed that plasma levels of IL-17, IL-31, and IL-33 were significantly elevated in CSU patients compared with healthy controls and that the severe group of patients had significantly higher IL-17 and IL-33 levels than the mild group.<sup>114</sup> Another study conducted in skin biopsies also demonstrated elevated levels of IL-33 in the lesional skin of CSU patients,<sup>115</sup> suggesting their use as potential biomarkers of disease severity or treatment response in CSU. An altered gut microbiota composition has been linked to inflammation. Patients with CSU demonstrated depletion of *Akkermansia muciniphila*, *Clostridium leptum*, and *Faecalibacterium prausnitzii* and a significant increase in relative amounts of the Enterobacteriaceae family compared with healthy controls.<sup>116</sup> Actually, *Akkermansia muciniphila* has been reported to exert anti-inflammatory properties, and Enterobacteriaceae family members are among the pro-inflammatory members of the gut microbiota.<sup>117</sup>

### 3.1.6 | Psoriasis

Psoriasis is a chronic, immune-mediated skin disease characterized by hyperproliferation and dysfunctional differentiation of keratinocytes.<sup>118</sup> The clinical manifestations are sharply demarcated, erythematous, pruritic plaques accompanied by silvery scales.<sup>119</sup> The prevalence of psoriasis is estimated to be between 2% and 4% of the population in Western countries<sup>120</sup> and appears to have an upward trend. The overall age- and sex-adjusted annual incidence of psoriasis in the United States has nearly doubled from 50.8 in the period 1970–1974 to 100.5 per 100,000 in the 1995–1999 time period.<sup>121</sup> Moreover, the age- and sex-standardized cumulative prevalence of psoriasis in Ontario, Canada, increased from 1.74% in 2000 to 2.32% in 2015.<sup>122</sup>

Clinical studies have shown that the IL-23–IL-17 axis plays a key role in the pathogenesis of psoriasis.<sup>123–125</sup> Activation of the IL-23–IL-17 axis is considered to be initiated by the activation of skin-resident DCs and their production of IL-23, driving T-cell production of type 17 cytokines such as IL-17 and IL-22. IL-17 activates epidermal keratinocytes to produce pro-inflammatory cytokines and chemokines, such as IL-1, IL-6, IL-31, CXCL1, and CCL20.<sup>126,127</sup> Moreover, in vitro studies show that IL-17 downregulates filaggrin expression and impairs skin TJs.<sup>128,129</sup> A defective barrier function and increased TEWL were also reported in psoriasis.<sup>130,131</sup> Takahashi et al. showed a 1.7-fold increase in TEWL of psoriatic skin compared with that of healthy skin.<sup>132</sup> A positive correlation has been shown between TEWL levels and the severity of psoriasis.<sup>130</sup> Moreover, psoriatic skin also revealed ameliorated stratum corneum hydration, a characteristic indicative of skin barrier disruption.<sup>132</sup> TEWL levels and stratum corneum hydration were restored to normal levels following clinical resolution of the psoriatic lesion,<sup>132</sup> suggesting that skin barrier function might be used to monitor disease activity and tailor appropriate psoriasis treatments to each patient.

New evidence suggests that the microbiome may play a pathogenic role in psoriasis.<sup>133</sup> A series of studies have compared compositional differences between the microbiomes of psoriatic and healthy skin.<sup>134–136</sup> Psoriatic lesional skin was demonstrated to have decreased relative abundance of *Propionibacterium*,<sup>135,136</sup> which is a major component of healthy skin microflora<sup>137</sup> that is known to modulate the immune system.<sup>138,139</sup> Loss of *Propionibacterium* has been shown to mitigate immune tolerance and increase the risk for psoriatic inflammation.<sup>140</sup>

### 3.1.7 | Bullous pemphigoid

Bullous pemphigoid (BP) is a common autoimmune bullous disease of the skin characterized by extremely polymorphic cutaneous manifestations, including urticaria-like and eczema-like lesions.<sup>141</sup> It mainly affects the elderly and the incidence has sharply increased over the past decades. The age- and sex-adjusted incidence of BP in the US white population showed an increase from 0.9/100,000 individuals in 1960–1969 to 4.2/100,000 individuals in 1990–1999.<sup>142</sup> A sharp increase in the incidence of BP was also reported in France

with an overall estimated incidence of 21.7 cases per 1 million individuals during the 2000–2005 period, indicating a nearly threefold increase in the incidence over the prior 15 years.<sup>143</sup> The increase in BP incidence was attributed to the concomitant increase in the elderly population and neurodegenerative disorders.<sup>142</sup>

BP is mainly induced and maintained by a Th2-polarized auto-immune response.<sup>144</sup> Type 2 cytokines, such as IL-4 and IL-6, and chemokines, thymus activation regulated chemokines (TARC), have been demonstrated to be significantly elevated in patients with BP compared with healthy controls.<sup>145</sup> TSLP, a cytokine that is secreted by barrier-defective skin into the systemic circulation, was upregulated in lesional skin and blister fluids of BP,<sup>145</sup> suggesting skin epithelial barrier dysfunction in BP patients. A disrupted epidermal barrier makes the skin particularly susceptible to colonization by many bacteria.<sup>146</sup> Emerging evidence revealed that BP might contribute to a loss of skin-protective microbiota and an increased abundance of *Staphylococcus aureus*.<sup>147</sup>

### 3.1.8 | Hidradenitis suppurativa

Hidradenitis suppurativa (HS) is a chronic, recurrent, inflammatory skin disorder with clinical manifestations of painful inflammatory nodules, abscesses, and draining sinus tracts in areas bearing apocrine glands, such as axillae, breasts, buttocks, and groins.<sup>148,149</sup> HS has been reported to be associated with smoking, obesity, and inflammatory bowel disease.<sup>150–152</sup> The incidence of HS has risen over the past four decades in the United States, showing an increase from 4.3 per 100,000 person-years in 1970–1979 to 9.6 per 100,000 person-years in 2000–2008.<sup>153</sup> Additionally, 70.2% of HS patients were smokers, 54.9% obese, 42.9% were diagnosed with depression, and 36.2% with acne. Of these, smoking was significantly associated with HS severity.<sup>153</sup>

A meta-analysis revealed that upregulated inflammation, altered epithelial cell differentiation, and dysregulated metabolism signaling may potentially contribute to HS pathogenesis.<sup>148</sup> Highly upregulated pro-inflammatory molecules, including IFN- $\gamma$  and IL-1 $\beta$ , have been identified in HS lesioned skin,<sup>154,155</sup> suggesting the involvement of an initial inflammatory reaction in HS patients. Moreover, overexpression of specific genes, such as *SERPINS*, *SPRR3*, *KRT6*, and *KRT16*, confirms the impairment of barrier function in the early phases of HS pathogenesis.<sup>148,156</sup> Multiple studies have demonstrated an altered skin structure in HS with abnormal expression and location of AJs, cytokeratins, desmosomes, and integrins.<sup>157–160</sup> Several downregulated genes associated with metabolic-related syndromes, including metabolic syndrome and obesity, have been identified in HS lesions, suggesting concomitant HS and metabolic-related disorders in the patients.<sup>148,161,162</sup>

Multiple studies in humans support a dysbiotic skin microbiome in HS patients and a consensus has been established that there is an increased abundance of anaerobic and opportunistic pathogens including *Corynebacterium*, *Prevotella*, and *Porphyromonas* at the expense of normal skin symbiosis (i.e., *Cutibacterium*) in HS skin.<sup>149</sup> The

pathogenic bacteria *Corynebacterium*, *Prevotella*, and *Porphyromonas* have been reported to activate Toll-like receptor 2 (TLR2) and/or TLR4 across various cell types.<sup>163–165</sup> Reverse transcriptase polymerase chain reaction and immunohistochemical analysis of HS skin revealed an elevated expression of TLR2 in dermal macrophages and DCs of HS skin.<sup>166</sup> This supports the potential for dysbiosis to promote inflammation in HS skin via TLRs.

## 3.2 | Airway diseases

The airway epithelial barrier represents the first line of defense against inhaled airborne particulate matter and pathogens. Inhalation of airborne pollutants may impair the airway epithelial barrier function and subsequently lead to excessive inflammatory responses and susceptibility to microbial infection,<sup>167</sup> which are key hallmarks of several airway diseases (Table 2), such as asthma, allergic rhinitis, chronic rhinosinusitis, chronic obstructive pulmonary disease, and idiopathic pulmonary fibrosis.

### 3.2.1 | Asthma

Asthma is a heterogeneous disease characterized by intermittent wheeze and airway inflammation,<sup>168</sup> affecting all ages with an estimated 300 million cases worldwide.<sup>169</sup> Asthma prevalence has been increasing over the past few decades. For example, a 20-fold increase in asthma, from 0.08% in 1961 to 1.79% in 1989, was reported in Finnish candidates for military recruitment.<sup>170</sup> The annual emergency hospital admissions for asthma in the UK rose across all age groups, from the early 1960s to the early 1970s.<sup>171</sup>

Allergic asthma is a type 2 immune disease and the majority of asthma patients are characterized by an overexpression of type 2 inflammatory pathways.<sup>172</sup> Exposure to environmental stimuli leads to airway epithelial damage and induces the production of alarmins (IL-25, IL-33, and TSLP), followed by type 2 inflammation.<sup>172</sup> Specifically, a subset of the patients demonstrates non-type 2 mechanisms in which they display a neutrophil-dominant presentation and are characterized by low (or even absent) Th2 cytokines.<sup>173</sup> Studies on airway biopsies from asthmatic patients showed patchy disruption of TJs with reduced expression of epithelial zonula occludens 1 (ZO-1), E-cadherin and  $\alpha$ -catenin, and an increased influx of eosinophils into the epithelium.<sup>12,174</sup> Moreover, airway epithelial brushings from subjects with asthma exhibited remarkably decreased claudin-18 mRNA levels compared with healthy controls, which showed an inverse association with type 2 inflammation.<sup>175</sup>

The link between microbial dysbiosis and the pathogenesis of asthma has been reported in the last decade.<sup>176</sup> In an analysis of data from the National Health and Nutrition Examination Survey based on the US population, nasal colonization with *Staphylococcus aureus* was linked to an elevated risk of asthma prevalence, symptoms, and aggravation in children and young adults.<sup>177</sup> In addition, 16S rRNA bacterial sequences from the airways of asthmatic children and

adults exhibited disordered microbial communities with higher levels of pathogenic Proteobacteria, particularly *Haemophilus*, and ameliorated levels of Bacteroidetes, particularly *Prevotella*, compared with controls.<sup>178</sup> Microbial production of histamine in the gut was highest in asthma patients with severe disease.<sup>179</sup> In addition, obese asthmatics displayed significantly greater changes in microbiota composition and inflammatory responses, compared with lean asthmatics or obese controls.<sup>180</sup> The development of asthma in childhood is strongly associated with alterations in the microbiota that results in a loss of the protective effects of the “normal” microbiota, including the production of immunoregulatory short-chain fatty acids; among adults with established asthma, variations in the microbiota were associated with the severity of asthma.<sup>176,181</sup>

### 3.2.2 | Allergic rhinitis

Allergic rhinitis (AR) is a common inflammatory disease of the nasal mucosa and its classic symptoms are nasal itch, sneezing, rhinorrhea, and nasal congestion.<sup>182</sup> Similar to allergic asthma, it involves an IgE-mediated response to inhaled allergens and mucosal inflammation driven by Th2 cells.<sup>183</sup> In general, the prevalence of AR has risen globally since the 1960s, coinciding with an increase in the prevalence of atopic disorders.<sup>184</sup> A 100-fold increase in AR prevalence was found in young Finnish men from 0.06% in 1966 to 6.46% in 1993, with a peak in 2000 (8.88%).<sup>78</sup> Currently, the worldwide prevalence of AR in adults was reported to be 18.1% based on 310 reported prevalences.<sup>185</sup>

Multiple investigations support the notion that the structure and function of the airway epithelial barrier are disrupted in AR, and it is regarded as one of the underlying causes for the onset of AR.<sup>186</sup> Patients with house dust mite-induced AR showed decreased transepithelial resistance in vitro and ex vivo, enhanced permeability of FITC-dextran 4 kDa and mitigated expression of TJ molecules occludin and ZO-1.<sup>187</sup> Moreover, an increased permeability of the nasal mucosa and decreased ZO-1 expression were also observed in an AR mouse model.<sup>188</sup> Th2 cells and their cytokines, as well as ILCs, appear to be key contributors to barrier leakiness in AR patients.<sup>189</sup>

A plethora of studies suggest that an altered microbial composition in the nasal mucosa is implicated in the development of AR.<sup>190</sup> Kim et al. demonstrated microbial alterations in AR patients at the genera and species levels, and *Staphylococcus aureus* showed the greatest abundance (37.69%) in the nasal mucosa and was associated with a positive response to house dust mites.<sup>191</sup> Another study found an increased abundance of *Streptococcus salivarius* in the nasal microbiome of patients with AR, promoting inflammatory cytokine release and morphological changes in the nasal epithelium.<sup>192</sup>

### 3.2.3 | Chronic rhinosinusitis

Chronic rhinosinusitis (CRS) is an inflammatory disease of the paranasal sinuses and diagnosed clinically with at least two of four

TABLE 2 Airway diseases in the context of the epithelial barrier theory.

Airway disease	Epidemiological evidence	Evidence for epithelial barrier disruption, microbial dysbiosis, and microinflammation
Asthma	The prevalence of asthma among Finnish candidates for military recruitment increased 20-fold from 0.08% in 1961 to 1.79% in 1989. <sup>170</sup> The annual emergency hospital admissions for asthma in the UK increased across all age groups from the early 1960s to the early 1970s. <sup>171</sup>	Asthma is a type 2 inflammatory disease with the majority of patients eliciting an overexpression of type 2 inflammatory pathways. <sup>172</sup> Airway biopsies from asthmatic patients showed a patchy disruption of TJs, reduced expression of epithelial zonula occludens 1 (ZO-1), E-cadherin, and $\alpha$ -catenin, and an increased influx of eosinophils in the epithelium. <sup>12</sup> The airways of asthmatic subjects displayed altered microbial communities with more pathogenic Proteobacteria, particularly <i>Haemophilus</i> spp. and reduced levels of <i>Bacteroidetes</i> , particularly <i>Prevotella</i> spp., compared with controls. <sup>178</sup>
Allergic rhinitis	The prevalence of allergic rhinitis in young Finnish men increased 100-fold, from 0.06% in 1966 to 6.46% in 1993, with a peak in 2000 (8.88%). <sup>78</sup>	Patients with house dust mite-induced allergic rhinitis showed a decreased transepithelial resistance in vitro and ex vivo, an increased permeability of FITC-dextran 4 kDa and a reduced occludin and ZO-1 expression. <sup>187</sup> Moreover, the microbiota in the nasal mucus of AR patients was altered at the level of microbial genera and species; <i>Staphylococcus aureus</i> showed the greatest abundance (37.69%) in the nasal mucus and was associated with a positive response to house dust mites. <sup>191</sup>
Chronic rhinosinusitis	Chronic rhinosinusitis affects nearly 15% of the US population, and an increasing prevalence has been reported since 1991. <sup>195,196</sup>	Air-liquid interface cultures of epithelia from patients with chronic rhinosinusitis showed a disrupted epithelial barrier with an altered expression pattern in TJs; the sinus epithelial integrity was downregulated by Th1 (IFN- $\gamma$ ) and Th2 (IL-4) cytokines in vitro. <sup>13</sup> Chronic rhinosinusitis subjects showed aberrant bacterial communities characterized by reductions in numerous common core bacterial taxa, decreased bacterial diversity, increased inter- and intra-subject variability, and increased bacterial burden. <sup>202</sup>
Chronic obstructive pulmonary disease	The incidence of chronic obstructive pulmonary disease (COPD) began increasing in the early 1960s in the population of Yokkaichi-city (Mie Prefecture, Japan). <sup>209</sup> From 1980 to 2000, annual mortality rates for COPD increased from 40.7 to 66.9 per 100,000 population in the United States. <sup>210</sup>	Airway sections from patients with COPD demonstrated a disrupted expression of tight junction proteins. <sup>213</sup> Cultured bronchial epithelial cells from ex-smoking patients with COPD displayed abnormalities with reduced capacity to form epithelial junctions during air-liquid interface differentiation in vitro. <sup>213</sup> Moreover, studies on sputum samples from subjects with COPD demonstrated that microbial dysbiosis and eosinophilic inflammation were associated with increased exacerbation severity. <sup>217</sup>
Idiopathic pulmonary fibrosis	Idiopathic pulmonary fibrosis (IPF) emerged during the second half of the 20th century, coinciding with an increase in cigarette smoking. <sup>219</sup> The number of recorded deaths from IPF clinical syndrome (IPF-CS) in England and Wales rose sixfold from 1968 to 2008, and the incidence of IPF-CS in primary care increased by 35% from 2000 to 2008. <sup>220</sup>	Lung specimens from patients with idiopathic pulmonary fibrosis showed an altered expression of tight junction proteins even those distant from fibroblastic foci, as in the case of claudin-2 and claudin-4, suggesting a generalized barrier dysfunction in the lungs of IPF patients. <sup>222</sup> Moreover, clinical evidence and animal models showed that lung microbiota changes may aggravate pulmonary inflammation and disease progression in IPF. <sup>224</sup>
Nonallergic rhinitis with eosinophilia syndrome	Nonallergic rhinitis with eosinophilia syndrome (NARES) was first described in 1981. <sup>523</sup> Although the epidemiology of NARES is not clear, it is estimated that 200 million people worldwide suffer from NARES, 50 millions of them living in Europe and 17 million living in the United States. <sup>524,525</sup>	Nonallergic eosinophilic inflammation in mice was demonstrated upon chronic airborne PM exposure, along with sinonasal epithelial barrier damage. <sup>526</sup>
Sarcoidosis	The number of reported cases of sarcoidosis in Japan has shown a sharp increase since 1960. <sup>527</sup>	Open lung biopsy specimens from patients with sarcoidosis exhibited ultrastructural lesions of the air-blood barrier; elevated levels of serum Clara cell protein (CC16) in sarcoidosis patients resulted from an increased intravascular leakage of the protein across the air-blood barrier. <sup>528,529</sup> The concentration of many cytokines and chemokines was elevated in serum and BAL of sarcoidosis patients. <sup>530</sup>

TABLE 2 (Continued)

Airway disease	Epidemiological evidence	Evidence for epithelial barrier disruption, microbial dysbiosis, and microinflammation
Pulmonary hypertension	In the late 1960s, an epidemic of primary pulmonary hypertension occurred in Switzerland, Austria, and Germany shortly after the introduction of aminorex fumarate, a potent anorexigen. <sup>531</sup> The age-adjusted proportion of pulmonary hypertension hospitalizations in the United States increased by 44%, from 91 per 100,000 in 2001/2002 to 131 per 100,000 in 2009/2010. <sup>532</sup>	A rat model of pulmonary hypertension indicated that early progression of pulmonary hypertension was associated with increased lung permeability. <sup>533</sup> An altered lung and gut metabolome was also observed in a pulmonary hypertension rat model. <sup>534</sup>
Cystic fibrosis	The number of cystic fibrosis patients reported by the US CF Registry Year Source increased from ~15,000 in 1986 to over ~26,000 in 2010. <sup>535</sup>	Intestinal paracellular permeability is 4–10 times higher in patients with cystic fibrosis than in healthy controls. <sup>536</sup> Moreover, patients with cystic fibrosis showed disrupted intestinal microbiota and intestinal inflammation. <sup>537,538</sup>

symptoms (e.g., sinus pressure, rhinorrhea, nasal obstruction, and hyposmia/anosmia) persisting for at least 12 weeks.<sup>193,194</sup> CRS affects nearly 15% of the US population and has been reported to be increasing in prevalence since 1991,<sup>195,196</sup> placing an immense burden on both patients and the healthcare system.

Although the pathogenesis of CRS is still elusive, there is strong evidence suggesting that epithelial barrier defects and inflammation play a role. Air-liquid interface cultures of epithelia from patients with CRS showed a disrupted epithelial barrier with an altered expression pattern in TJs,<sup>13</sup> and claudin-3 has been identified as a potential biomarker for predicting nasal epithelial barrier defects and disease severity in CRS with nasal polyps (NPs).<sup>197</sup> Evidence showed that the sinonasal epithelial integrity was downregulated by Th1 (IFN- $\gamma$ ) and Th2 (IL-4) cytokines in vitro.<sup>13</sup> Van Bruaene et al. also reported that CRS with NPs patients in Western populations display a Th2 type inflammatory profile,<sup>198</sup> whereas CRS patients without NPs show a Th1 type.<sup>199</sup> In addition, patients with the same phenotype of CRS (e.g., CRS with NPs) may have different endotypes due to different functional or pathophysiologic findings. NPs from patients with eosinophilic CRS (eCRS) showed elevated levels of expression of *IL4*, *IL5*, *IL13*, *TSLP*, and *IL1RL1* (ST2 [an IL-33 receptor]), whereas NPs from patients with non-eCRS showed elevated levels of expression of *IL17A*.<sup>200</sup>

There is mounting evidence linking sinus microbiota dysbiosis to the pathogenesis of CRS.<sup>201</sup> Clinical studies have revealed that the CRS microbiome is characterized by a loss of numerous common core bacterial taxa, decreased bacterial diversity, and colonization by pathogenic bacteria as compared to healthy controls.<sup>202,203</sup> Anaerobic taxa, such as *Bacteroides*, *Corynebacterium*, *Fusobacterium*, *Peptostreptococcus*, *Prevotella*, and *Veillonella*, gradually replace the persistent aerobic microorganisms in the healthy sinuses with the development of CRS.<sup>204</sup>

### 3.2.4 | Chronic obstructive pulmonary disease

Chronic obstructive pulmonary disease (COPD) is a slowly progressing chronic respiratory disorder characterized by partially reversible

airflow obstruction, chronic airway inflammation, and an accelerated decline of lung function.<sup>205,206</sup> Common symptoms include breathlessness, wheezing, coughing, and sputum production.<sup>207</sup> COPD has been listed as the third leading cause of death worldwide,<sup>208</sup> and increases in its incidence and mortality were reported in the last decades. The incidence of COPD began increasing in the early 1960s in the population of Yokkaichi City (Mie Prefecture, Japan).<sup>209</sup> Between 1980 and 2000, annual rates for deaths with COPD increased from 40.7 to 66.9 per 100,000 population in the United States.<sup>210</sup> Although the most common cause of COPD is cigarette smoking, several other factors can cause or worsen COPD, including environmental exposures (e.g., air pollution, chemical vapors, and heavy exposure to dust) and genetic predisposition.<sup>207</sup>

Numerous studies have shown that airway epithelial barrier dysfunction is involved in the pathogenesis of COPD. Genome-wide gene expression analysis revealed an association of COPD with genes enriched for epithelial barrier function.<sup>211</sup> Clinical evidence demonstrated that patients with COPD showed loss of epithelial cell–cell contact, increased permeability, and disrupted expression of AJ and TJ proteins, including E-cadherin,  $\beta$ -catenin, occludin, and ZO-1.<sup>39,212,213</sup> In addition, airway barrier dysfunction may lead to altered immune responses and increased susceptibility to infection, which also plays an important role in the pathogenesis of COPD. Clinical trials have shown that eosinophilic airway inflammation and upregulated interleukin IL-1 $\beta$ , IL-17A, and IL-22 levels are present in a subset of COPD patients.<sup>214–216</sup> Moreover, a shift in pulmonary microbiota toward Proteobacteria and Firmicutes was observed in COPD patients.<sup>39</sup> Of note, studies on sputum samples from subjects with COPD demonstrated that microbial dysbiosis and eosinophilic inflammation were associated with increased exacerbation severity.<sup>217</sup>

### 3.2.5 | Idiopathic pulmonary fibrosis

Idiopathic pulmonary fibrosis (IPF) is a chronic, progressive interstitial lung disease characterized by recurrent epithelial cell injury, senescent alveolar epithelium, and aberrant accumulation of fibrotic

tissue in the lungs parenchyma.<sup>218</sup> IPF emerged during the second half of the 20th century, coinciding with the increase in cigarette smoking.<sup>219</sup> The number of recorded deaths of IPF clinical syndrome (IPF-CS) in England and Wales rose sixfold from 1968 to 2008, and the incidence of IPF-CS in primary care increased by 35% from 2000 to 2008.<sup>220</sup> Besides smoking, genetic factors and environmental exposures have also been linked to the onset of IPF.<sup>221</sup>

Mounting evidence points IPF as an epithelial-driven disease. IPF lung specimens showed elevated claudin-2 expression in broncholar and alveolar epithelium and ameliorated claudin-4 expression in type II pneumocytes, suggesting epithelial barrier damage in the lungs of IPF patients.<sup>222,223</sup> Moreover, lung microbial dysbiosis was closely associated with IPF disease progression.<sup>224</sup> Molyneaux and colleagues demonstrated a twofold higher bacterial burden in the BAL of IPF patients compared with healthy controls.<sup>225</sup> Lung bacterial burden predicts fibrosis progression, and notably, decreased lung bacterial diversity is associated with the production of alveolar profibrotic cytokines, such as IL-1Ra and IL-1 $\beta$ .<sup>224</sup> Thus, the lung microbiota contributes to alveolar inflammation and IPF progression. Recently studies have been focused on pirfenidone, a synthetic chemical that inhibits the prevention or removal of excessive scar tissue deposition in several organs through the production of multiple factors, such as transforming growth factor-beta 1 (TGF- $\beta$ 1), tumor necrosis factor-alpha (TNF- $\alpha$ ), platelet-derived growth factor (PDGF), interleukin 1 beta (IL-1 $\beta$ ), and collagen 1 (COL1A1).<sup>226</sup>

### 3.3 | Digestive tract diseases

A wide range of environmental antigens, including food-derived antigens, emulgators/emulsifiers, detergents, and commensal bacteria, interact with the epithelial layer of the digestive tract. Disruption of this epithelial barrier has been implicated in the pathogenesis of a number of digestive tract diseases (Table 3). This may be due to an impaired epithelial barrier function that facilitates the translocation of microbiota and their metabolites, penetration by allergens, and/or migration of activated immune cells.

#### 3.3.1 | Eosinophilic esophagitis

Eosinophilic esophagitis (EoE) is a chronic type 2-associated inflammatory disease primarily induced by food antigens and characterized by esophageal dysfunction and eosinophil-predominant inflammation.<sup>227</sup> EoE, first reported in the 1970s as a case-reportable disorder<sup>228</sup> and characterized as a clinicopathologic entity in the 1990s,<sup>229</sup> has been steadily increasing in its incidence and prevalence. A population-based study found that the EoE incidence among children in Olmsted County, Minnesota, USA, was 5.31 per 100,000 population person-years in 1995, 15.2 in 2005, and 19.2 in 2015 after adjusting for age and sex.<sup>230</sup> The current prevalence of EoE in adults and children is 32.5 and 30.9/100,000 inhabitants, respectively, according to a large meta-analysis.<sup>231</sup> Several risk factors

were associated with EoE, including genetic predisposition, allergic/atopic conditions, antibiotic use, and environmental factors.<sup>232</sup> Importantly, EoE may be successfully treated by food elimination in a fraction of patients, frequently even with an exclusive single-food milk elimination, strongly undermining the notion, that EoE may be one distinctive and extreme form of food allergy.<sup>233,234</sup>

Studies have reported that epithelial barrier dysfunction plays a crucial role in the pathogenesis of EoE. Esophageal mucosal impedance values, which represent an indirect surrogate of barrier dysfunction, were significantly lower in patients with active EoE (1909 $\Omega$ ) than inactive EoE (4349 $\Omega$ ) or controls (5530 $\Omega$ ).<sup>235</sup> Analysis of biopsies from patients with EoE identified elevated expression levels of TSLP, cathelicidin, and proteases, as well as a decreased expression of filaggrin, E-cadherin, claudin, occludin, and demoglein-1.<sup>236</sup> A damaged epithelial barrier may provide a favorable environment for antigen presentation, leading to persistent chronic inflammation associated with microbial dysbiosis.<sup>237</sup> Multiomics analysis revealed dysbiosis of esophageal microbiota as a main feature of EoE.<sup>238</sup> An elevated bacterial load was demonstrated in EoE subjects, regardless of treatment status, showing the enrichment of *Proteobacteria*, *Haemophilus*, and *Streptococcus*.<sup>239</sup>

#### 3.3.2 | Gastroesophageal reflux disease

Gastroesophageal reflux disease (GERD) is a gastrointestinal motility disorder that results from the involuntary backflow of stomach contents into the esophagus, causing heartburn, regurgitation, mucosal damage, and epigastric pain.<sup>240</sup> The prevalence of GERD has been on the rise since the 1970s. A study by the US Department of Veterans Affairs found that the rate of GERD hospitalizations increased from 61.2 per 10,000 hospitalizations in 1970–1974 to 315.6 per 10,000 hospitalizations in 1990–1995.<sup>241</sup> A meta-analysis demonstrated that obesity was associated with a significant increased risk of GERD.<sup>242</sup>

Of notice, the most common manifestation of GERD is heartburn, a reflection of acid damage to the esophageal epithelium. Studies have indicated that an acid-induced enhanced paracellular permeability of the esophageal epithelium is involved as an early event in the pathogenesis of GERD.<sup>243,244</sup> In addition to gastric acid, components of duodenal reflux, such as bile salts and pancreatic enzymes, may also disrupt esophageal barrier function by modulating the expression of AJ and TJ proteins.<sup>245</sup> Other studies found that exposure of esophageal squamous epithelial cells to acidified bile salts sharply promoted IL-8 and IL-1 $\beta$  secretion, supporting an alternative concept that gastroesophageal reflux evokes a cytokine-mediated immune response, resulting in the esophageal epithelial damage.<sup>246</sup> Moreover, accumulating data support the role of esophageal microbiota in the development of GERD. Microbial dysbiosis was also found in GERD patients when compared to controls. There was a loss of the dominant genera in the GERD group with concomitant increase in Gram-negative bacteria, particularly *Campylobacter* which is closely associated with IL-18 production in epithelial cells.<sup>247</sup>

TABLE 3 Digestive tract diseases in the context of the epithelial barrier theory.

Digestive tract disease	Epidemiological evidence	Evidence for epithelial barrier disruption, microbial dysbiosis, and microinflammation
Eosinophilic esophagitis	The incidence of eosinophilic esophagitis (EoE) among children in Olmsted County, Minnesota, USA, was 5.31 per 100,000 population person-years in 1995, 15.2 in 2005, and 19.2 in 2015 after adjusting for age and sex. <sup>230</sup> The current prevalence of EoE in adults and children is 32.5 and 30.9/100,000 inhabitants, respectively, according to a large meta-analysis. <sup>231</sup>	Esophageal mucosal impedance values, which represent an indirect surrogate of barrier dysfunction, were significantly lower in patients with active EoE (1909 Ω) than inactive EoE (4349 Ω) or controls (5530 Ω). <sup>235</sup> Analysis of EoE tissue samples showed increased expression levels of TSLP, cathelicidin, and proteases, and decreased expression of filaggrin, E-cadherin, claudin, occludin, and demogelin-1. <sup>236</sup> Multiomic analysis revealed dysbiosis of esophageal microbiota as a main feature of eosinophilic esophagitis. <sup>238</sup>
Periodontitis	The global prevalence of periodontitis increased 99.0% from 546,434,147 to 1,087,367,744 from 1990 to 2019. <sup>539</sup>	Periodontitis gingival tissues exhibited reduced expression of genes involved in epithelial barrier defense. Upregulation of IL-17 was also found, which is associated with a hyperinflammatory response and a distinct microbial community in periodontitis. <sup>540</sup>
Gastroesophageal reflux disease	The prevalence of gastroesophageal reflux disease began to rise in the 1970s. A study by the US Department of Veterans Affairs found that the proportion of hospitalizations with gastroesophageal reflux disease increased from 61.2 per 10,000 hospitalizations in 1970–1974 to 315.6 per 10,000 hospitalizations in 1990–1995. <sup>241</sup>	Endoscopic biopsies of gastroesophageal reflux disease patients and a rat model of gastroesophageal reflux disease indicated a loss of esophageal barrier function and elevated expression of inflammatory markers, including IL-8. <sup>245,246</sup> An altered microbiota composition was also found in patients with gastroesophageal reflux disease when compared with controls. <sup>247</sup>
Barrett's esophagus	The first Barrett's esophagus (>3 cm) was found in 1969. A study of Olmsted County, Minnesota residents found that the incidence of clinically diagnosed Barrett's esophagus (>3 cm) increased 28-fold from 0.37/100,000 person-years in 1965–1969 to 10.5/100,000 in 1995–1997. <sup>250</sup>	Patients with Barrett's esophagus manifested a near threefold increase transepithelial leakage, a strong difference in the expression of claudin TJ protein, and an alteration of the microbiome, when compared with healthy controls. <sup>254,255</sup> This condition was associated with an increased risk for the development of esophageal adenocarcinoma. <sup>541</sup>
Food allergy	In the UK, the rates of hospital admissions for food anaphylaxis rose from 1.2 to 2.4/10 <sup>5</sup> population between 1998 and 2012, with children aged 0–4 years being the most susceptible. <sup>260</sup> In Australia, the rates of hospital admissions for food anaphylaxis increased fourfold, from 2 to 8.2/10 <sup>5</sup> population between 1998/1999 and 2011/2012. <sup>261</sup> In New Zealand, the rates of hospital admissions for food anaphylaxis increased from 3.3 to 5.8/10 <sup>5</sup> population between 2002 and 2011 in individuals aged 15 years or greater. <sup>542</sup> In the United States, the rates of hospital admissions for food anaphylaxis more than doubled in those aged 0–18 years between 2000 and 2009. <sup>543</sup>	96% of patients with food allergy exhibited functional and structural barrier defects as visualized in the terminal ileum and at two colorectal sites by confocal laser endomicroscopy. <sup>265</sup> Moreover, increasing evidence from human studies and mouse models of food allergy showed an association of food allergy with microbial dysbiosis, type 2 inflammation, and epithelial cell-derived cytokine (TSLP, IL-33, and IL-25) production. <sup>266,267,269</sup>
Food protein-induced enterocolitis syndrome	The incidence of food protein-induced enterocolitis syndrome (FPIES) diagnosis increases across the time span 2010–2014, and then again from 2015 to 2018. <sup>544</sup>	Serum samples of patients with FPIES exhibited significantly increased expression of regenerating family member 1 alpha, which is regarded as the mucosal damage marker, as well as elevated levels of cytokines and chemokines including IL17A, IL-22, IL-17C, and CCL20. <sup>545</sup> FPIES infants showed an alteration of the gut microbiome when compared with allergy-free infants. <sup>546</sup>
Inflammatory bowel disease	There is a clear increase in incidence and prevalence of IBD on a global scale, with an even steeper rise in emerging countries. Between 1995 and 2016, the incidence per 100,000 person-years in Denmark increased from 9.1 to 17.8 for Crohn's disease, and from 21.0 to 28.4 for ulcerative colitis. <sup>273</sup>	Biopsy specimens from patients with inflammatory bowel disease showed an impaired intestinal barrier function, as evidenced by significantly reduced epithelial resistance, reduced and discontinuous tight junctions, and changes in the expression of claudins. <sup>277,278</sup> Patients with inflammatory bowel disease showed alterations in the gut microbiota, mainly manifested by loss of bacterial diversity and changes in the composition of the microbiota, which were reported to be associated with local inflammation. <sup>280–282</sup>

(Continues)

TABLE 3 (Continued)

Digestive tract disease	Epidemiological evidence	Evidence for epithelial barrier disruption, microbial dysbiosis, and microinflammation
Celiac disease	The prevalence of diagnosed celiac disease has doubled every decade in Denmark from 14 per 100,000 persons in 1986 and 180 per 100,000 persons in 2016. <sup>284</sup> Current estimations of the prevalence are at least 0.7% in the general population in the western countries and the majority of patients are considered undiagnosed, that is, tip of the iceberg phenomenon. <sup>286</sup>	Duodenal biopsies from celiac disease patients showed an altered expression of TJ proteins claudin-2, -3, -5, and -7 and ZO-1, reduced and discontinuous TJ strands, and an increase in paracellular biotin-NHS uptake. <sup>287,289</sup> Patients with celiac disease showed alterations in the intestinal microbiota, particularly with an increase in Gram-negative bacteria and a decrease in Gram-positive bacteria. <sup>291</sup>
Irritable bowel syndrome	Irritable bowel syndrome is increasing in incidence and prevalence in Asia resulting from an uptake of a Westernized diet and lifestyle. The prevalence was reported to be <5% in a cross-sectional study from Thailand that was published in 1988, while studies published since 2000 found a prevalence of 6%–9%. <sup>292</sup>	Diarrhea-predominant irritable bowel syndrome patients show altered epithelial permeability and mucosal microinflammation in both proximal and distal regions of the intestine. <sup>295,296</sup> These findings can potentially be used for diagnostic purposes in the near future to identify food items triggering barrier dysfunction and symptoms. <sup>297</sup> Moreover, microarray analysis in colonic biopsies of irritable bowel syndrome patients describes significant changes in the expression and secretion of selected pro-inflammatory cytokines and the impairment of mucosal immune response to microbial pathogens. <sup>299,300</sup>
Colonic diverticulosis	Annual age-standardized hospital admission rates for diverticular disease of the colon in England increased by 16% for males (from 20.1 to 23.2 per 100,000) and 12% for females (from 28.6 to 31.9 per 100,000) between 1989/1990 and 1999/2000. <sup>302</sup> The prevalence of colonic diverticulosis has increased from 13% in 1990–2000 to 24% in 2001–2010 in Asia. <sup>303</sup>	Patients with colonic diverticulosis displayed lower transepithelial electrical resistance, increased paracellular permeability, increased colonic macrophages, and depletion of microbiota members with anti-inflammatory activity associated with mucosal macrophage infiltration when compared to the control group. <sup>310,311</sup>
Microscopic colitis	The incidence of microscopic colitis in Denmark increased from 2.3 cases per 100,000 person-years in 2001 to 24.3 cases per 100,000 person-years in 2016. <sup>547</sup>	Biopsies from the sigmoid colon of patients with microscopic colitis showed decreased epithelial resistance and increased levels of IL-1 $\beta$ , IFN- $\gamma$ , and TNF- $\alpha$ . <sup>548</sup> A significant higher microbial dysbiosis index was observed in active microscopic colitis when compared to healthy controls. <sup>549</sup>

### 3.3.3 | Barrett's esophagus

Barrett's esophagus (BE) is a precancerous condition in which a specialized columnar epithelium replaces squamous cells in the distal esophagus.<sup>248</sup> It has become a global health concern due to the consumption of processed foods, greenhouse emissions, and smoking, affecting 1.6% to 6.8% of the global population.<sup>249</sup> A study of Olmsted County, Minnesota, USA, residents found that the incidence of clinically diagnosed BE (>3 cm) increased 28-fold from 0.37 per 100,000 person-years in 1965–1969 to 10.5 per 100,000 person-years in 1995–1997.<sup>250</sup> Patients usually do not experience symptoms, except in those that have been previously diagnosed with GERD and might be a pre-developmental case,<sup>251</sup> of which around 10%–15% of GERD patients may be at risk of converting the lining of the esophagus and develop BE.<sup>252</sup>

Studies indicate that Barrett's epithelium is a typical precancerous epithelium that forms a highly paracellular leaky area across the otherwise highly efficient epithelial barrier of the normal esophagus. BE patients showed nearly three times higher upper gastrointestinal

sucrose leakage than healthy controls, which might be attributed to different TJ barriers in Barrett's metaplasia compared with a healthy esophagus.<sup>253,254</sup> Endoscopic examination confirmed a higher expression of claudin-2 and claudin-3 but markedly lower claudins-1 and -5 in Barrett's metaplasia compared with the normal esophageal mucosa.<sup>253</sup>

Disruption of the mucosal barrier in the distal esophagus exposes the squamous epithelium to a diverse esophageal microbiome and induces chronic inflammation. Biopsy samples of the distal esophagus collected from BE patients showed an altered microbiome with a significant colonization in Gram-negative bacteria and a loss of Gram-positive bacteria compared with healthy controls.<sup>255</sup> Gram-negative bacteria can produce lipopolysaccharides (LPS), which may activate the NF- $\kappa$ B pathway of the epithelial cells and induce the production of pro-inflammatory cytokines, such as IL-1 $\beta$  and TNF- $\alpha$ .<sup>256</sup> Esophageal biopsies from BE patients demonstrated elevated epithelial expression of pro-inflammatory enzymes, such as COX-2,<sup>257</sup> revealing that inflammation in BE may be associated with microbial dysbiosis.

### 3.3.4 | Food allergy

Food allergy is characterized as a recurrent adverse reaction after exposure to a specific food allergen that elicits an IgE-mediated immunological response.<sup>258</sup> The prevalence of food allergies across the globe was estimated to be between 1% and 10% of the global population and has been on the rise over the last two decades.<sup>259</sup> In the UK, food anaphylaxis hospital admissions increased from 1.2 to 2.4 per 100,000 population between 1998 and 2012, with the highest rates observed in children aged 0–4 years.<sup>260</sup> Similarly, a fourfold increase in the rate of food anaphylaxis hospital admissions was observed in Australia from 1998–1999 to 2011–2012.<sup>261</sup>

Oral tolerance to food allergens usually occurs via the gastrointestinal tract or the skin, and intestinal epithelial barrier dysfunction or skin barrier impairment can lead to sensitization to food allergens.<sup>262–264</sup> Rath et al. demonstrated that 96% of patients with food allergies showed structural and functional barrier defects visualized in the terminal ileum and at two colorectal sites using confocal laser endomicroscopy.<sup>265</sup> Moreover, elevated levels of epithelial cell-derived cytokines (TSLP, IL-33, and IL-25) were observed in food allergy patients.<sup>266,267</sup> Suppression of all three epithelial cytokines with antagonists inhibited established food allergy in a mouse model.<sup>268</sup> Gut microbiota play a key role in maintaining the integrity of the intestinal epithelial barrier, and microbial dysbiosis has been significantly associated with the pathogenesis of food allergy. Patients with food allergy showed distinct gut microbiota compared with healthy controls,<sup>269</sup> and food allergy-associated dysbiosis was found to transmit food allergy susceptibility in microbial transfer experiments.<sup>270</sup> High levels of bifidobacterial in the gut were associated with reduced risk of food allergy.<sup>271</sup>

### 3.3.5 | Inflammatory bowel disease

Inflammatory bowel disease (IBD) is a chronic recurrent inflammatory disease that includes Crohn's disease and ulcerative colitis with characteristic symptoms such as fever, abdominal tenderness, rectal bleeding, fatigue, and weight loss.<sup>272</sup> The incidence and prevalence of IBD are increasing worldwide, with an even steeper rise in emerging countries. Between 1995 and 2016, the incidence per 100,000 person-years in Denmark increased from 9.1 to 17.8 for Crohn's disease, and from 21.0 to 28.4 for ulcerative colitis.<sup>273</sup> Currently, IBD is estimated to affect approximately 1 million people in the United States and 2.5 million people in Europe posing a significant socio-economic burden.<sup>274</sup>

Studies into the pathophysiology of IBD have long focused on genetic polymorphisms and immune cell-mediated mechanisms. However, these two factors would not serve as a valid explanation for the substantial epidemiological rise starting in the western world after the industrial revolution and around a century thereafter in the emerging industrializing countries.<sup>275</sup> Instead, there is a growing body of evidence implicating environmental factors and intestinal barrier dysfunction in the development and long-term persistence of IBD.<sup>276</sup>

Biopsy specimens from patients with IBD showed significantly ameliorated epithelial resistance, loss and discontinuous tight junctions, and an altered claudin expression.<sup>277,278</sup> Barrier dysfunction has been considered as a potential cause of intestinal inflammation in IBD.<sup>276</sup> IL10-deficient mice that develop idiopathic colitis during aging display elevated ileal and colonic permeability before the onset of intestinal inflammation.<sup>279</sup> In addition, IBD patients show changes in the gut microbiota, which primarily manifested in a loss of bacterial diversity and an altered composition of the microbiota, which have been reported to be associated with local inflammation.<sup>280–282</sup>

### 3.3.6 | Celiac disease

Celiac disease is an immune-mediated gastrointestinal disorder with gluten intolerance that is triggered by ingestion of gluten in genetically susceptible individuals.<sup>283</sup> A steady increase in the incidence of celiac disease has been observed in Western countries in recent decades. The prevalence of diagnosed celiac disease in Denmark has doubled every decade from 14 per 100,000 persons in 1986 and 180 per 100,000 persons in 2016.<sup>284</sup> A fivefold increase in the prevalence of celiac disease was observed in the United States between 1975 and 2000.<sup>285</sup> The prevalence is currently estimated to be at least 0.7% in the general population (with the majority of patients being considered undiagnosed, i.e., tip of the iceberg phenomenon) in Western countries.<sup>286</sup>

Gluten is a major environmental factor that contributes to the onset of celiac disease. It contains peptide sequences that may elicit HLA-DQ2- or HLA-DQ8-restricted T-cell responses in the small intestine.<sup>287</sup> Gluten-activated T cells release pro-inflammatory cytokines (mainly IL-17, IL-21, and IFN- $\gamma$ ) that induce mucosal inflammation and cause direct disruption of the intestinal barrier.<sup>288</sup> Duodenal biopsies from patients with celiac disease showed an altered expression of TJ proteins claudin-2, -3, -5 and -7, and ZO-1, reduced and discontinuous TJ strands, and an increase in paracellular biotin-NHS uptake.<sup>287,289</sup> In addition, epidemiological and clinical studies revealed that other environmental factors besides gluten play an important role in the development of celiac disease, such as early feeding practices, infections, and changes in gut microbiota composition.<sup>290</sup> Patients with celiac disease showed an increase in pathogenic Gram-negative bacteria and a decrease in beneficial Gram-positive bacteria.<sup>291</sup> This microbial disturbance has been observed not only in untreated celiac disease patients, but also in patients with underlying celiac disease and those following a gluten-free diet, as well as in infants at high genetic risk of celiac disease.<sup>288</sup>

### 3.3.7 | Irritable bowel syndrome

Irritable bowel syndrome (IBS) is one of the most common disorders of the gut-brain axis. Its cardinal feature is the recurrent abdominal pain associated with defecation or change in frequency and form of stool.<sup>292</sup> IBS was described in the 1960s as a disorder of civilization

that was extremely common in Western countries.<sup>293</sup> The prevalence of IBS in developing countries is rising in recent decades due to the consumption of processed foods and increased psychosocial stress.<sup>294</sup> A cross-sectional study from Thailand reported a <5% prevalence in 1988, while studies published since 2000 have found a prevalence of 6%–9%.<sup>292</sup>

Although the pathophysiologic mechanisms of IBS are not yet well understood, accumulating evidence supports the role of the intestinal epithelial barrier dysfunction. Clinical data indicated that increased intestinal permeability and mucosal microinflammation occurred in both the proximal and distal bowel of IBS patients, which was closely linked to an ameliorated expression of ZO-1 and redistribution of proteins from the TJ to the cytoplasm.<sup>295,296</sup> Interestingly, epithelial barrier defects were shown to be provokable using endomicroscopy upon ingestion with several food allergies in some patients with IBD.<sup>297,298</sup> Moreover, microarray investigation of IBS patients' colonic biopsies revealed a decreased expression of chemokines (IL-8, CXCL9, and MCP-1) and an impaired mucosal immune response to microbial pathogens.<sup>299,300</sup> Thus, epithelial barrier dysfunction and associated microinflammation and microbial dysbiosis may be involved in the pathophysiological mechanisms driving IBS.

### 3.3.8 | Colonic diverticulosis

Colonic diverticulosis (CoLD) is defined as the presence of sac-like protrusions, termed diverticula, in the colonic wall.<sup>301</sup> Its prevalence has increased over the last few decades in developed countries due to a Western lifestyle. In the UK, the age-standardized hospitalization rate for CoLD increased by 12% from 25.1 to 28.2 per 100,000 population between 1989/1990 and 1999/2000.<sup>302</sup> In fact, the prevalence of CoLD has risen in some Asian countries due to an altered lifestyle and modern food habits. This is particularly evident in Japan where CoLD rose from 13.0% in 1990–2000 to 23.9% in 2001–2010.<sup>303</sup> A multivariate logistic analysis revealed a significant positive correlation of CoLD prevalence with smoking, alcohol consumption, and severe weight gain in adulthood.<sup>303</sup>

Some reports have linked CoLD to a chronic inflammatory state, referred to as segmental colitis associated with diverticulosis (SCAD). Notably, many of the dietary and lifestyle risk factors that contribute to CoLD, such as a low fiber and high red meat diet,<sup>304,305</sup> smoking,<sup>306</sup> obesity,<sup>307</sup> and physical inactivity,<sup>308</sup> are linked to chronic inflammation. A nested case-control study demonstrated that participants with CoLD had elevated plasma levels of inflammatory markers including IL-6, C-reactive protein, and TNF receptor superfamily member 1B (TNFRSF1B).<sup>309</sup> It is well-established that damage to the TJ barrier under inflammatory conditions is closely related to the pathogenesis of intestinal diseases. A study on the colonic mucosa using the Ussing chamber technique revealed that CoLD patients' permeability was significantly higher than that of controls, as evidenced by markedly reduced transepithelial electrical resistance and significantly enhanced paracellular permeability to fluorescein isothiocyanate-dextran.<sup>310</sup> Another study showed that

CoLD patients exhibited a depletion of microbiota members with an anti-inflammatory effect, including *Lactobacillaceae*, *Fusobacterium*, *Clostridium* cluster IV, and *Clostridium* cluster IX.<sup>311</sup> Additionally, it was demonstrated that the diverticular area of biopsy samples from CoLD patients had ameliorated levels of the mucus-degrading *Akkermansia muciniphila*, which can protect the integrity of the epithelial barrier by mitigating inflammation, as compared to the distal colonic regions.<sup>311</sup> In view of these studies, gut dysbiosis may contribute to the pathogenesis of mucosal inflammation and the development of colonic diverticulosis.

## 3.4 | Neuropsychiatric diseases

In addition to diseases occurring directly in affected tissues, leakiness of the gut epithelium is linked to systemic diseases, such as obesity, impaired glucose metabolism, or neuropsychiatric diseases, as demonstrated in many recent animal and human studies. Regarding the latter, these diseases include autism spectrum disorders, Parkinson's disease, Alzheimer's disease, stress-related psychiatric disorders, chronic depression, multiple sclerosis, and amyotrophic lateral sclerosis (Table 4), which have significantly increased in incidence at the same time as allergic diseases.<sup>312–314</sup>

### 3.4.1 | Alzheimer's disease

Alzheimer's disease is the most common neurodegenerative disorder among the elderly. It causes a steady deterioration in cognitive function, eventually leading to a loss of memory, thinking, and reasoning. The incidence of Alzheimer's disease has increased over the past few decades and has reached pandemic levels, affecting over 50 million people worldwide. The incidence of Alzheimer's disease at the age of ≥60 increased from 44.92/100,000 inhabitants in 1980–1994 to 72.83/100,000 inhabitants in 1995–2006.<sup>315</sup>

Imbalances in the homeostasis of the gastrointestinal system are considered to be underlying factors in the pathogenesis and progression of Alzheimer's disease. Several clinical and in vivo studies have shown pathophysiological alterations of the GI system in Alzheimer's disease. Animal models of Alzheimer's disease showed abnormal epithelial cell turnover, dysfunctional intestinal barrier, and elevated inflammation.<sup>316–318</sup> Moreover, Alzheimer's disease patients displayed a loss of microbial diversity and altered composition of the gut microbiome compared with age- and sex-matched controls.<sup>319,320</sup> Specifically, loss of *Firmicutes* and *Bifidobacterium* and colonization by Bacteroidetes, were observed in the microbiome of Alzheimer's disease individuals, shifting the gut microbiome toward a pro-inflammatory state.<sup>319</sup>

### 3.4.2 | Parkinson's disease

Parkinson's disease (PD) represents the second most common neurodegenerative disorder in the elderly after Alzheimer's disease. It

TABLE 4 Neuropsychiatric diseases in the context of the epithelial barrier theory.

Neuropsychiatric disease	Epidemiological evidence	Evidence for epithelial barrier disruption, microbial dysbiosis, and microinflammation
Alzheimer's disease	The incidence of Alzheimer's disease at the age of $\geq 60$ increased from 44.92/100,000 inhabitants in 1980–1994 to 72.83/100,000 inhabitants in 1995–2006. <sup>315</sup>	Animal models of Alzheimer's disease showed abnormal epithelial cell turnover and a dysfunctional intestinal barrier. <sup>316</sup> Microbial dysbiosis and intestinal inflammation were frequently observed in patients with Alzheimer's disease and animal models. <sup>320</sup>
Parkinson's disease	The global prevalent number of PD in 204 countries/territories increased 155.50% from 1990 and reached $8511.02 \times 10^3$ in 2019. <sup>323</sup>	An aberrant subcellular distribution and reduced expression of occludin and ZO-1 were observed in colon biopsies from patients with Parkinson's disease. <sup>326</sup> Clinical evidence and animal models showed changes in gut microbiota composition and mitigated fecal SCFA levels. <sup>320</sup>
Autism spectrum disorders	The prevalence of autism spectrum disorders among children aged 0–17 years in Sweden increased by almost 250% from 4.20/1000 in 2001 to 14.40/1000 in 2011. <sup>329</sup>	Duodenal biopsies from patients with autism spectrum disorders showed reduced mRNA expression of barrier-forming TJ components ( <i>CLDN-1</i> , <i>OCLN</i> , <i>TRIC</i> ). <sup>338</sup> Accumulating evidence showed altered gut microbiota in children with autism spectrum disorders. <sup>339</sup>
Stress-related psychiatric disorders	The prevalence of neurotic, stress-related, and somatoform disorders in Japan rose from 0.33% to 0.56% for men and from 0.48% to 1.06% for women during 1999–2017. <sup>550</sup>	Several animal studies have demonstrated that psychological stress can induce chronic disturbances of intestinal barrier function with concomitant gut microbiota dysbiosis. <sup>344,551</sup>
Chronic depression	The annual prevalence of chronic depression in the United States increased from 6.6% in 2005 to 7.3% in 2015. <sup>340</sup> Depression prevalence in South Korea increased from 2.8% in 2002 to 5.3% in 2013. <sup>341</sup>	Patients and animal models with chronic depression showed a disturbed gut microbiota composition and immune responses to gut commensal bacteria. <sup>342,345</sup>
Ischemic stroke	In the early 2000s, ischemic stroke incidence was on the rise in young adults in high-income countries, including Europe, as well as in developing countries. <sup>348</sup> The incidence of ischemic stroke among young adults (<50 years) in the Netherlands increased by 42% from 7.6 in 2000 to 10.8 per 100,000 person-years in 2010. <sup>349</sup>	Studies in mice demonstrated an increased intestinal permeability, a disruption of intestinal barrier integrity, and a translocation of gut microbiota in cerebral ischemic stroke. <sup>353</sup> Studies in humans demonstrated that stroke and transient ischemic attacks altered the gut microbiota, including an increased abundance of opportunistic pathogens and decreased beneficial commensals. <sup>352</sup>
Migraine	The prevalence of migraine among adults in the United States increased from 25.8 per 1000 persons in 1980 to 41.0 per 1000 persons in 1989. <sup>355</sup> The prevalence of migraine among children in southwestern Finland increased from 1.9% in 1974 to 5.7% in 1992. <sup>356</sup>	Migraine patients showed enhanced intestinal permeability and levels of pro-inflammatory cytokines, such as TNF- $\alpha$ and IL-1 $\beta$ . <sup>357,360</sup> Fecal samples obtained from elderly women with recurrent migraines demonstrated significant differences in the gut microbiota composition compared with healthy controls. <sup>362</sup>
Multiple sclerosis	The standardized prevalence of multiple sclerosis in Denmark increased from 58.8 in 1950 to 154.5 per 100,000 inhabitants in 2005. <sup>552</sup> Multiple sclerosis incidence in the Province of Padua, Northeast Italy, increased from 0.9 in the decade 1960–1965 to 6.5 in the decade 2011–2015. <sup>553</sup>	Various biomarkers of intestinal barrier function, such as ZO-1 and occluding, were altered in patients with multiple sclerosis and correlated with disease severity. <sup>554</sup> Mounting evidence showed an altered gut microbiome in patients with multiple sclerosis. <sup>555</sup>
Amyotrophic lateral sclerosis	The age-standardized incidence of amyotrophic lateral sclerosis in Sweden climbed from 2.32 per 100,000 person-years in 1991–1993 to 2.98 per 100,000 person-years in 2003–2005. <sup>556</sup> The prevalence in Norway rose from 3.67 per 1,00,000 population in 1988 to 4.10 per 1,00,000 population in 2015; meanwhile, the incidence rose from 1.60 per 1,00,000 person-years in 1978–1988 to 2.10 person-years in 2000–2015. <sup>557</sup>	The gut epithelial barrier of a mouse model with amyotrophic lateral sclerosis showed a damaged tight junction structure, increased permeability with a significant reduction in the expression levels of tight junction protein ZO-1 and the adherens junction protein E-cadherin, and an altered intestinal microbiome profile. <sup>558</sup>

is characterized by progressive motor symptoms (bradykinesia, rest tremor, and rigidity) and non-motor manifestations (cognitive decline, depression, dysphagia, and constipation).<sup>321,322</sup> It is currently the fastest growing neurological disorder and disability among the elderly. A study of the prevalence of PD in 204 countries reported a 156% increase since 1990, reaching an estimated  $8511.02 \times 10^3$  patients in 2019.<sup>323</sup> These concerning numbers may be associated with smoking trends or other harmful lifestyle and environmental factors originating from the second half of the 20th century.<sup>313</sup>

In recent decades, there has been growing evidence that PD is also a gastrointestinal disorder.<sup>324</sup> A compromised intestinal epithelial barrier, intestinal inflammation, and gut dysbiosis could represent early events in the pathogenesis of PD.<sup>320</sup> Forsyth et al. demonstrated an increased intestinal permeability in PD subjects with a strong positive correlation to intestinal mucosal staining for *Escherichia coli* bacteria, nitrotyrosine, and alpha-synuclein, as well as elevated levels of serum LPS-binding protein (a marker of endotoxin exposure).<sup>325</sup> Furthermore, an aberrant subcellular distribution and reduced expression of occludin and ZO-1, were observed in colon biopsies from PD patients.<sup>326,327</sup> An impaired intestinal barrier facilitates the spread of bacteria across the TJs into circulation. Numerous clinical findings and animal models showed that the composition of the gut microbiota is altered in PD and that the content of SCFAs in the stool is reduced.<sup>320</sup>

### 3.4.3 | Autism spectrum disorders

Autism spectrum disorders (ASD) are neurodevelopmental disorders characterized by deficits in social interaction, repetitive behaviors, and sensory sensitivity.<sup>328</sup> In most cases, ASD begins in infancy, no later than the first 3 years of life, and often continues into adolescence and adulthood.<sup>328</sup> A dramatic increase in the prevalence of ASD has been observed worldwide over the past few decades.<sup>312</sup> The prevalence of autism spectrum disorders among children aged 0–17 years in Sweden showed an increase from 4.20/1000 in 2001 to 14.40/1000 in 2011.<sup>329</sup> Several environmental factors, including air pollution, pesticide exposure, infections, inflammation, and use of antibiotics during pregnancy, have been shown to be associated with an increased risk for children with ASD.<sup>330–332</sup>

Although the pathogenesis of ASD is still poorly understood, several studies support the involvement of an inflammatory response.<sup>333–335</sup> A compromised gut barrier allows the entry of pathogenic antigens into the bloodstream that pass the blood–brain barrier and may contribute to the development of ASD. Clinical studies have shown increased intestinal permeability and decreased mRNA expression of barrier-forming TJ components (*CLDN-1*, *OCLN*, and *TRIC*) in ASD patients compared with healthy controls.<sup>336–338</sup> Disruption of barrier function may facilitate the transfer of microbiota and their metabolites from the gut to circulation, leading to microbial dysbiosis. Accumulating evidence suggests an aberrant gut microbiome in children with ASD correlating with disease severity.<sup>339</sup>

### 3.4.4 | Chronic depression and stress-related psychiatric disorders

Chronic depression and stress-related psychiatric disorders are regarded as civilization diseases because of their wide range and frequency, especially in highly developed countries. The annual prevalence of chronic depression in the United States increased from 6.6% in 2005 to 7.3% in 2015.<sup>340</sup> Depression prevalence in South Korea increased from 2.8% in 2002 to 5.3% in 2013.<sup>341</sup>

The immune system plays an important role in the development of depression, and especially in periods of excessively activated stress reactions, negatively affects the tightness of the intestinal barrier and the intestinal microbiota.<sup>342</sup> A recent study also showed that chronic stress disrupts intestinal barrier homeostasis by decreasing expression of jejunum tight junctions, increasing serum lipopolysaccharide-binding protein, and altering microbial populations in conjunction with the manifestations of depressive-like behaviors in a sex-dependent manner in mice.<sup>343</sup> Bacterial translocation following microbial dysbiosis is commonly observed in patients suffering from chronic depression and stress-related psychiatric disorders.<sup>344,345</sup>

### 3.4.5 | Ischemic stroke

Ischemic stroke is the most common type of stroke, accounting for ~80% of stroke cases.<sup>346</sup> It occurs when blood flow is blocked in cerebral vessels or major arteries leading to the brain.<sup>347</sup> Although the risk of stroke rises with age, it can occur at any age. Notably, there has been a sharp rise in ischemic stroke among young adults in recent decades. In the early 2000s, ischemic stroke incidence was on the rise in young adults in affluent countries, including Europe, as well as in developing countries.<sup>348</sup> The incidence of ischemic stroke among young adults (<50 years) in the Netherlands increased by 42% from 7.6 in 2000 to 10.8 per 100,000 person-years in 2010.<sup>349</sup> The increase in ischemic stroke among young people is believed to be driven by the same lifestyle factors that cause stroke in the elderly, such as high blood pressure, obesity, diabetes, hyperglycemia, hyperlipidemia, and smoking.<sup>350</sup>

Mounting evidence in recent years suggests that the pathophysiological process of ischemic stroke is strongly associated with the gut–brain axis, comprising intestinal barriers, intestinal microbiota, flora metabolites, and the central nervous system.<sup>351</sup> Clinical data revealed that individuals with ischemic stroke had a relative loss in beneficial commensal bacteria such *Bacteroides*, *Faecalibacterium*, and *Prevotella* and a relative increase in opportunistic pathogenic bacteria, including *Desulfovibrio*, *Enterobacter*, *Megasphaera*, and *Oscillibacter* when compared to healthy controls.<sup>352</sup> Pathogenic bacteria can disrupt the intestinal barrier after a disturbance of the intestinal flora induced by ischemic stroke. Animal studies also demonstrated an enhanced intestinal permeability, damage to the intestinal barrier integrity, and a translocation of gut microbiota following an ischemic stroke in both young and aged mice.<sup>353</sup> The

intestinal barrier may play an intermediate role in the relationship between intestinal flora disturbance, intestinal inflammation, intestinal neurological dysfunction, and ischemic stroke.

### 3.4.6 | Migraine

A migraine is a frequent, complex, recurring neurogenic inflammatory disorder characterized by throbbing headaches, with certain associated characteristics such as photophobia, phonophobia, and nausea.<sup>354</sup> The prevalence of migraine has been increasing globally over the years, with studies reporting an increase among adults in the United States from 25.8 per 1000 persons in 1980 to 41.0 per 1000 persons in 1989,<sup>355</sup> and among children in southwestern Finland from 1.9% in 1974 to 5.7% in 1992.<sup>356</sup>

A growing number of gastrointestinal disorders were demonstrated to be closely related to migraines.<sup>357</sup> A cohort study reported that more than half of the patients with migraine also suffer from IBS,<sup>358</sup> and patients with IBD are 2.7 times more likely to experience migraines than healthy controls.<sup>359</sup> Possible mechanisms underlying migraine and gastrointestinal disorders may be enhanced intestinal permeability and inflammation. Similar to individuals with gastrointestinal disorders, migraine patients showed an impaired intestinal barrier function and elevated levels of pro-inflammatory cytokines, such as TNF- $\alpha$  and IL-1 $\beta$ .<sup>360,361</sup> The notion that both increased intestinal permeability and inflammation produced by irritable bowel syndrome and inflammatory bowel disease are associated with gut microbes suggests an important role for intestinal bacteria in migraines. Indeed, the migraine group revealed a significant loss of alpha diversity in the gut microbiome compared with the healthy controls, possibly due to the depletion of certain highly abundant beneficial bacteria active in energy metabolism and SCFAs synthesis.<sup>362</sup> Therefore, further research is warranted to unravel the pathogenesis of migraines in the context of the gut-brain axis.

## 3.5 | Autoimmune, autoinflammatory, and metabolic diseases

Intestinal epithelial barrier defects and microbial dysbiosis have been demonstrated in autoimmune, autoinflammatory, and metabolic diseases such as autoimmune thyroid disease, systemic lupus erythematosus, ankylosing spondylitis, granulomatosis with polyangiitis, autoimmune hepatitis, Behçet's syndrome, rheumatoid arthritis, osteoarthritis, diabetes, obesity, and metabolic dysfunction-associated steatotic liver disease (Table 5).

### 3.5.1 | Autoimmune thyroid disease

Autoimmune thyroid disease (AITD) is an organ-specific autoimmune condition that consists of two primary clinical entities:

Graves' disease (GD) and Hashimoto's thyroiditis (HT). Both are pathologically characterized by lymphocytic infiltration of the thyroid and clinically by a dysfunction of the thyroid (hyperthyroidism in GD and hypothyroidism in HT).<sup>363</sup> AITD is not only caused by genetic susceptibility, but also associated with environmental risk factors (e.g., cigarette smoking, excess iodine intake, infections, and stress).<sup>363,364</sup> GD was associated with smoking,<sup>365</sup> and showed an increased incidence in Sweden from 17.7 cases/100,000/year in 1970–1974 to 22.3 cases/100,000/year in 1988–1990.<sup>366,367</sup> A similar trend was reported in Denmark, where the incidence of GD increased from 14.8 cases/100,000/year in 1987–1988 to 31.2 cases/100,000/year in 1997–2000.<sup>368</sup> In Slovenia, after the introduction of iodized salt in 1999, the incidence of HT sharply increased from 73.2 cases/100,000/year in 1999 to 166.4 cases/100,000/year in 2009.<sup>369</sup>

According to the gut-thyroid axis hypothesis, epithelial leakage due to microbial dysbiosis may facilitate the passage of antigens and trigger a pro-inflammatory immune response, further aggravating thyroid dysfunction and the risk of developing autoimmune thyroid disease. In turn, thyroid hormone imbalance may aggravate intestinal barrier disruption, inducing bacterial translocation.<sup>370</sup> Multiple studies have observed increased intestinal permeability and alterations of the gut microbiota in patients with GD or HT.<sup>371–374</sup> Although GD and HT patients share some gut microbiome profile features at family and genus levels, they also differ in terms of abundance and their respective core microbiomes which are closely related to the onset of the disease.<sup>375</sup>

### 3.5.2 | Osteoarthritis

Osteoarthritis, a leading cause of chronic pain and disability in affluent countries, is recognized as a degenerative joint disease involving multiple risk factors, such as genetic predisposition, age, prior joint injury, obesity, and a sedentary lifestyle.<sup>376</sup> Although osteoarthritis can affect every joint in the body, knee osteoarthritis is the most common, followed by hip osteoarthritis,<sup>377</sup> both of which have been increasing in prevalence over the past decades. Long-term historical statistics show that knee osteoarthritis has more than doubled in prevalence since the mid-20th century.<sup>378</sup> In the United States, the prevalence of knee osteoarthritis was reported to be 16% in the postindustrial era (late 1900s to early 2000s), albeit only 6% in the early industrial era (1800s to early 1900s).<sup>378</sup> Similarly, the prevalence of hip osteoarthritis doubled from 4.0% in the 1970s to 8.6% in the 2000s.<sup>379</sup> These epidemiological findings were mainly attributed to the increasing life expectancy and risk factors that contribute to osteoarthritis, especially obesity and a sedentary lifestyle.<sup>376</sup>

Recent findings from studies in humans and animals indicate that gut microbial dysbiosis via the gut-joint axis is an emerging pathogenic factor for osteoarthritis.<sup>380</sup> Its mechanism of action in osteoarthritis is quite complex, with both direct and indirect effects. On the one hand, gut microbes produce pro-inflammatory metabolites such as LPS which enhance intestinal permeability, and further

TABLE 5 Autoimmune, autoinflammatory, and metabolic diseases in the context of the epithelial barrier theory.

Autoimmune, autoinflammatory, and metabolic diseases	Epidemiological evidence	Evidence for epithelial barrier disruption, microbial dysbiosis, and microinflammation
Graves' disease	The incidence in Sweden increased from 17.7 cases/100,000/year in 1970–1974 to 22.3 cases/100,000/year in 1988–1990 <sup>368</sup> ; in Denmark, 14.8 cases/100,000/year in 1987–1988 to 31.2 cases/100,000/year in 1997–2000 <sup>368</sup> ; in Austria, 12.2 cases/100,000/year in 1987 to a peak of 27.0 cases/100,000/year in 1993. <sup>368</sup>	Patients with Graves' disease showed bacterial translocation and a disrupted intestinal barrier characterized by elevated levels of zonulin. <sup>371</sup>
Hashimoto's thyroiditis	The incidence of Hashimoto's thyroiditis in Slovenia increased from 73.2 cases/100,000/year in 1999 to 166.4 cases/100,000/year in 2009. <sup>369</sup>	Patients with Hashimoto's thyroiditis demonstrated morphological changes in gut epithelial cells, increased colonic intraepithelial lymphocytes, and an altered gut microbial profile. <sup>372,559,560</sup>
Systemic lupus erythematosus	Age- and sex-adjusted incidence rates of systemic lupus erythematosus in Northwestern Spain increased from 1.9 per 100,000 in 1987–1991 to 5.7 per 100,000 in 1997–2001. <sup>561</sup>	Patients with systemic lupus erythematosus display distinct patterns of gut dysbiosis, impaired gut barrier integrity, and immune responses. <sup>562,563</sup>
Ankylosing spondylitis	Annual prevalence of ankylosing spondylitis in Northern Norway rose from 0.043% in 1970 to 0.26% in 1990. <sup>564</sup>	Ileal biopsies from patients with ankylosing spondylitis displayed increased zonulin expression and intestinal inflammation. Adherent and pathogenic bacteria were present in the ileum of patients, which were associated with an impaired epithelial barrier. <sup>565</sup>
Granulomatosis with polyangiitis	The annual incidence rate of granulomatosis with polyangiitis in Italy increased from 1.7/million/year during 1995–1999 to 3.4 during 2005–2009, and the point prevalence increased from 17.8 per million in 1999 to 34.3 per million in 2009. <sup>566</sup>	Nasal samples from individuals with granulomatosis with polyangiitis showed upregulation of genes associated with epithelial structural proteins including keratin and small proline-rich proteins, <sup>567</sup> as well as a markedly different microbial composition and lower relative abundance of <i>Propionibacterium acnes</i> and <i>Staphylococcus epidermidis</i> when compared with controls. <sup>568</sup>
Autoimmune hepatitis	Age- and sex-standardized incidence rates of autoimmune hepatitis in Denmark indicated a 1.7-fold increase, from 1.37 in 1994 to 2.33 in 2012. <sup>569</sup> The prevalence of autoimmune hepatitis in Japan tripled over a 12-year period, from 8.7% in 2004 to 23.9% in 2016. <sup>570</sup>	Increased intestinal permeability, decreased expression of ZO-1 and occludin, derangement of the gut flora and bacterial translocation were observed in patients with autoimmune hepatitis and these changes were correlated with the severity of the disease. <sup>571</sup>
Behçet's syndrome	The prevalence of Behçet's syndrome in Japan increased from 6.3–8.5 per 100,000 population in 1972 to 13.5 per 100,000 population in 1991. <sup>572</sup> In Berlin-West, Germany, the prevalence increased from 0.65 in 1984 to 2.26 patients per 100,000 inhabitants in 1994. <sup>572</sup>	Patients with Behçet's syndrome demonstrated significantly higher intestinal permeation and compositional changes of gut microbes compared with the healthy controls. <sup>573–575</sup>
Rheumatoid arthritis	The prevalence of age- and sex-standardized rheumatoid arthritis in Ontario, Canada, increased steadily from 0.49% in 1996 to 0.9% in 2010, while its incidence ranged from 62 to 54 per 100,000 population during 1996–2010. <sup>576</sup>	Increased intestinal permeability, elevated zonulin levels, intestinal inflammation, and intestinal microbial changes were observed in rheumatoid arthritis patients or mice, which were correlated with the onset of rheumatoid arthritis. <sup>577</sup>
Osteoarthritis	Knee osteoarthritis prevalence in the postindustrial sample from the United States was 16%, which was 2.6 times higher than in the early industrial sample (6%) and 2 times higher than in the prehistoric sample (8%). <sup>378</sup> The prevalence of hip osteoarthritis rose from 4.0% in the 1970s to 8.6% in the 2000s. <sup>379</sup>	Studies in humans correlated an increased intestinal permeability to the development of osteoarthritis. <sup>578</sup> Patients with osteoarthritis showed significant alterations in the gut microbial composition and function compared with healthy controls. <sup>579</sup>

TABLE 5 (Continued)

Autoimmune, autoinflammatory, and metabolic diseases	Epidemiological evidence	Evidence for epithelial barrier disruption, microbial dysbiosis, and microinflammation
IgA Nephropathy	Increasing prevalence has been shown especially in industrialized regions	The pathophysiology was strongly associated to a disturbance in the gut, particularly the small intestine, where IgA-misfolding to galactose-deficient IgA1 (Gd-IgA1) is taking place (Hit 1). <sup>388</sup> Autoimmunity with recognition of misfolded IgA (Gd-IgA1) by circulating IgG or IgA leads to the phenotype in the glomerulum with the formation of immune complexes as well as the activation of the complement system (Hit 2). <sup>389,390</sup>
Diabetes	Self-reported prevalence of diabetes in Portugal increased between 1987 and 2009 in middle-aged and older adults, more than doubling in women and tripling in men. <sup>580</sup>	Patients with type 1 diabetes showed increased intestinal permeability, changes in the expression levels of tight junctions, and intestinal inflammation. <sup>581-583</sup> Children with type 1 diabetes showed gut microbial dysbiosis with lower abundance of SCFA-producing bacteria, which was associated with increased intestinal permeability. <sup>584</sup> Gut microbial dysbiosis, breaching of intestinal barriers and immune-related low-grade inflammation were demonstrated to be directly or indirectly related to insulin resistance in T2D. <sup>585</sup>
Obesity	The prevalence of obesity in the United States has risen dramatically since the 1960s, <sup>586</sup> increasing from 15% to 34% in adults and from 5% to 17% in children and adolescents from 1976–1980 to 2007–2008. <sup>586-588</sup>	Intestinal mucosal biopsies from patients and animal models with obesity exhibited increased intestinal permeability, altered expression of tight junction proteins (ZO-1), and inflammation. <sup>589,590</sup> Evidence from obese patients showed perturbation of the intestinal microbiota with phylum-level changes and mitigated bacterial diversity, <sup>591,592</sup> which was associated with a leaky intestinal barrier and inflammation in obesity. <sup>593</sup>
Metabolic dysfunction-associated steatotic liver disease	The prevalence of metabolic dysfunction-associated steatotic liver disease (MASLD) among US adolescents increased from 3.9% in 1988–1994 to 10.7% in 2007–2010. <sup>594</sup> MASLD incidence in a US community increased fivefold, from 62 to 329 in 100,000 person-years. <sup>595</sup>	Patients with MASLD revealed increased intestinal permeability and decreased ZO-1 expression, indicating the disruption of the intestinal epithelial barrier. <sup>596</sup> Accumulating evidence showed changes in the intestinal microbiota of patients with MASLD. <sup>597</sup>
Cirrhosis	Cirrhosis prevalence nearly doubled from 2001–2013 in US veterans (664 to 1058 per 100,000 enrollees). <sup>396</sup> The age-standardized incidence in Canada rose from 70.6 per 100,000 person-years in 1997 to 89.6 per 100,000 person-years in 2016 and the prevalence increased from 0.42% in 1997 to 0.84% in 2016. <sup>397</sup>	Decreased transepithelial resistance, increased duodenal permeability and increased claudin-2 were detected in patients with decompensated cirrhosis. <sup>398</sup> Distinct fecal microbial communities were found in patients with cirrhosis compared with healthy individuals. <sup>598</sup>

circulate throughout the body to induce chronic low-grade intestinal inflammation.<sup>381</sup> A positive association was found between osteoarthritis and gut microbiota-producing LPS.<sup>382</sup> On the other hand, numerous risk factors for osteoarthritis, such as obesity and metabolic syndromes, disturb the intestinal microbiota, leading to dysfunction of the intestinal barrier and immune system, promoting the onset of osteoarthritis.<sup>383,384</sup> Transplantation with fecal microbiota from patients with metabolic syndrome to germ-free mice increased gut permeability (reflected by decreased mRNA levels of ZO-1 and occludin, elevated plasma LPS level, and gut barrier visualized by fluorescence in situ hybridization), endotoxemia, systemic low-grade inflammation, and exacerbated the severity of injury-induced osteoarthritis.<sup>385</sup>

### 3.5.3 | IgA Nephropathy

IgA nephropathy is the most common cause of glomerulonephritis across the globe, with a heterogenous distribution, more prevalent in Asia and less in Africa.<sup>386</sup> Even though the overall incidence may vary due to different diagnostic definitions across the world, an underdiagnosing and generally increasing prevalence was reported, especially in affluent countries.<sup>387</sup> Its pathophysiology seems to be strongly associated with a disturbance in the gut, particularly the small intestine, where IgA-misfolding to galactose-deficient IgA1 (Gd-IgA1) is taking place, namely the hit 1.<sup>388</sup> Autoimmunity with recognition of misfolded IgA (Gd-IgA1) by circulating IgG or IgA (hit 2) leads to the formation of immune complexes (hit 3),

activation of the complement system and deposition in the glomerulus with the disease phenotype (hit 4).<sup>389,390</sup> Associations between forms of IgA nephropathy and gastrointestinal diseases with epithelial barrier defects are well-reported, such as liver cirrhosis, coeliac disease, and inflammatory bowel disease.<sup>391,392</sup> Furthermore, the role of circulating cytokines is a hot topic in current studies on the disease. The innate immune activation via Toll-like receptor 9 (TLR9) is associated with Gd-IgA1 production. A B-cell proliferation-inducing ligand (APRIL) and IL-6 also enhance Gd-IgA1 synthesis in IgA nephropathy.<sup>393</sup> Recently, a potential role for the gut microbiota was shown where gut microbiota dysbiosis contributes to IgA1 deglycosylation and the generation of autoantigens in patients with IgA nephropathy.

### 3.5.4 | Liver Cirrhosis

Cirrhosis develops after prolonged inflammation that leads to the healthy liver parenchyma being replaced by fibrotic tissue and regenerative nodules, which results in portal hypertension and end-stage liver disease.<sup>394</sup> Globally, cirrhosis currently causes 1.16 million deaths annually, making it the 11th leading cause of mortality.<sup>395</sup> Cirrhosis poses a heavy health burden on many countries and shows increased prevalence and incidence over the past two decades due to obesity, high alcohol consumption, nonalcoholic fatty liver disease, and hepatitis B or C infection.<sup>394</sup> The prevalence of cirrhosis among US veterans increased from 664 per 100,000 individuals in 2001 to 1058 per 100,000 individuals in 2013, as did the incidence (from 159 to 193 per 100,000 patient-years).<sup>396</sup> Similar trends in the prevalence and incidence of cirrhosis have been observed in Canada, where the age-standardized prevalence doubled from 0.42% in 1997 to 0.84% in 2016 and the incidence increased from 70.6 to 89.6 per 100,000 person-years.<sup>397</sup>

Several studies have observed decreased transepithelial resistance, increased duodenal permeability, and altered TJs in patients with cirrhosis, implying an impairment of intestinal epithelial barrier function.<sup>398-400</sup> Barrier dysfunction in cirrhosis may involve various factors and mechanisms. Multiple contributing factors such as obesity and alcohol consumption may influence the barrier dysfunction directly and indirectly, which can lead to chronic liver disease and eventually cirrhosis.<sup>401,402</sup> On the contrary, cirrhosis-related features such as portal hypertension, altered intestinal microbiota, inflammation, and oxidative stress can compromise the barrier function in both the small and large intestines.<sup>403,404</sup>

## 3.6 | Ocular diseases

The ocular surface is directly exposed to the external environment and is protected by two barrier layers: One is a transcellular barrier at the foremost apical cell membrane, also known as the epithelial glycocalyx, and the other layer is a paracellular barrier that includes the layered structures of the corneal and conjunctival epithelia.<sup>66</sup> In

addition to acting as a physical barrier against the external environment, the ocular surface epithelium plays a crucial role as the innate immune system's first line of defense.<sup>405</sup> Dysfunction of this barrier may lead to ocular surface inflammation and the onset of ocular diseases (Table 6), such as ocular allergy, age-related macular degeneration, dry eye disease, glaucoma, and uveitis.

### 3.6.1 | Ocular allergy

Ocular allergy (OA), also named as allergic conjunctivitis, refers to a series of hypersensitivity disorders of the ocular surface (eyelid, conjunctiva, and cornea), and includes acute diseases such as seasonal and perennial allergic conjunctivitis and chronic diseases such as vernal, atopic keratoconjunctivitis, and contact blepharoconjunctivitis.<sup>406</sup> It is pathologically characterized by the mucosal infiltration of eosinophils, neutrophils, basophils, and T lymphocytes, and manifested by the redness, swelling, and itching triad.<sup>407,408</sup> The prevalence of OA has been rising globally over the past few decades and was demonstrated to be associated with exposure to air pollutants.<sup>409</sup> The prevalence of ocular symptoms in the United States increased 3.3-fold from 9.0% in 1976-1980 to 29.9% in 1988-1994.<sup>410</sup> A similar trend was observed in Japan, where the lifetime prevalence of OA increased from 24.5% in 1996 to 30.0% in 2006.<sup>409</sup> Multivariate analysis demonstrated a significant association between the level of airborne particulate matter (PM<sub>2.5</sub>) and the prevalence of OA.<sup>411</sup>

Several studies demonstrated a pivotal role of ocular surface epithelial barrier dysfunction in the pathology of OA. Epithelial barrier integrity is primarily maintained by AJ proteins (i.e., E-cadherin, CD44, and keratins) and TJ proteins (i.e., occludin, claudin, and ZO-1), and changes in their expression and function lead to barrier dysfunction.<sup>66</sup> Conjunctival biopsy samples from "out of season" seasonal and perennial allergic conjunctivitis patients showed downregulated expression of E-cadherin, CD44 and keratin-14 as compared to healthy controls.<sup>412</sup> Similarly, ameliorated expression of ZO-1 and E-cadherin was observed in a murine model of OA.<sup>413</sup> Using a mouse model of OA, a recent study proposed that the IL-33/ST2/IL-9/IL-9R signaling cascade disrupts ocular surface barrier integrity, potentially exacerbating allergic inflammation.<sup>67</sup>

### 3.6.2 | Dry eye disease

Dry eye disease (DED) is defined as a multifactorial disease of the ocular surface characterized by a loss of tear film homeostasis and accompanied by ocular symptoms, with tear film instability and hyperosmolarity, ocular surface inflammation and damage, and neurosensory abnormalities play etiological roles.<sup>414</sup> With an increasing trend, its global prevalence varies from 4.6% to 47.6%.<sup>415</sup> An epidemiological report showed that the annual prevalence of DED in the United States tripled in the course of 7 years from 2005 to

TABLE 6 Ocular diseases and the epithelial barrier theory.

Ocular disease	Epidemiological evidence	Evidence for epithelial barrier disruption, microbial dysbiosis, and microinflammation
Ocular allergy/allergic conjunctivitis	The prevalence of oculonasal symptoms in the United States increased 3.3-fold from 9.0% in 1976–1980 to 29.9% in 1988–1994. <sup>410</sup> A similar trend was observed in Japan, where the lifetime prevalence of OA increased from 24.5% in 1996 to 30.0% in 2006. <sup>409</sup>	Eye specimens from patients with keratoconjunctivitis (AKC) showed ocular surface inflammation and alterations of the ocular surface epithelial MUC 1, 2, 4, and 16. <sup>599</sup> Specimens from seasonal allergic conjunctivitis (SAC) patients showed increased expression of conjunctival epithelial PAR-2, which was positively correlated with epithelial permeability. <sup>600</sup> Chronic vernal keratoconjunctivitis (VKC) patients showed significant alterations in the distribution of goblet cells, increased expression of genes encoding pro-inflammatory cytokines, and altered conjunctival microbiota composition. <sup>601,602</sup>
Age-related macular degeneration	A meta-analysis of incidence studies showed that since the 1960s, there were 3.5 per 1000 aged 50 years and older, equivalent to 293,000 new cases in white Americans per year, and the incidence rates approximately quadrupled per decade in age. <sup>603</sup>	The pathogenesis was strongly associated with chronic oxidative stress and inflammation that ultimately leads to protein damage, aggregation, and degeneration of retinal pigment epithelium. <sup>604</sup> Studies also showed that an intestinal dysbiosis occurs in advanced age-related macular degeneration. <sup>605</sup>
Dry eye	From the epidemiological report, the annual prevalence of dry eye tripled over the 7 years from 2005 to 2012 in the United States. <sup>416</sup>	Mice with dry eye-like ocular surface damages showed squamous metaplasia in the ocular surface and epithelial barrier dysfunction. <sup>421,606</sup> In addition, experimental dry eye stimulated production of inflammatory cytokines and MMP-9. <sup>421</sup> Samples from the inferior fornix of the conjunctiva of dry eye patients displayed decreased microbial diversity. <sup>425,426</sup>
Glaucoma	The prevalence of glaucoma in Denmark increased from 0.79% in 1996 to 1.72% in 2011; the incidence of glaucoma increased from 0.137% in 1996 to 0.155% in 2011. <sup>607</sup>	Patients with glaucoma exhibited epithelial barrier defects as observed by fluorescein staining. <sup>608</sup> The eyelid and buccal microbiomes in patients with uveitic glaucoma showed lower alpha diversity and higher beta diversity than those in controls, as well as depletion of <i>Lactococcus</i> . <sup>609</sup>
Uveitis	An annual incidence of uveitis in the United States was estimated to be around 17.4 per 100,000 population in the 1960s, and it has increased to be 52.4 per 100,000 in 1998–1999. <sup>610,611</sup>	A murine model of uveitis showed disrupted tight junctions and infiltrating T cells detected in retinal pigment epithelial flat mounts. <sup>612</sup> Moreover, uveitis patients showed a significant decrease in the gut fungal richness and diversity compared with healthy controls. <sup>613</sup>

2012.<sup>416</sup> Epidemiological studies have identified some risk factors for the development of DED, such as aging, hormonal changes, autoimmune diseases, low humidity, use of contact lenses, alcohol consumption, pollution, computer use, and certain preservatives in topical drugs,<sup>417</sup> may have contributed to the increased prevalence observed for DED.

Evidence indicates that DED is a mucosal autoimmune disease<sup>418</sup> manifested by a compromised epithelial barrier<sup>66,419</sup> and increased levels of inflammatory cytokines on the ocular surface,<sup>420,421</sup> which has been shown to be associated with TLRs expressed by epithelial and immune cells in the eye and activated by LPS.<sup>422</sup> Epithelial barrier disruption during DED induces greater exposure of LPS to TLR4+ cells, which contributes to production of IL-1 $\beta$  and TNF- $\alpha$ .<sup>422</sup> Notably, IL-1 $\beta$  has been shown to disrupt the corneal epithelial barrier through upregulation of MMP-9.<sup>423,424</sup> This, in turn, may lead to higher exposure to TLR4 initiating a vicious cycle of inflammation that disrupts ocular surface homeostasis. A range of studies have

found altered ocular surface microbiota diversity and composition in DED patients compared with healthy controls,<sup>425–427</sup> implying a critical role of the ocular surface microbiota in DED pathogenesis.

### 3.7 | Other diseases

#### 3.7.1 | End-stage renal disease (ESRD)

End-stage renal disease (ESRD) is characterized by a progressive, irreversible loss of kidney function, which is severe enough to cause death without dialysis or kidney transplant.<sup>428</sup> The steadily increasing number of ESRD patients is recognized as a global public health issue. A report showed that an increase in the incidence of ESRD in children under the age of 18 years in Australia and New Zealand began in the 1960s and that the incidence increased continued until the early 1980s.<sup>429</sup> In a study of a California cohort from 1973

to 2000, ninety percent of documented cases of treated ESRD occurred after 1983, and 80% after 1987 (Table 7).<sup>430</sup> The increased incidence observed for ESRD may be attributed to its independent risk factors, including overweight and obesity,<sup>431</sup> cigarette smoking,<sup>432</sup> higher serum uric acid level,<sup>433</sup> and a family history of kidney disease.<sup>433</sup>

The disruption associated with uremia is crucial for the progression of ESRD. Exposure of human colonic epithelial cells to uremic plasma from ESRD patients induced a significant decrease in transepithelial electrical resistance along with a marked reduction in TJ protein expression, such as claudin-1 (85%), ZO1 (70%), and occludin (15%),<sup>434</sup> suggesting an impaired intestinal epithelial barrier structure and function in ESRD patients. The influx of endotoxins and other harmful luminal products into the internal environment through damaged TJs can lead to systemic inflammation. Clinical evidence demonstrated that in the ESRD population, the severity of systemic inflammation as measured by C-reactive protein levels correlated with plasma endotoxin levels.<sup>435</sup> In addition, impairment of the intestinal epithelial barrier integrity can induce intestinal bacterial translocation, leading to intestinal microbial dysbiosis. Studies suggest significant changes in the composition and function of gut microbiota in patients with ESRD and animal models.<sup>436</sup> Overall, uremia-induced intestinal barrier dysfunction in ESRD triggered intestinal microbial dysbiosis, resulting in chronic inflammation.

### 3.7.2 | Osteoporosis

Osteoporosis is a form of bone metabolic disease with manifestations of low bone mass and deterioration of skeletal microarchitecture leading to bone fragility and fracture risk.<sup>437</sup> Osteoporosis is a global health concern as its prevalence has been increasing over the past decades, especially in postmenopausal women. The estimated annual prevalence of osteoporosis in Malmö (Sweden) increased from 1061 per 10,000 women aged 50 years or above in 1970 to 1698 per 10,000 women aged 50 years or above in 1999 (Table 7).<sup>438</sup> Aging, ameliorated estrogen levels, persistent calcium loss, and smoking are all significant independent risk factors for postmenopausal osteoporosis.<sup>439,440</sup>

Bone homeostasis depends on the balance between osteoblast-mediated bone formation and osteoclast-mediated bone resorption.<sup>441</sup> Osteoporosis is caused by an imbalance in bone homeostasis associated with gut microbiota via multiple potential mechanisms.<sup>442</sup> Osteoclast activity can be inhibited by short-chain fatty acids or bacterial components such as exopolysaccharides in a TLR-2-dependent mechanism.<sup>443,444</sup> In addition, the association between gut microbiota and bone homeostasis is partially regulated by immune cells. An imbalance in gut microbiota, on the one hand, induces the differentiation of Th17 cells, which belong to the CD4<sup>+</sup> T-cell osteoclast population; on the other hand, it inhibits the differentiation of Th1 and Th2 cells as well as Tregs, which induces the differentiation and proliferation of osteoclasts, exacerbating bone loss.<sup>445</sup> Young female SD rats with transplanted fecal microbiota from senile

osteoporotic rats exhibited gut microbiota dysbiosis, impaired intestinal structure, reduced expression of occludin, claudin, and ZO-1, and osteoporosis.<sup>446</sup> Thus, gut microbial dysbiosis induces the impairment of the intestinal barrier and contributes to the pathogenesis of osteoporosis.

### 3.7.3 | Severe COVID-19

Coronavirus disease-2019 (COVID-19) is a highly infectious respiratory disease caused by the coronavirus severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) with symptoms including fever, dry cough, respiratory failure, and pneumonia. It can cause other complications such as fatigue, diarrhea, dysgeusia, and anosmia.<sup>447,448</sup> The SARS-CoV-2 outbreak was first reported in Wuhan, China, in December 2019.<sup>447,449</sup> Its rapid global transmission led the COVID-19 disease to reach pandemic status on March 11, 2020.<sup>450</sup> As of 2024, there have been over 800 million confirmed cases of COVID-19 worldwide according to the World Health Organization.<sup>451</sup>

Infection with SARS-CoV-2 can directly and/or indirectly induce epithelial barrier disruption. Directly, SARS-CoV-2 can infect the airway and gut cells<sup>452</sup>; indirectly, lung infection can promote systemic inflammation, which may compromise the intestinal barrier, enhancing permeability to intestinal microorganisms and their metabolites and aggravating inflammation.<sup>453</sup> Levels of the zonulin family peptides and bacterial DNA, which are markers of intestinal permeability and microbial translocation, were significantly elevated in COVID-19 patients compared with healthy controls.<sup>454</sup> Other studies using a multiomics approach showed that severe COVID-19 was associated with high levels of markers of TJ permeability and microbial translocation.<sup>455,456</sup> Moreover, 23 markers of systemic inflammation showed elevated levels in severe COVID-19 patients compared with mild COVID-19 patients or healthy controls.<sup>455</sup> Distinct mechanistic modules have been shown to link host and microbiome metabolic processes with fatal outcomes to SARS-CoV-2 infection and a recent meta-analysis demonstrated consistent microbiota correlations with COVID-19 disease severity.<sup>457,458</sup> These findings demonstrate that the pathophysiology of severe COVID-19 fits the epithelial barrier theory.

### 3.7.4 | Long COVID

SARS-CoV-2 infection can result in a prolonged multisystem disorder termed long COVID, which may affect up to 10% of people following COVID-19 disease.<sup>459</sup> It is currently unclear why certain individuals do not fully recover following SARS-CoV-2 infection. Post-infectious disorders have been previously described,<sup>460</sup> but the current number of cases is unprecedented. Multisystem involvement in individual patients is common, with one study reporting the median number of symptoms reported at any given time to be eight.<sup>461</sup> The most common symptoms reported in this cohort were fatigue, post-exertional malaise, palpitations, chest pain, stomach upset/nausea, memory

TABLE 7 Other diseases in the context of the epithelial barrier theory.

Other diseases	Epidemiologic evidence	Evidence for epithelial barrier disruption, microbial dysbiosis, and microinflammation
End-stage renal disease	An increase in the incidence of end-stage renal disease (ESRD) in children under the age of 18 years in Australia and New Zealand began in the 1960s, and the incidence increased continuously until the early 1980s. <sup>429</sup> In a California cohort study from 1973 to 2000, ninety percent of the documented cases of treated ESRD occurred after 1983, and 80% of the cases occurred after 1987. <sup>430</sup>	Addition of uremic pre-dialysis plasma from ESRD patients to cultured human enterocytes damaged the barrier function and tight junction protein constituents of the intestinal epithelium. <sup>434</sup> Further studies revealed significant changes in the composition and function of gut microbiota in patients and animals with ESRD. <sup>436</sup>
Heart failure	Cross-sectional studies have shown increases in the point prevalence of heart failure in the United States and Europe since the 1970s. <sup>614,615</sup>	Heart failure patients showed the structural disruption of the intestinal epithelial barrier, a significantly decreased diversity of the intestinal microbiome and depletion of core intestinal microbiota. <sup>616–619</sup>
Myocarditis	Data from Italy showed that the prevalence of myocarditis rose from 0.4% in 1975–1984 to 1.2% in 1985–1994. <sup>620</sup> The death certificate-based incidence of fatal myocarditis collected from the database of Statistics Finland showed an increase from 0.32/100,000 person-years in 1985–1989 to 0.62/100,000 in 1990–1994. <sup>621</sup>	Mice with experimental autoimmune myocarditis showed elevated serum levels of the epithelial gut damage markers and pro-inflammatory mediators as well as a lower bacterial diversity in gut microbiota composition. <sup>622</sup>
Osteoporosis	The estimated annual prevalence of osteoporosis in Malmö, Sweden, increased from 1061 per 10,000 women aged 50 years or above in 1970 to 1698 per 10,000 women aged 50 years or above in 1999. <sup>438</sup>	Female SD rats of old age with transplanted fecal microbiota from senile osteoporotic rats exhibited gut microbiota dysbiosis, impaired intestinal barrier, and osteoporosis. <sup>446</sup>
Anemia	The prevalence of anemia (4.0% to 7.1%) and moderate–severe anemia (1.0% to 1.9%) in the general US population nearly doubled from 2003–2004 to 2011–2012. <sup>623</sup>	Anemic mouse pups displayed increased intestinal permeability, reduced tight junction protein ZO-1 expression, and increased macrophage pro-inflammatory cytokine levels. <sup>624,625</sup> Studies on patients with iron deficiency anemia, gestational anemia, or aplastic anemia showed a close correlation between dysbiosis of gut microbiota and anemia. <sup>626–628</sup>
Hemolytic uremic syndrome	The annual incidence of hemolytic uremic syndrome in Minnesota, United States, showed an increase from 0.5 cases per 100,000 child years among children less than 18 in 1979 to 2.0 cases per 100,000 in 1988. <sup>629</sup> The annual incidence in Washington, United States, rose from 0.69 cases per 100,000 children under age 15 years between 1971 and 1975 to 1.77 cases between 1976 and 1980 and 1.74 cases between 1981 and 1986. <sup>630</sup>	The classic post-diarrheal hemolytic uremic syndrome begins when bacteria dying from host immunity and other causes release Stx into the intestinal lumen and initiate intestinal damage. Patients with hemolytic uremic syndrome have elevated circulating inflammatory cytokines (IL-8, IL-1 $\beta$ , TNF- $\alpha$ ). <sup>631</sup>
Sepsis syndrome	The incidence of sepsis in the United States increased annually between 1979 and 2000, from approximately 82.7 cases per 100,000 people to nearly 240.4 cases per 100,000 people. <sup>632</sup>	Individuals with sepsis frequently manifest damaged epithelia in numerous organs, such as alterations in vectorial ion transport, impaired barrier function, and increased cell-to-cell, paracrine, and endocrine communication. <sup>633</sup> The composition and function of the intestinal microbiota were significantly disturbed in patients with sepsis as shown by 16S rDNA sequencing, metabolomics, and metaproteomic analysis, and such enteric dysbiosis induced more organ inflammation and injury during sepsis. <sup>634</sup>
Severe COVID-19	The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) outbreak originated in Wuhan, China, <sup>447,449</sup> and its rapid spread worldwide caused COVID-19 disease to reach a pandemic status on March 11, 2020. <sup>450</sup> As of July 5, 2023, there have been over 767 million confirmed cases of COVID-19 worldwide as reported by the World Health Organization (WHO). <sup>451</sup>	Patients with severe COVID-19 infection displayed intestinal epithelial barrier dysfunction, altered upper respiratory and gut microbiota composition, and immune dysfunction. <sup>454,455,635–637</sup> Biomarkers of epithelial barrier defects at the time of hospital admission were proposed as predictors of a severe disease course. <sup>454</sup>

(Continues)

TABLE 7 (Continued)

Other diseases	Epidemiologic evidence	Evidence for epithelial barrier disruption, microbial dysbiosis, and microinflammation
Cardiovascular diseases	The incidence of cardiovascular disease (CVD) is rising globally, making it the primary cause of death in both developing and affluent countries. CVD is responsible for the death of 17.9 million people worldwide in 2016, accounting for 31% of all global deaths. Moreover, the prevalence of CVD increased from 257 million in 1990 to 550 million in 2019. <sup>638</sup>	Animal and human studies show differences in gut microbial composition between hypertensive individuals and controls, with a loss of diversity and higher levels of Gram-negative bacteria, which were correlated with elevated blood pressure. <sup>467</sup> In hypertensive mice, an increased gut permeability allows lipopolysaccharides (LPS) found in the outer membrane of Gram-negative bacteria to trigger systemic inflammation via Toll-like receptor 4. The pro-inflammatory effects of systemic LPS were demonstrated in endothelial subpopulations. <sup>470</sup> Chronic heart failure (HF) patients exhibit a loss of gut microbiota diversity that correlates with HF severity and ameliorated levels of beneficial bacteria. <sup>473,474</sup>
Polycystic ovary syndrome	The worldwide prevalence of polycystic ovary syndrome (PCOS) varies between 8 and 13%. There is mounting evidence that the condition has become more common over the past few decades. <sup>481,482,485</sup>	PCOS patients have exhibited gut dysbiosis compared with healthy controls, characterized by a reduction in short-chain fatty acid-producing and bile acid-metabolizing bacteria, suggesting a shift toward a pro-inflammatory environment. <sup>498</sup> A low fiber, high fat, and high sugar diet, along with obesity, can cause gut dysbiosis, leading to impaired intestinal permeability and a leaky gut. This, in turn, contributes to metabolic endotoxemia, chronic inflammation, and hyperinsulinemia in individuals susceptible to PCOS. <sup>490,502</sup>

problems, muscle pain, and joint pain. The mechanisms underpinning long COVID are thought to include an inappropriate immune response to acute SARS-CoV-2 infection, immune cell metabolic reprogramming, a persistent SARS-CoV-2 reservoir, an effect of reactivation of other viruses such as Epstein-Barr virus, inflammatory responses impacting the central nervous system, autoimmunity (including effects on the autonomic nervous system), coagulopathy, complement activation, and microbiome dysbiosis.<sup>462-465</sup> Given the breadth of symptoms described by long COVID patients, it is possible that distinct or a combination of multiple immune and epithelial barrier mechanisms are relevant for specific patient subgroups.

### 3.7.5 | Cardiovascular diseases: hypertension and structural heart disease

#### Hypertension

Hypertension is a leading chronic cardiovascular disease that results from the interplay between genetic predisposition, environmental factors, and lifestyle choices. In recent years, research has focused on investigating the crucial role of the gut barrier and microbiota in the pathogenesis of hypertension.<sup>466</sup>

Animal and human studies show distinct gut microbiota profiles in hypertensive individuals and controls, with aberrant microbial diversity and elevated levels of Gram-negative bacteria, linked to high blood pressure. Hypertensive individuals also show loss of beneficial bacteria that producing anti-inflammatory SCFAs. Dietary salt intake was demonstrated to alter gut microbiota composition. In mice models, supplementation with *Lactobacillus* spp. was found to mitigate salt-sensitive hypertension, possibly through TH-17 cell

modulation. In humans, probiotics containing *Lactobacillus* spp., lowered blood pressure in healthy controls. In animal models, the SCFA butyrate was shown to mitigate hypertension through histone deacetylase inhibition, impacting cytokine production.<sup>467-469</sup> In hypertensive mice, an increased gut permeability allows LPS found in the outer membrane of Gram-negative bacteria to trigger systemic inflammation via TLR-4. The pro-inflammatory effects of systemic LPS have been demonstrated in a small group of individuals.<sup>470</sup>

Trimethylamine-N-oxide (TMAO), a metabolic by-product of gut microbiota processing animal-derived L-carnitine and choline, plays a significant role in cardiovascular diseases. TMAO disrupts lipid metabolism, promotes atherosclerosis by increasing cholesterol accumulation, activates inflammatory pathways, and exacerbates vascular inflammation, contributing to oxidative stress and cytokine release also via activation of the NLRP3 inflammasome pathway. Therapeutic options to mitigate TMAO levels for the treatment of hypertension are currently under investigation, such as 3,3-dimethyl-1-butanol (DMB), resveratrol, and enalapril.<sup>471</sup>

#### Structural heart disease

Heart failure (HF) caused by cardiac injuries leading to structural and functional impairment remains a major health concern and is linked to rising morbidity and mortality rates. Emerging evidence suggests that dysfunctional gut barriers and dysbiosis may play important roles in the disease progression of several cardiomyopathies leading to HF.<sup>472</sup>

Chronic HF patients exhibited attenuated gut microbial diversity, correlating with HF severity and loss of beneficial bacteria, such as certain *Bacteroides* and *Lactobacillus* spp., and an overgrowth of pathogens, such as *Shigella*, *Campylobacter*, and *Salmonella*. In mouse

models, TAMO supplementation induced the onset of fibrosis and hypertrophy. In humans, TMAO levels were associated with HF severity and disease outcomes.<sup>473,474</sup>

The development of autoimmune myocarditis is induced by the gut microbe *Bacteroides thetaiotaomicron* as it triggers an immune response via an enzyme similar to the myosin heavy chain 6 (MYH6), leading to the proliferation and differentiation of pro-inflammatory T cells that infiltrate the heart. In certain patients, its abundance is linked to disease severity, suggesting a gut microbiome-host genotype interplay.<sup>473</sup> Myocarditis mouse models revealed that disease progression to lethal outcomes may involve heart-specific T cells, imprinted in the gut by a commensal *Bacteroides* species peptide mimic. Elevated *Bacteroides*-specific T-cell and B-cell responses in human myocarditis patients suggest that production of myosin-peptide mimics from commensal bacteria may promote inflammatory cardiomyopathy.<sup>475</sup> The presence of LPS in the bloodstream has also been associated with the development of HF. Studies indicate that LPS may impair myocardial function, exacerbating HF or triggering atrial fibrillation (AF).<sup>476</sup> HF with preserved ejection fraction (HFpEF) is characterized by a preserved left ventricular systolic function and objective evidence of left ventricular diastolic dysfunction. In the last decades, the prevalence of HFpEF has been simultaneously increasing with its risk factors, including hypertension, obesity, and diabetes. Recent studies demonstrated the association between circulating levels of the gut microbial metabolite phenylacetylglutamine (PAGln) with adverse HFpEF outcomes. PAGln mitigated cardiomyocyte contraction in vitro and elevated the expression of B-type natriuretic peptide.<sup>477</sup>

Furthermore, HFpEF-mouse models demonstrated attenuated indole-3-propionic acid (IPA) levels the benefits of IPA supplementation as it ameliorates diastolic dysfunction, oxidative stress, and inflammation. Human studies also confirmed diminished IPA levels in HFpEF patients.<sup>478</sup>

Atrial fibrillation (AF) plays a significant role in the development and progression of cardiomyopathies. Recent preclinical and observational studies have shown that gut barrier dysfunction with elevated circulating LPS leads to an upregulated atrial inflammation and exacerbates AF susceptibility.<sup>479</sup> In animal models, inhibition of the NLRP3 inflammasome has been associated with ameliorated AF and atrial fibrosis.<sup>480</sup>

Tailored approaches for the management of cardiomyopathies and heart failure have emerged that can potentially reshape the gut microenvironment and control inflammation. These include individual nutrition plans, probiotics, antibiotic therapy, and fecal transplantation. Further research on the skin and gut epithelial barriers is warranted in refining these interventions.

### 3.7.6 | Polycystic ovary syndrome

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorder in women of childbearing age which is characterized by polycystic ovaries, androgen excess, and ovulatory dysfunction accompanied by insulin resistance. This syndrome is the leading cause

of infertility mostly due to anovulation.<sup>481–483</sup> Although genetic predisposition has been emphasized in PCOS etiology, not more than 10% of cases are linked.<sup>481,484</sup> There are still unclear points in the etiology and pathophysiology of PCOS, which appears like PCOS is a multifactorial disease with genetic, epigenetic, and environmental backgrounds.<sup>481</sup> Despite the worldwide prevalence varies between 8% and 13%, there is a growing body of evidence of an increase in the prevalence of PCOS over the past decades.<sup>481,482,485</sup>

While in definition PCOS seems to be related to the ovaries and the reproductive system, remarkably it is associated with many other clinical outcomes including impaired glucose tolerance, type-2 diabetes, obesity, and dyslipidemia. Gestational diabetes, preeclampsia, miscarriage, premature labor, intrauterine growth retardation, endometrial hyperplasia, and endometrial cancer, in addition to cardiovascular complications, nonalcoholic fatty liver disease, depression, anxiety, negative body image, decreased self-confidence, and mood disorders are among the comorbidities seen in PCOS patients.<sup>486–488</sup> Reduced physical activity, sedentary lifestyle, altered light exposures, sleep disturbances, increased stress in addition change in diet, and exposure to environmental endocrine disrupter chemical agents are among the proposed causative factors.<sup>489–493</sup>

There are two main facts related to the adverse metabolic effects in PCOS. Primarily insulin resistance and compensatory hyperinsulinemia that can be accounted in nearly 70% of cases, and as a consequence majority of them are overweight or obese.<sup>494</sup> Besides, there is a well-recognized lean body type in PCOS patients due to the selective insulin resistance in the ovaries rather than whole body type insulin resistance.<sup>495,496</sup> Secondly, there is a chronic low-grade inflammation lead by metabolic endotoxemia.

Several studies have highlighted the role of gut microbiota in regulating insulin synthesis and secretion, and affecting androgen metabolism and follicle development in PCOS.<sup>497</sup> In a recent meta-analysis, gut dysbiosis has been marked in PCOS patients compared with healthy controls, which is characterized by the reduction in short-chain fatty acid-producing and bile acid-metabolizing bacteria that is suggesting a shift favoring a pro-inflammatory environment.<sup>498</sup> For example, the alpha diversity of gut microbiota and the relative abundance of Bacteroidaceae in women with PCOS were found high.<sup>499</sup> Mice transplanted with stool from individuals with PCOS displayed several features of the disease including insulin resistance.<sup>500</sup> Nowadays, Western-type diet can cause a reduction in beneficial bacteria like *Bifidobacterium* and *Lactobacillus*,<sup>489,492,501</sup> while an increase in pathogenic bacteria such as Gram-negative ones. Lipopolysaccharides (LPS) as a component of these bacteria can disrupt gut permeability, damage the enterocytes, and may cause a strong activation of the innate immune system.<sup>490,502</sup> In other words, low fiber/ high fat-high sugar diet, and obesity cause gut dysbiosis, which leads to impaired intestinal permeability causing a leaky gut making metabolic endotoxemia, chronic inflammation, and hyperinsulinemia in PCOS susceptible individuals. The chronic inflammatory state of PCOS is not limited to the ovaries, but also the changes in the level of relevant inflammatory markers such as C-reactive protein, interleukin-6, TNF- $\alpha$  ensue.<sup>503,504</sup>

Furthermore, hyperinsulinemia and hyperandrogenism, which are results of insulin resistance in PCOS patients, make these individuals more prone to obesity that further increase insulin resistance as a vicious circle. Androgen excess itself increases insulin resistance by malfunctioning of islets of Langerhans, thereby compromising the pancreatic functions making this vicious circle more complicated in which hyperinsulinemia and insulin resistance stimulating hyperandrogenemia, hyperandrogenemia stimulating insulin resistance as a never-ending cycle.<sup>505</sup>

Recently, research needs to be focused on altered gut microbiota, their products, metabolites, and increased intestinal permeability as a reason for insulin resistance, hyperandrogenism, and chronic low-grade inflammation in PCOS patients.<sup>506-508</sup>

## 4 | CONCLUSION

The epithelial barrier is attracting attention as mounting evidence implicates it in the pathogenesis of many chronic noncommunicable conditions. Diseases associated with an impaired epithelial barrier have been continuously rising in prevalence over the past six decades or after the 2000s; most of which have been shown to be linked to environmental factors (including air pollutants, cigarette smoke, toxic chemicals used in cleaning, and processed food). Western lifestyles and genetic susceptibility. Epithelial barrier-damaging agents induce the crosstalk between the epithelial barrier, microbiota, and an immune response, as reported in numerous studies of the pathogenesis of epithelial barrier-associated diseases. The studies presented within this review emphasize the significant implications of the epithelial barrier theory in unraveling the pathogenesis of chronic noncommunicable diseases and to elucidate novel strategies for the development of preventive or therapeutic approaches.

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All authors contributed to the conception, structure, development, writing, and review of the manuscript.

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#### DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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