# Are the Skin and Gastrointestinal Microbiomes Related to Skin Disease?

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## Introduction to Microbiomes

As humans we are home to trillions of microorganisms that live both on and inside us. This entire community is referred to as the human microbiome. Before the 21st century, culture methods were predominantly used to identify these organisms; contributing to an underestimated and inaccurate picture of our microbiome[1]. The development of molecular sequencing methods have allowed researchers to now more accurately describe the microbiome and the functional roles of its metagenome[1]. Through such methods we can begin to understand how our microbiome contributes to both health and disease.

***Figure 1: Dominant skin microorganisms by location***

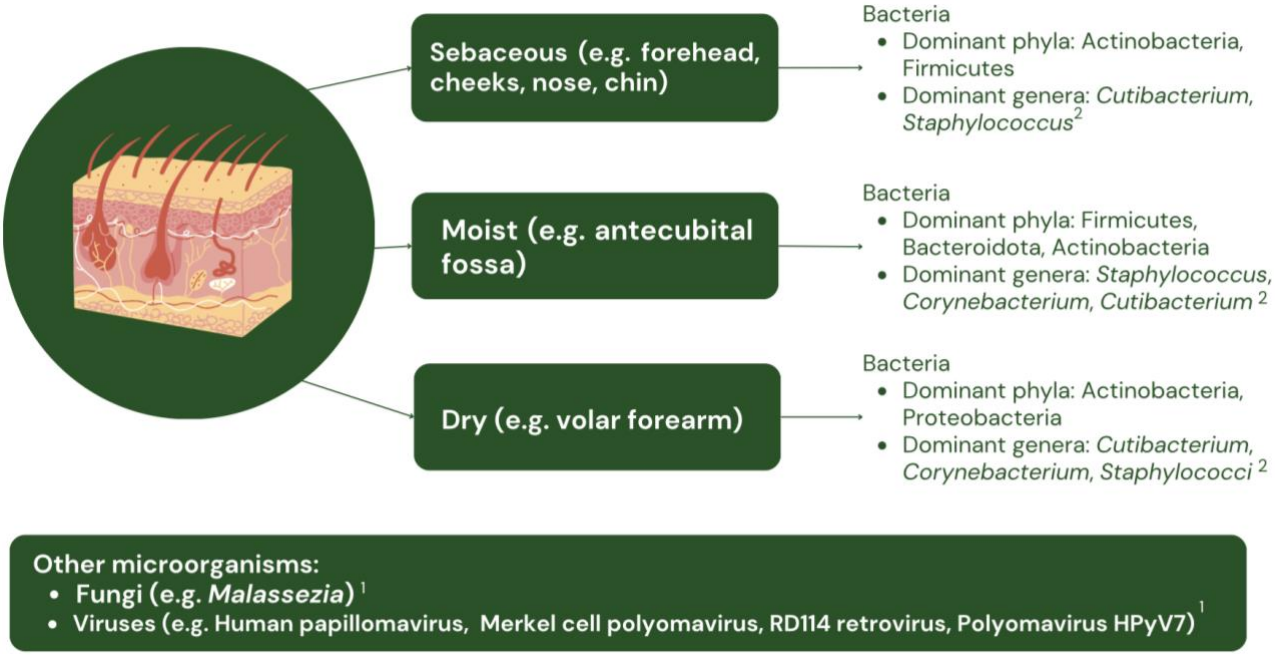
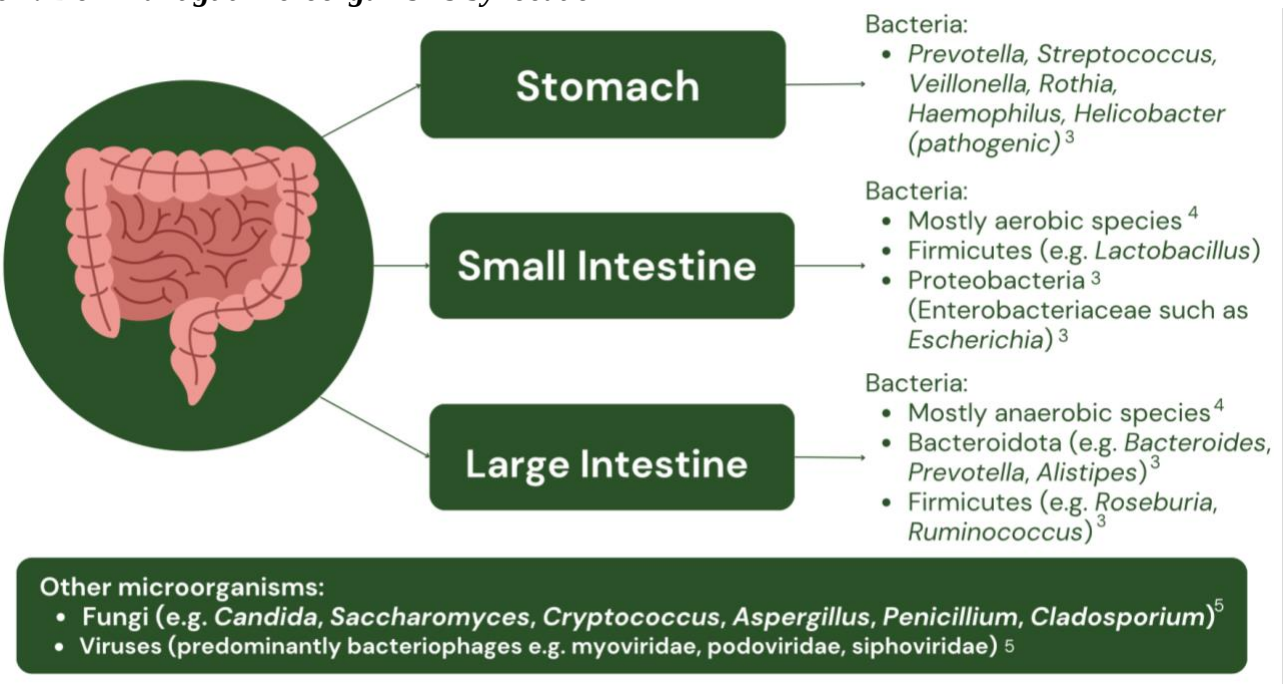



***Figure 2: Dominant gut microorganisms by location***



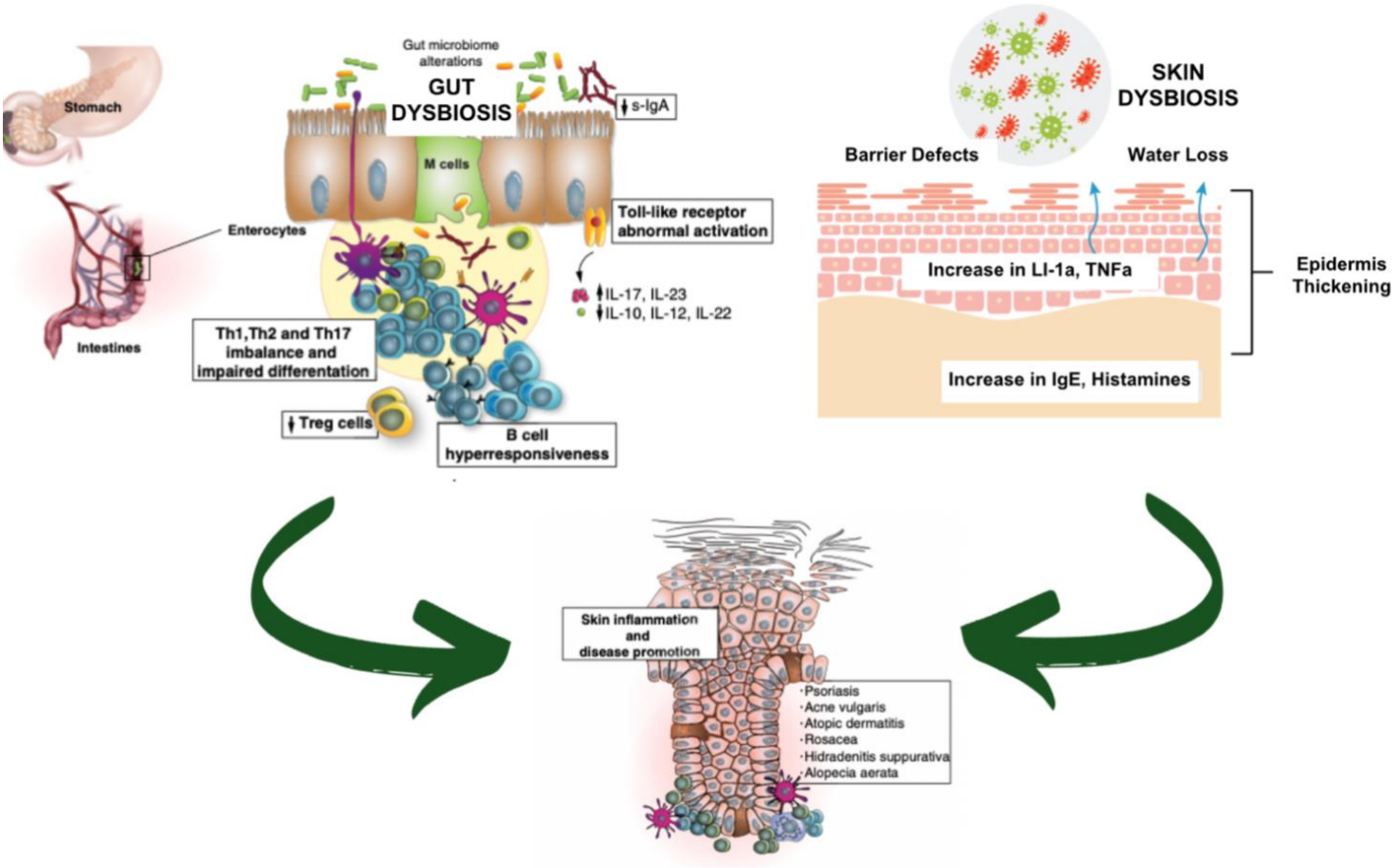
## How Skin & Gut Microbiomes Relate to Skin Disease

Skin is our largest organ and one visible to the outside world – meaning its disease can be extensive and affect patients biopsychosocially. The skin is also first line of defense against pathogenic microbial invasion. Tight connections between corneocytes form a physical barrier, and antimicrobial peptides and lipids secreted by keratinocytes and glands provide a chemical barrier[6].

In eubiosis, the skin microbiome contributes towards health. Commensals help maintain the barrier function and prevent colonization of pathogens by utilizing space and resources, as well as producing antimicrobial compounds[2]. A eubiotic microbiome also contributes to proper regulation of the immune system as well as environmental factors such as skin pH[2,7]. In dysbiosis, these beneficial commensals are reduced whilst pathogens increase[7]. This can lead to a decrease in the skin's protective functions, and modifications in immune system reactivity that leads to the development of inflammatory disease[8].

In a similar way, dysbiosis of the gut microbiome can lead to skin disease[8]. This mechanism is termed the gut-skin axis and is one of the reasons there are cutaneous manifestations for many gastrointestinal conditions[9]. A healthy functioning gut microbiome prevents the passage of noxious substances across the gut mucosal surface[10]. Dysbiosis can lead to such substances and pathogens crossing the mucosal barrier and entering the bloodstream - allowing them to travel to peripheral sites such as the skin[10].

***Figure 3: Mechanisms by which dysbiosis can lead to skin disease (adapted from Polkowska-Pruszynska et al.[11] and blis.co.nz/health-areas/skin-health[12]).***



## Evidence & Potential Mechanisms

### Atopic Dermatitis

Atopic dermatitis (AD) is the commonest skin disease worldwide, and is characterised by dry skin and itchy, scaly rashes[13]. Factors contributing to AD are epidermal barrier impairment, immune activation and microbiome dysbiosis[1].

Skin-Microbiome Relation

Longitudinal studies have shown that the relative abundance of *S. aureus* increases during an AD flare up compared to the post-flare state[1]. Increased *S. aureus* is also directly correlated with increased disease severity[14,15,16]. The relationship between this microbe and AD is further highlighted with the success of bleach baths[17] – an intervention that improves disease severity by decreasing the prevalence of *S. aureus*.

Two skin areas that are commonly affected in AD are the inner elbow and popliteal regions. These areas have been shown to have decreased microbial diversity in AD patients relative to the same skin area in healthy controls[15]. Therefore, a decrease in microbial diversity may also contribute to AD development.

Gut-Microbiome Relation

Antibiotic use during pregnancy and C-section delivery is associated with a higher risk of AD development in children[11]. These factors lead to impaired bacterial colonisation of the gut in neonates, which is the likely mechanism behind this association. This is in line with the hygiene hypothesis[7] which states that a lack of microbial exposure leads to poor immune tolerance – causing increased sensitisation and allergy. As AD is part of the atopic triad, it is likely such microbiome interferences contribute to its development. Further supporting this theory is the finding that children supplemented with probiotics were found to be at a lower risk of developing AD[11].

### Psoriasis

Psoriasis is a T-cell mediated inflammatory skin disease characterised by well demarcated, erythematous, scaly plaques[18].

Skin-Microbiome Relation

Most studies report that psoriatic lesions are characterised by higher relative abundances of Firmicutes and lower relative abundances of Actinobacteria compared to controls[18]. At the genus level, lesional samples contain more *Streptococcus*, *Staphylococcus*, and *Corynebacterium* compared to controls, as well as decreased *Cutibacterium*[18]. A decrease in alpha diversity is also characteristic of psoriatic lesions[18].

Gut-Microbiome Relation

Numerous studies have highlighted a difference in beta diversity between the gut microbiome of psoriasis patients and healthy controls[19]. Bacteroidota are found to be decreased in psoriasis patients and Firmicutes and Actinobacteria increased[20]. The mechanism by which such changes may contribute to psoriasis has been investigated using experimental models. These models demonstrated that gut dysbiosis aids Th17-mediated skin inflammation[21,22]. They showed that dysbiosis affects metabolite production and induces immune cell activation through the IL-23/IL-17 signalling pathway – resulting in keratinocyte hyperproliferation[4].

## Acne Vulgaris

Acne is a chronic condition which affects the pilosebaceous unit. It is highly prevalent in adolescents, affecting 85% of 16 to 18-year-olds[23].

Skin-Microbiome Relation

It has long been thought that *C. acnes* is the acne causing culprit. Despite its abundance in acne affected skin, it does not however fulfil all Koch's postulates – with increasing evidence that *C. acnes* is equally abundant in unaffected skin[24]. It has now been found that an imbalance between certain *C. acnes* phylotypes (instead of *C. acnes* presence overall), is what contributes to acne development[24].

A metagenomic study highlighted that *C. acnes* strains associated with disease contain several virulence-associated gene elements[25]. For example, a CRISPR/Cas locus is present in health-associated strains and absent in acne-related strains[24]. CRISPR is an immune mechanism bacteria have against foreign DNA, and its presence in *C. acnes* may prevent the acquisition of genetic elements that promote acne pathogenesis[24]. Emphasising this was the finding of a novel plasmid present in acne-associated *C. acnes* strains which contained a tight adhesion locus – this is essential for biofilm formation, colonisation and virulence[26,27].

Biofilm formation is an important virulence mechanism, as polymicrobial biofilms containing *C. acnes*, *Staphylococcus* and *Malassezia* were reported to be more frequent in the follicles of acne lesions compared to controls[28]. These biofilms can act as a glue in the pilosebaceous unit and restrict the passage of sebum into the infundibulum. This leads to comedo formation and accumulation of corneocytes in the lumen – ultimately resulting in a keratinaceous plug and comedone development[29].

Gut-Microbiome Relation

In a study analysing the faecal bacterial diversity in acne patients versus controls, distinct differences in microbial diversity were found between the two groups[30]. Acne patients' gut microbiome was less diverse and had a higher ratio of Bacteroidetes to Firmicutes[30]. They also had decreased *Clostridia*, *Ruminococcaceae*, *Bifidobacterium*, *Coprobacillus* and *Lactobacillus* compared to healthy controls[30,31]. Those with moderate to severe disease have been found to have a decrease in gut Actinobacteria and an increase in Proteobacteria[31,32].

There is also an increased prevalence of hypochlorhydria amongst acne patients[33]. This can cause gut dysbiosis and small intestinal bacterial overgrowth (SIBO) leading to skin inflammation[33].

## Rosacea

Rosacea is a chronic inflammatory skin disease, characterised by recurrent episodes of facial flushing, erythema, pustules and telangiectasia[34].

Skin-Microbiome Relation

The skin of rosacea patients has increased densities of mites (specifically *D. brevis* and *D. folliculorum*) compared to healthy controls[34]. An association between *D. folliculorum* and raised inflammatory markers has also been shown, suggesting the mite may have a role in activating the immune system pathologically[35]. Cytokines activated in *D. folliculorum* associated inflammation include IL-8 and TNF-a. These cytokines promote angiogenesis, so may be a cause of the telangiectasis which is present in rosacea[34].

*S. epidermidis* is another microorganism which may have a role in rosacea. When comparing skin affected by rosacea and adjacent unaffected skin, researchers observed a significant increase in *S. epidermidis* in the affected areas[36]. Abundant levels of *S. epidermidis* have also been detected in pustular lesions of rosacea patients[37]. In addition to this, it has been shown that in rosacea patients there is increased cutaneous blood flow to the face which leads to an elevated detectable temperature. At these higher temperatures, *S. epidermidis* produces proteins that may act as virulence factors – proteins that aren't found in healthy controls[37].

Gut-Microbiome Relation

SIBO is suspected to be related to rosacea, with one study finding that patients with rosacea were 13 times more likely to have SIBO compared to controls[34]. Administration of rifaximin to eradicate SIBO in these patients lead to significant regression of skin lesions in almost all patients[34] and persisted in the majority for over 3 years. It was concluded that SIBO, and not antibiotic, was responsible for rosacea clearance, as in rosacea patients without SIBO antibiotic therapy did not lead to regression of lesions. In another study, 51% of rosacea patients had SIBO, whilst only 23% of rosacea-free individuals had SIBO[34].

A mechanism underlying the relation of the gut microbiome to rosacea may be the activation of the plasma kallikrein-kinin system (PKKS). These pathways are significantly activated in patients with intestinal inflammation and dysbiosis, and also in patients with rosacea when compared to controls[34].

**Hidradenitis Suppurativa**

Hidradenitis suppurativa (HS) is an autoinflammatory skin condition that affects skin in the axilla, groin and under the breasts[38]. It is characterised by persisting boil-like nodules and abscesses that result in purulent discharge, sinuses, and scarring[38].

Skin-Microbiome Relation

It has been found that the skin microbiome in HS is significantly different from healthy controls in both lesional and non-lesional skin areas[39]. This includes a significant loss of variety in HS patients' skin microbiome and increased anaerobe presence in lesional skin[40]. Microorganisms found to be abundant in HS skin compared to healthy skin include *Porphyromonas*, *Peptoniphilus*, *Prevotella* and *Fusobacteria*[40]. Interestingly, *Cutibacterium* are commonly decreased in HS patients[39]. As *Cutibacterium* are an abundant commensal that contributes to skin health via its bactericidal properties, its reduction may be involved in the pathogenesis of HS.

Gut-Microbiome Relation

A recent systematic review included 5 meta-genomic sequencing studies investigating the gut microbiota in patients with HS[40]. These studies collectively highlighted that HS is associated with alterations in the gut microbiome composition – with both reduced overall diversity and changes in specific bacterial species. *Robinsoniella*, *Bilophila*, *Holdemania* and *Ruminococcus* were commonly present in HS samples compared to healthy controls, suggesting they might have a role in the pathogenesis of the disease[40].

**Malignant Diseases**

Melanoma is the third most common cancer in New Zealand and accounts for 80% of deaths from skin cancer[41]. A study looking at the relationship between the gut microbiome and melanoma found that alpha diversity was higher in healthy controls compared to those with melanoma[42]. Alpha diversity was also decreased in melanoma patients with late-stage disease compared to those at early stages. This suggests that a loss of gut microbiome diversity is related to both disease state and disease progression in melanoma.

There is also a compelling causal link between the presence of the oncovirus called Merkel Cell Polyomavirus and the rare but aggressive neuroendocrine skin cancer termed Merkel Cell Carcinoma (MCC)[43]. This oncovirus develops in hair follicles beneath the skin and can be found in 80% of MCCs[43].

## Conclusions & Future Implications

The skin and gut microbiomes are related to skin disease, with dysbiosis and decreased microbial diversity being common hallmarks. Whilst this relationship exists, there is uncertainty around its mechanisms. Studies often cannot conclude whether its the microbiome changes causing disease, or disease causing the microbiome changes. It is important that more in depth investigations are done to figure out the intricacies of this relationship. Future studies will need to rigorously account for a number of factors (e.g. sex, ethnicity, antibiotic use, comorbidities, family history, neuroendocrine involvement), as many variables have the potential to influence the microbiome.

In saying that, this report highlights how specific patterns of microbiome composition are associated with particular skin diseases. Understanding these patterns and the mechanisms underlying their pathogenicity has the potential to both aid in diagnosis (e.g. microbiome based biomarkers for certain conditions) as well as therapeutically (correcting the dysbiosis). In today's world there is rising public concern over treatment such as topical steroids, making investing into producing effective pre/probiotic treatment methods especially worthwhile. The changing climate and the environmental effects of global warming are also impacting our microbiomes[44]. We must understand this relationship between microbiomes and disease and utilise it to maximise health.

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