



REVIEW

Metabolic phenotyping of the human microbiome [version 1; peer review: 2 approved]

Wiley Barton ¹⁻³, Orla O'Sullivan ¹⁻³, Paul D. Cotter¹⁻³

¹Department of Food Biosciences, Teagasc Food Research Centre, Moorepark, Fermoy, Cork, P61C996, Ireland

²APC Microbiome Ireland, University College Cork, National University of Ireland, Cork, T12YT20, Ireland

³VistaMilk SFI Research Centre, Teagasc, Moorepark, Fermoy, Cork, P61C996, Ireland

v1 **First published:** 22 Nov 2019, 8(F1000 Faculty Rev):1956 (<https://doi.org/10.12688/f1000research.19481.1>)
Latest published: 22 Nov 2019, 8(F1000 Faculty Rev):1956 (<https://doi.org/10.12688/f1000research.19481.1>)

Abstract

The human microbiome has been identified as having a key role in health and numerous diseases. Trillions of microbial cells and viral particles comprise the microbiome, each representing modifiable working elements of an intricate bioactive ecosystem. The significance of the human microbiome as it relates to human biology has progressed through culture-dependent (for example, media-based methods) and, more recently, molecular (for example, genetic sequencing and metabolomic analysis) techniques. The latter have become increasingly popular and evolved from being used for taxonomic identification of microbiota to elucidation of functional capacity (sequencing) and metabolic activity (metabolomics). This review summarises key elements of the human microbiome and its metabolic capabilities within the context of health and disease.

Keywords

microbiome, metagenomics, metabolomics, short chain fatty acids, bile acids

Open Peer Review

Reviewer Status

	Invited Reviewers	
	1	2
version 1 published 22 Nov 2019		

F1000 Faculty Reviews are written by members of the prestigious **F1000 Faculty**. They are commissioned and are peer reviewed before publication to ensure that the final, published version is comprehensive and accessible. The reviewers who approved the final version are listed with their names and affiliations.

- 1 **Robert E Brown**, George Mason University, Manassas, USA
- 2 **Jack A Gilbert**, University of California San Diego, La Jolla, USA

Any comments on the article can be found at the end of the article.

Corresponding author: Orla O'Sullivan (orla.osullivan@teagasc.ie)

Author roles: **Barton W:** Conceptualization, Visualization, Writing – Original Draft Preparation; **O'Sullivan O:** Conceptualization, Funding Acquisition, Supervision, Writing – Review & Editing; **Cotter PD:** Conceptualization, Funding Acquisition, Supervision, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

Grant information: This work was funded by Science Foundation Ireland (SFI) in the form of a centre grant (APC Microbiome Institute Grant Number SFI/12/RC/2273). Research in the PDC laboratory is funded through a principal investigator award, 'Obesibiotics' (11/PI/1137). OOS is funded by the SFI starting investigator research grant (13/SIRG/2160). WB is currently supported by a joint research centre grant from SFI and the Department of Agriculture, Food and Marine on behalf of the government of Ireland (VistaMilk, 16/RC/3835)

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Copyright: © 2019 Barton W *et al.* This is an open access article distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

How to cite this article: Barton W, O'Sullivan O and Cotter PD. **Metabolic phenotyping of the human microbiome [version 1; peer review: 2 approved]** F1000Research 2019, 8(F1000 Faculty Rev):1956 (<https://doi.org/10.12688/f1000research.19481.1>)

First published: 22 Nov 2019, 8(F1000 Faculty Rev):1956 (<https://doi.org/10.12688/f1000research.19481.1>)

Introduction

The human microbiome as it relates to metabolic function and health

It has been established that communities of microorganisms, *microbiota*, reside on or within nearly every physical substrate on our planet (and associated artificial satellites)^{1–10}. Composed of organisms encompassing multiple divisions of the tree of life, such as protozoa^{11–16}, fungi^{17–20}, viruses^{21–24} and prokaryota^{25–29}, these microbial communities are intricate ecological structures driven by the production and exchange of metabolic products^{29–34}. Indeed, these communities can cause metabolic cascades that have measurable influences on their macroscopic hosts. Through recognition of these influences, the importance of the microbiome as an integral component of human biology has come to be appreciated, not only by microbiologists but by clinicians and the general public. This review describes essential background to the human microbiome, providing an overview of microbiomes delineated by human anatomy within the framework of microbe–host metabolic interaction before focusing on these interactions as they relate to the gut.

Womb to tomb

Present from birth to death, an individual's microbiome maintains a constant presence as a chimeric organ^{35–38}. Seeding of this microbial system occurs at the beginning of life via transmission of a mother's microbiome to her infant during the birthing process^{39–43}. Influenced by direct environmental transmission, a delivered infant will inherit either the mother's vaginal and faecal microbiota as it passes through the birthing canal or the skin microbiota during caesarean delivery^{39–41}. Either route of delivery imposes prolonged multifaceted effects on the infant^{44,45}. Vaginal birth confers a microbiome of the mother's urogenital system which has undergone specific alterations throughout the pregnancy which are conducive to the development of robust and functional immune and gastrointestinal (GI) systems of the infant⁴². Alternatively, numerous deleterious health effects for infants delivered by caesarean section have been identified. Immediate influences upon the infant include increased risk of exposure to antibiotic-resistant bacteria from the mother's skin⁴⁰. Long-term insults to health arising from caesarean delivery include greater risk of developing obesity, sensitivity to food and inhalant allergens, and asthma^{44–48}. In light of increasing awareness of potential negative health effects associated with caesarean delivery, an experimental procedure of vaginal seeding has been developed to simulate the microbial exposures present in vaginal birth via administration of vaginal swabs to newly delivered infants⁴⁹. However, implementing vaginal seeding is a contentious issue, and many clinical practitioners are wary of the intervention prior to extensive investigation of its effects^{50,51}.

Throughout infancy, an individual's core microbiome is continuously influenced by the mother and environment. Whether nourished by the mother's natural breast milk or formula, the infant microbiome continues to be moulded through supplied nutrition. In this regard, a positive health bias towards biological 'tradition' persists, as both the process of breast feeding and breast milk itself, and potentially the microbes therein, convey health benefits superior to those of formula^{42,52,53}.

Progressing through infancy, the microbiome goes through highly variable changes, beginning to stabilise at about 2 years of age. Flux of the microbiome during this period is attributed to numerous factors, including dietary variations (for example, milk versus solid food), immunological development, introduction to novel microbes, and antibiotic exposure^{40,42,43,53–55}.

Through the transition from infancy to childhood and onto adulthood, the microbiome of an individual stabilises while still being influenced by drug exposure^{29,56–59}, physical activity^{60–70}, the environment³ and diet^{21,71,72} (discussed more elaborately in proceeding sections)^{73,74}. The microbiome changes again with old age^{75–77}, and microbes ultimately contribute to decomposition after death^{78–80}.

The human body: a microbiome perspective

Microbial communities take form within any accessible area of a host's body. The defined niches with stable communities in humans and other mammals are currently generalised to the respiratory system^{20,81–84}, nasal^{25,85,86} and oral^{17,25,26,87} cavities, skin^{22,25,26,41,88–93}, vagina and urinary tract^{25,40,41,49,94–96}, and GI system^{21,25–27,29,36–38,40,97}. For each of these unique communities, varied challenges are involved in their sampling and analysis and in interpreting their impact on health or disease.

The skin

Comprising a relatively large surface area (~1.8 m² for an adult human) and an array of subsystems defined by folds, crevices, pH, secretion profiles, and environmental exposures, the skin supports highly varied microbial communities functioning in diverse ecological constraints (Figure 1A)^{89,98,99}. Ecological partitioning of the skin microbiome is further defined by elementary biological traits of the host. Microbial composition at specific anatomical locations coordinates with gender^{98,100,101}. Indeed, topical sampling of hand palms demonstrates greater diversity of bacterial taxa in women than men, and specific taxa are differentially abundant between the two sexes^{100,101}. Similar results have been presented for other body sites, such as the thigh and torso^{98,100}. Expectedly, cohabitation of sexually active partners results in a shared skin microbiome that accurately matches couples 86% of the time¹⁰⁰. Ancestral host genetics have also been demonstrated to influence the composition of the skin microbiome. Male participants of diverse ethnic backgrounds, all dwelling in a single geographic location, were shown to have microbial differences specific to ethnicity¹⁰². Furthermore, a study of both monozygotic and dizygotic twins described an association between *Corynebacterium jeikeium* and single-nucleotide polymorphisms of a host gene involved in epidermal barrier function¹⁰³. This finding suggests that the establishment of specific skin microbes is dependent on heritable factors of the host. Despite such associations with the skin microbiome, ancestral genetics have been shown to exert a negligible influence on the gut microbiome, where instead other factors, such as environment, play a more profound role in the form and function of the microbial community¹⁰⁴.

Continuous environmental interaction unsurprisingly results in the skin being our most exposed microbial ecosystem. Environmental factors shown to be influential include hygiene

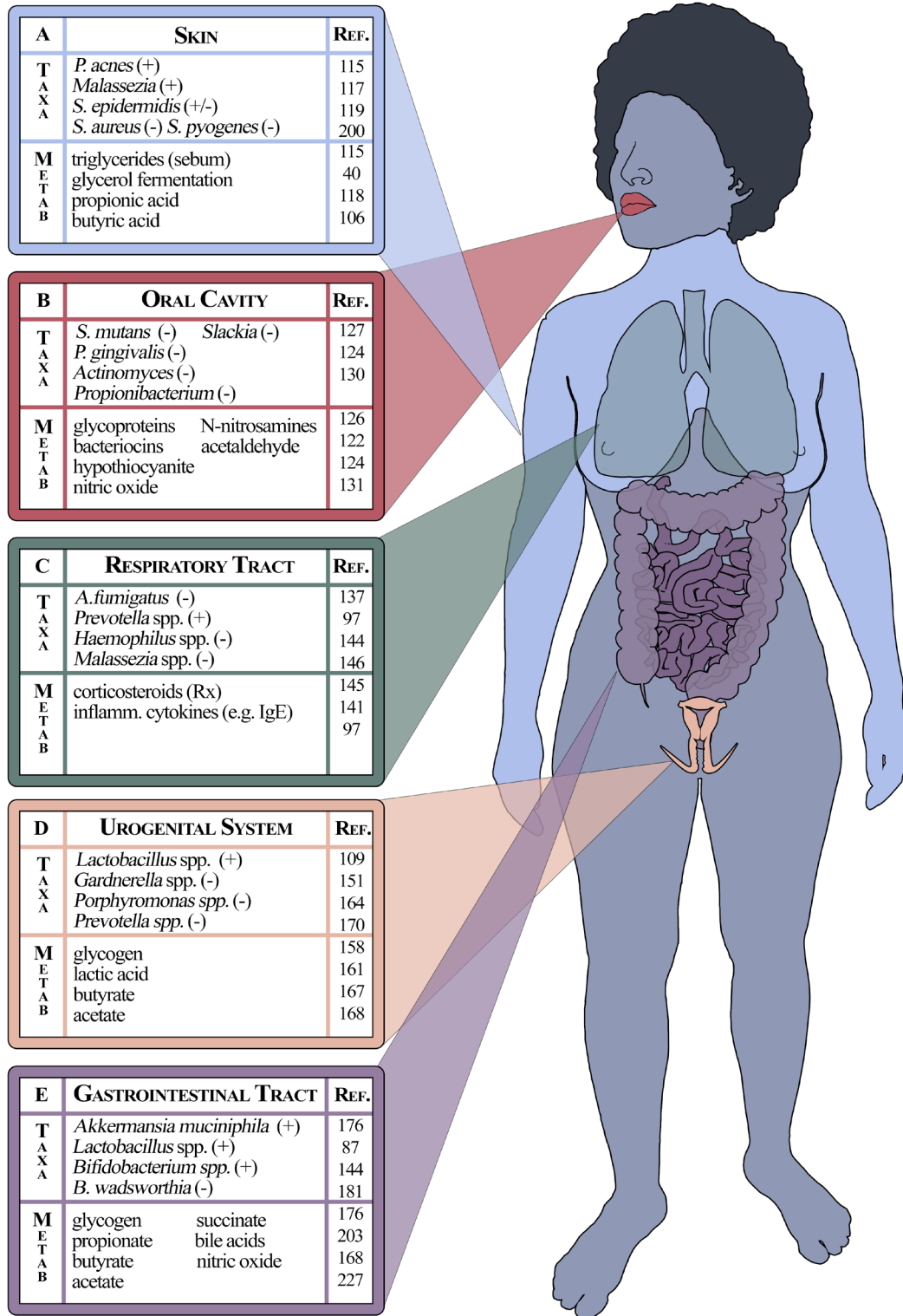


Figure 1. Demonstration of key microbiota and metabolites of the human microbiome, delineated according to human physiology. (A) The skin, (B) oral cavity, (C) respiratory tract, (D) urogenital system and (E) gastrointestinal tract are each highlighted with examples of microbiota (Taxa) and relevant metabolic activity (Metab). Beneficial associations to host health are denoted as (+) and negative associations as (-).

routines, topical medication and cosmetic use, and residential environment (for example, rural versus urban)^{89,91,98,101,105}. Despite its vulnerability to external perturbations, an individual's skin microbiome maintains a consistent core structure¹⁰⁶. Though capable of opportunistic pathogenicity under certain conditions, constituents of this stable community perform homeostatic functions and act as a barrier against transient and potentially pathogenic species, subsequently maintaining a role in a variety of cutaneous conditions^{93,106–108}. Among these residential members are strains of *Propionibacterium acnes*, the fungal genus *Malassezia*, and *Staphylococcus epidermidis*^{106,108–110}. Lipophilic *P. acnes* and species of *Malassezia* proliferate in sebaceous gland-rich body sites, such as the face and back^{89,108,109}. The rich pool of triglycerides found in sebum are hydrolysed by microbes to produce fatty acids that assist in bacterial adherence and maintaining an acidic pH^{108,111}. Low pH environmental conditions select for lipophilic commensals while inhibiting colonisation by potentially pathogenic strains of *Staphylococcus aureus* and *Staphylococcus pyogenes*^{108,112}. *P. acnes* additionally contributes to suppression of methicillin-resistant *S. aureus* through glycerol fermentation to short-chain fatty acids (SCFAs) and in particular propionic acid, which also inhibits growth of *Escherichia coli* and *Candida albicans*^{107,112,113}.

The mouth

The oral cavity microbiome represents a reasonably well-defined ecosystem (Figure 1B). Structure morphology and different tissue types within the human mouth offer a variety of microbial habitats, further delineated by conditions of oxygenation, pH, and nutrient availability^{114,115}. Control of the oral microbiome is mediated in concert by factors produced by the host and the microbiota^{114,116–118}.

Immunological training by microbiota seeded early in life enables the host to distinguish between the commensal core and transient pathogenic microbes, wherein selected commensals create biological barriers through biofilm formation, alter pH and oxygen levels, and produce antimicrobial molecules^{116,118,119}. Bacteriocins (that is, small peptide antimicrobials that include the lantibiotics and microcins) are one such means of microbial-derived molecular regulation of community composition within the mouth (and other microbial systems)¹¹⁸. The underlying mechanisms coordinating this antagonistic inter-microbe regulation of community structure require further elucidation; however, its complexity is highlighted by findings of at least 1,169 putative lantibiotic gene clusters within the oral metagenomes defined by the Human Microbiome Project¹²⁰.

Within this environment, saliva moistens the mouth, aiding in the mastication, swallowing and digestion of food. Saliva also provides an essential nutrient source for microbes, containing complex molecules such as glycoproteins (for example, mucins)^{114,116,121,122}. Similarly, saliva-derived proline-rich glycoproteins contribute to pellicle formation on mouth surfaces, immobilising microbes through their adherence to the structures^{114,116}. Bioactive compounds found within saliva also include potent factors that inhibit growth or otherwise modify the microbial

complex's activity within the mouth. For example, bacterial growth is curbed by lysozyme-mediated cell lysis and interference of glucose metabolism with lactoperoxidase-catalysed conversion of hydrogen peroxide and thiocyanate to hypothiocyanite^{114,116}.

Sustaining a balanced oral microbiome is thought to confer numerous local and systemic health benefits. Nitric oxide (NO) is an important cellular signalling molecule, crucially involved with various physiological functions: metabolism, nerve function, and cardiovascular function. Key oral microbiome constituents have demonstrated the ability to reduce dietary nitrates to nitrite^{116,122,123}. Converted nitrite is deposited into saliva, which is ingested after oral cavity circulation, leading to NO conversion and the subsequent transmission to tissues across the body^{122,123}. Countering the potential health benefits of bacterial nitrite supplementation, the compound may stimulate cancer development through formation of carcinogenic N-nitrosamines¹²³. Posing a similar risk of carcinogenesis, acetaldehyde is produced from ethanol by oral bacteria¹²².

Dysfunction of the oral microbiome contributes directly to dental diseases; the most widely recognised such condition is tooth decay or dental caries. Caries formation begins with bacterial fermentation of carbohydrates to organic acids, resulting in localised pH reduction and subsequent tooth demineralisation^{114,116,119,122}. Once the site has been acidified, the affected environment becomes increasingly selective for bacteria that are tolerant of low pH conditions, thus stimulating proliferation of destructive communities and worsening of the condition^{114,116,122}. Although *Streptococcus mutans* is implicated in tooth decay, it is evident that no single organism is the causative agent, and instead polymicrobial activity drives the condition with diverse actors from genera such as *Actinomyces*, *Slackia*, *Propionibacterium* and *Lactobacillus*¹¹⁹.

Periodontal disease is also caused by microorganisms. Prolonged biofilm formation at the interface of gingival tissue and the tooth surface leads to the accumulation of pathogenic bacteria that exacerbate inflammation through cytotoxic compounds such as lipopolysaccharides^{116,122}. Resultant bleeding from inflammation provides a source of iron from heme, a molecule used by pathogenic microbes (for example, *Porphyromonas gingivalis*)^{116,122}. Without disruption, periodontitis-associated microbes thrive and, with continued immunological antagonisation of the gingival tissue, contribute to induction of a dysregulated inflammatory response, permanently damaging connective tissue and bone^{116,122}.

The nose and respiratory system

At one time, the human lung had been considered a sterile biological system unless challenged with disease. Now, however, it is clear that a respiratory microbiome exists (Figure 1C).

When healthy, the lung environment reflects many characteristics of the mouth and nose interiors, namely moderate thermal stability, high oxygen availability, mucosa-lined internal surfaces, and a continuous influx of environmental

microbes. Despite these similarities, modern investigation of respiratory-related microbes in the lungs projects a microbiome of low phylogenetic diversity^{124–126}. The simplicity of the lung microbiome contrasts with that of the oral cavity, although the latter acts as a major channel for microbiota translocation, and microaspiration of aerosolised material from the upper respiratory tract and direct migration along the oropharynx mucosa occur^{126,127}.

Whereas some human microbial communities exhibit high levels of diversity when healthy, presenting associations between disease and reduced diversity, the respiratory microbiome is thought to be more susceptible to malignancy when the complexity of its composition increases^{25,116,126,128,129}. This is observed as far up in the respiratory system as the nasal cavity, and elevated diversity of the inner nostril is associated with a number of allergies¹⁰⁰. Conversely, post-surgical outcome of sinus surgery is better with more diverse sinonasal microbial communities, suggesting an unpredictable complex relationship between upper respiratory tract microbial diversity and health¹³⁰. Ultimately, caution needs to be used when considering diversity as a marker of health.

A clear association between the lung microbiota and compromised pulmonary health has been demonstrated with asthma, an inflammatory disease^{20,83,85,129,131,132}. As is the case for many microbiome–health interactions, evidence supports early-life microbial exposures as being critically influential with respect to respiratory health. Strong epidemiological associations assert an increased risk of inflammatory respiratory disease with caesarean birth and reduced risk from diverse antigen presentation (such as rural and farm exposures)^{46,47,133–135}. More specifically, bacterial species of *Lachnospira*, *Veillonella*, *Faecalibacterium* and *Rothia* were found at low relative abundance in the guts of children deemed to be at higher risk of developing asthma¹³⁵. Other studies have highlighted differences in community complexity of airways that relate to asthma phenotype^{20,83,85,129,131,132}. For example, patients with type 2-high (T2-high) asthma, a form of the disease marked by specific type 2 immunological responses, were shown to have significantly lower diversity of fungal species in airway samples when compared with other patients with asthma¹³². The same study reported an enrichment of species from the *Trichoderma* fungal genus in T2-high patients. Among the extensive work carried out in characterising the role of microbes in asthma, associations have been made between a deviation from the typical predominance of Bacteroidetes members (for example, species of *Prevotella*) to those of Proteobacteria (for example, *Haemophilus* species)^{83,136,137}. Given the observation that Proteobacteria are a predominant component of the skin microbiome, it may be that a detrimental transposition of skin-associated microbiota into the lungs plays some role in the aetiology of the disease^{100,108}. Although this possibility is intriguing, more robust characterisation of which specific Proteobacteria species are present in the separate sites would be needed to further the theory. Similarly, some analysis of the fungal component of the pulmonary microbiome implicates the presence of *Malassezia* species in asthma¹³⁸. This fungal species is better known

as a factor in atopic and seborrhoeic dermatitis, providing a further potential link between the deleterious translocation of skin microbiota and asthma¹¹⁰. It should be noted that these potential links need to be definitely established.

Although our understanding of the respiratory microbiome's general role in health is continuing to evolve, there is evidence of compositional alterations in the asthmatic lung microbiome in response to corticosteroid treatment^{131,137}. Patients with asthma, regardless of whether the asthma is resistant or sensitive to corticosteroid treatment, show reduced Bacteroidetes abundance and increased levels of Proteobacteria and Actinobacteria species¹³¹. Additionally, host-derived peripheral blood monocytes from the lungs of corticosteroid-resistant patients had inhibited corticosteroid response when co-cultured with an isolate of *Haemophilus parainfluenzae*, a potential pathogen associated with asthma¹³¹.

The vagina and urinary tract

The urogenital microbiome influences female health in a variety of ways. It is also responsible for seeding the microbiome of infants passing through the birth canal in the case of vaginal delivery. The establishment of this microbiome can have lifelong influences on the health of the infant^{43,44,139–141}.

Substantial effort has been put towards characterisation of vaginal microbial components and associated metabolic function (Figure 1D). The healthy vaginal microbiome is characterised as maintaining low microbial diversity, and *Lactobacillus* species typically dominate^{25,96,142}. Disruptions to the healthy vaginal microbiome's stable low complexity are linked to severity of cervical intra-epithelial neoplasia and bacterial vaginosis (BV), and the latter is also associated with an increased susceptibility to acquiring sexually transmitted infection, pelvic inflammatory disease, and preterm birth^{94,143–148}.

Lactobacillus dominance of the vaginal microbiome appears to be specific to humans and contrasts greatly with levels found in other animals (>70% and ~1%, respectively)¹⁴⁹. Several theories have been proposed for the *Lactobacillus*-centric human vaginal microbiome, including a suggestion of a conserved common function of vaginal microorganisms that in humans happens to be fulfilled by *Lactobacillus* species, and that these species are also adapted to the starch rich diets that are typical of humans¹⁴⁹. Indeed, the diet hypothesis further suggests that the high glycogen concentrations found within the human vaginal tract reflect dietary carbohydrate catabolism which is facilitated by abundant salivary amylase levels.

Irrespective of its evolutionary basis, the growth of lactobacilli in the vaginal environment is supported by glycoprotein- and mucin-rich genital fluid and high levels of glycogen and α -amylase, and the latter increases the energy availability of glycogen through its by-products^{149–151}. With *Lactobacillus* proliferation, the oestrogen-mediated low pH of the vagina is further acidified by microbial-derived lactic acid, which is metabolised from glycogen through anaerobic glycolysis^{152–157}. Low pH (~3.5) and high lactic acid concentrations contribute in

conjunction with cervicovaginal fluid, a highly effective anti-microbial and antiviral medium, to maintain a healthy vaginal environment^{155,157}. With BV, when the vaginal pH rises (>4.5) and microbial composition shifts away from being *Lactobacillus*-dominant to allow other taxa (such as *Gardnerella*) to proliferate, lactic acid levels drop and a more prominent SCFA profile develops¹⁵⁵. Although SCFAs are generally associated with health benefits, particularly in the gut, an undesirable pro-inflammatory response appears to be induced by acetate and butyrate within the vaginal tract^{93,107,113,155,158,159}.

The vaginal microbiome appears to considerably influence the efficacy of microbicide HIV prevention therapy⁹⁴. Tenofovir microbicide gel was 59.2% effective in HIV infection prevention for *Lactobacillus*-dominant vaginal communities, but in individuals with a microbiome containing greater proportions of *Gardnerella*, the prevention rate was only 18%⁹⁴. Controlled doses of tenofovir administered to patients with either *Gardnerella*- or *Lactobacillus*-oriented microbiomes showed significantly lower concentrations of the drug in *Gardnerella*-dominated vaginal communities; indeed, detected drug concentration negatively correlated with *Gardnerella* abundance⁹⁴. *In vitro* analysis demonstrated that *Gardnerella* and other BV-associated microbes efficiently metabolised the drug through a cleavage of an oxy-methylphosphonic acid side chain of the compound⁹⁴.

The male urogenital tract microbiome has received less attention. However, emerging investigation of the subject suggests health-relevant microbial activity within this system. Circumcision significantly modifies microbial composition of the coronal sulci of the penis, decreasing the total microbial load, including anaerobic taxa putatively associated with BV^{160,161}. Reduced HIV infection rates have independently been associated with circumcision, but the underlying factors of this protective effect are unknown¹⁶².

The gut

Of the microbial communities delineated by human physiology, those associated with the GI system have been investigated with the greatest intensity (Figure 1E)^{12,21,27,29}.

Microbes travel, generally in a uni-directional manner, through the GI tract within ingested material, and the associated communities follow a gradient of community complexity that peaks in the colon^{163–165}. Once established, the gut microbiome is subject to influence from a limited number of known factors. Perhaps the factor that most profoundly affects this community is host diet, supplying both microbes and nutrients to influence the microbiome's function and composition^{55,72,159,166,167}. Plant-based complex carbohydrates, which intestinal microbiota process with enzymes that are absent from the human host, are one such important dietary factor^{159,167,168}. Through metabolism of these polysaccharides, microbial fermentation yields SCFAs, compounds with a broad range of purportedly profound effects on the host^{159,167,168}.

In addition to dietary constituents, host-derived metabolites can be used by the gut microbiome^{167,169–172}. Examples

highlighting this host–microbe interaction include bile acids (BAs), which, once acted upon by bacteria, can trigger complex host–microbe signalling cascades, and intestinal mucins, compounds used by mucin specialists (for example, *Akkermansia muciniphila*), providing protective properties to the host^{167,169–173}. It is worth noting that, in addition to drugs explicitly affecting microorganisms (that is, antibiotics), the interaction between other medications and microorganisms can be key, affecting microbe composition and function as well as the pharmacokinetics of the drugs^{171,174–177}. Indeed, an *in vitro* screen of more than 1000 pharmaceutical compounds to assess their activity against core representative strains of gut bacteria demonstrated that growth of at least one strain was inhibited by 24% of compounds intended to target human cells¹⁷⁷. Similarly, the type 2 diabetes drug metformin was shown to alter both the composition and function of the human intestinal microbiota, resulting in an enrichment of genes associated with SCFA metabolism and faecal concentrations of propionate and butyrate¹⁷⁶. However, the specifics of microbial metabolic interactions with metformin have yet to be elucidated.

It should also be noted that drugs of intoxication (for example, alcohol and cannabis) are indicated to interact with the microbiome, although studies in this field are somewhat rare and often limited to non-human animal models^{59,178–182}. An exception to the pattern, whereby the gut microbiome of chronic cannabis users was investigated¹⁸¹, revealed that, in comparison with controls, chronic cannabis users had a 13-fold reduction in the ratio of *Prevotella* to *Bacteroides*. Lower *Prevotella* abundance was further associated with poor cognition test performance and reduced mitochondrial ATP production¹⁸¹.

Host behaviour, and more specifically physical exercise and fitness, are also recognised as potential modulators of microbial composition and function^{60–70}. Illustrating the potential influence of extremes of exercise, professional athletes have been shown to harbour a gut microbiome that exhibits a high compositional diversity of microbial taxa and contains a gene profile with robust potential for environmental energy capture^{60,63}. More specifically, the gut microbiome of a cohort of professional rugby players, in comparison with age-matched controls with similar body mass index to represent the range of body composition in the athletes, contained greater proportions of metabolic pathways associated with potential health benefits. These pathways ranged from those associated with organic cofactor and antibiotic biosynthesis to degradation and biosynthesis of carbohydrates. Such biosynthetic pathways could result in an increased capacity for energy utilisation by the microbiome⁶⁰. Metabolomic profiling of the athlete gut microbiome revealed elevated levels of SCFAs, which (as noted above) are metabolites with wide health-associated attributes (detailed further below) and are associated with a lean body composition¹⁸³. The faecal metabolome of these athletes also exhibited elevated levels of trimethylamine-N-oxide (TMAO), a compound that has been associated with cardiovascular disease and atherosclerosis, although these negative associations have been disputed because of the occurrence of high levels of TMAO in populations with a low occurrence of

cardiovascular disease¹⁸⁴, and thus the significance of these findings with respect to athletes has yet to be determined. From another study (in this instance, of the microbiome of high-performance cyclists), it was shown that the genus *Prevotella* was significantly associated with reported time of exercising⁶⁸. The study further revealed higher transcriptional activity of *Methanobrevibacter smithii* genes, particularly those related to methanogenesis, in professional cyclists when compared with amateurs. Investigation of amateur half-marathon runners demonstrated that, through the course of high-intensity running, significant changes occurred in certain taxa (for example, *Coriobacteriaceae*) and metabolites within the gut environment⁷⁰. Intriguingly, the introduction of exercise as a novel stimulus appears to elicit more subtle changes in the gut microbiome. After undergoing a short period (8 weeks) of moderate-intensity exercise, healthy but inactive adults were shown to exhibit only minor changes in the composition of their gut microbiome⁶⁹. A separate analysis of a combination of lean and obese individuals undergoing a period of structured exercise conversely asserted that concentrations of faecal SCFAs increased in lean participants following exercise while an obesity-dependent shift in microbial diversity was present after exercise and dissipated after a washout period¹⁸⁵. In sum, it is apparent that there remains much to be done to completely understand the mechanisms underlying the interaction of exercise and the gut microbiome.

Gut microbiome analysis is carried out predominantly on the terminal end of the GI tract because of the relative ease with which samples can be non-invasively acquired as stool. These samples provide insight into the intestinal microbiome as excreted samples retain microbial cells and metabolites from the lumen and mucosa, although it is important to note that stool does not provide an exact recapitulation of the intestine's various subsites^{163,164,186}.

Systemic implication of the gut microbiome in health and disease

The GI system acts as the primary site for the uptake and metabolic processing of nutrients. The gut accordingly contributes substantially to health regulation. As extensive evidence now indicates, intestinal microbes have similar significance in health maintenance and modulation of various disease states via interaction with the host's biology and intestinal environment. Microbial contributions to this health dynamic are mediated by numerous metabolic modalities. The most prominent such metabolic *circuit* is between the microbiome and ingested nutrients, whereby microbes use dietary nutrients to proliferate and produce metabolites, such as SCFAs, that are involved in cross-talk with the host (Figure 2)^{29,37,72,166,167,187,188}.

Short-chain fatty acids

SCFAs act locally within the intestinal system but also impact on hepatic, neurological and immunological function^{158,159,188–192}. As previously noted, microbial SCFA generation results primarily from polysaccharide utilisation, although it has also been demonstrated that some gut microbes have the capacity to produce butyrate from the metabolism of protein^{188,193–195}.

Upon excretion from microbial cells, SCFAs entering the intestinal environment are used by colonocytes as an energy source or pass into broader circulation via the portal vein^{159,188}. Acting locally on colonocytes, butyrate is incorporated into luminal cells through diffusion or direct transport mediated by the Na⁺-coupled transporter SLC5A8^{159,196}. Butyrate within colonocytes contributes to energy production through conversion to acetyl-CoA or alternatively inhibits histone deacetylase (HDAC) activity^{159,196,197}. HDAC inhibition occurs within colorectal cancer cells, wherein glucose is preferentially used as an energy source, leading to butyrate accumulation and the subsequent action upon HDAC which results in a cascade of effects on cell proliferation, differentiation and apoptosis^{159,196,197}.

Propionate enters systemic circulation through the portal vein, where it is metabolised primarily in the liver while acetate is more broadly circulated, for example, crossing the blood–brain barrier, where it may influence satiety through action on the hypothalamus¹⁹⁰. On the basis of murine studies, gut-derived acetate and propionate have separately been suggested to influence asthma^{159,198,199}. While regulatory T-cell activity is enhanced by acetate-mediated inhibition of histone deacetylase 9 (HDAC9), resulting in suppression of environmental allergen hypersensitivity, propionate affects lung dendritic cells, dampening promotion of T helper type 2 cell-driven inflammation while leaving the cells' phagocytic ability intact^{81,159,198–200}.

Bile acids

BAs have been shown to be at the centre of a metabolic interplay between the host and microbes^{72,169,170,174,176,201–203}. Following post-meal metabolic cues, bile released from the canalicular membrane of hepatocytes enters the intestinal system. Primary BAs, cholic acid and chenodeoxycholic acid are converted from cholesterol and conjugated with taurine or glycine and, within the context of host physiology, are used as detergents to allow intestinal absorption of dietary lipids and fat-soluble vitamins^{201,203,204}. Microbial bile salt hydrolases (BSHs) facilitate the hydrolysis of conjugated BAs (CBAs), converting the compounds back to BAs, which permits small intestine reabsorption or additional metabolic processing^{203,204}. Unconjugated and glycine-CBA absorption by passive diffusion and active transport creates a circulating pool of BAs, establishing continuous bioavailability of the compounds^{202–204}. As detergents, BAs have the capacity to disrupt the lipid membrane of bacterial cells, subsequently exerting considerable influence on the microbiome. Microbes accordingly employ myriad strategies to circumvent the antimicrobial action of BAs, such as outer membrane lipid and protein modifications^{203,204}. In conjunction with BA resistance, microbial alterations to BAs, affecting the hydrophobicity of the compounds, also enable some microbes to evade lipid membrane degradation while creating an inhospitable environment for competing organisms^{203,204}. Microbial BSH-driven hydrolysis of CBAs to unconjugated primary BAs enables subsequent conversion to secondary BAs deoxycholic acid (DCA) and lithocholic acid^{203,204}. DCA, in particular, accumulates in the enterohepatic BA pool. Relatively high concentrations of DCA result from intestinal diffusion and hepatic

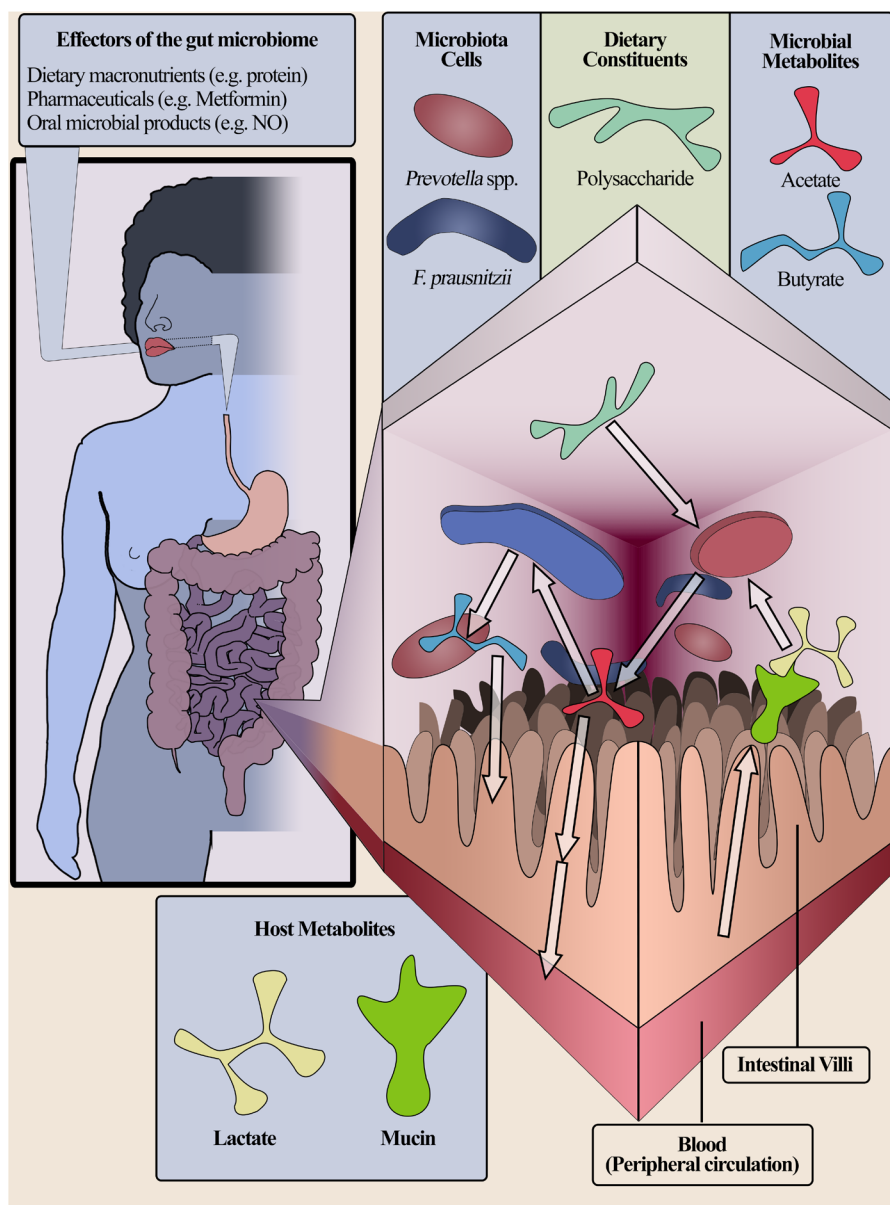


Figure 2. Host-microbe metabolic interaction. A simplified demonstration of the metabolic interactions between host and microbiome. The cross-section of the small intestine illustrates the metabolic exchange between the intestine and two taxonomic representatives (*Prevotella* spp. and *Faecalibacterium prausnitzii*). Polysaccharides act as an example of dietary substrate used by the microbiota for the production of short-chain fatty acid (butyrate and acetate). Similarly, host-derived substrate in the form of lactate presented with excretion of mucin from the intestine can be used by the microbiota. Within the example, acetate can be either absorbed by the intestine and subsequently the bloodstream where systematic influences take place or converted to butyrate, exerting a localised effect on intestinal epithelial cells. NO, nitric oxide.

reuptake that is facilitated by the compound's hydrophobicity and the human liver's inability to rehydroxylate DCA²⁰³.

Notably, the fat- and protein-enriched 'Western' diet that contributes to obesity development modifies not only gut microbiome composition but also microbial BA pool contributions^{72,167,202,205,206}.

Indeed, the negative consequences of dietary insult have been shown to be ameliorated through intervention with BA-binding resins²⁰⁷. Roux-en-Y gastric bypass surgery has intriguingly been shown to also have an effect on BAs, and serum concentrations are raised in individuals who have undergone the procedure when compared with obese and severely

obese controls, suggesting that anatomical manipulation of the procedure modifies the dynamics of the BA pool^{208,209}.

Among the numerous detrimental effects of obesity, evidence supports a role for microbial-derived DCA as a potent tumour promoter, contributing to the development of hepatocellular carcinoma and the colorectal cancer precursor colorectal adenomas^{72,202,210–212}. Although the associated mechanisms involved have not been studied in the human gut, DCA-driven hepatocellular carcinoma in mice is suggested to result from the compound's provocation of the senescence-associated secretory phenotype (SASP) in hepatic stellate cells²¹¹. SASP is characterised by broad alterations in gene expression and secretory profile, which affect neighbouring cells through numerous factors, namely the release of cytokines (for example, interleukin-1 α and -1 β), insulin-like growth factor-binding proteins, NO and reactive oxygen species and potentially the glycoprotein fibronectin^{211,213}. The influence of DCA on colorectal tumorigenesis is proposed to mediate derangement of epidermal growth factor receptor–mitogen-activated protein kinase (EGFR-MAPK) regulation, specifically with DCA preventing degradation of EGFR through calcium signalling of MAPK²¹⁰. There is still much to be elucidated with respect to the interactions between gut microbes, BAs and health. Furthermore, SCFAs and BAs represent only a small component of the numerous bioactive compounds within the gut environment and thus considerable additional investigation in this area is needed.

Conclusions and Outlook

Examination of microbiome–host interaction has revealed the integral role of microbiota in health and disease. Extensive characterisation of the microbiome's taxonomic structure and associations between states of microbial composition and aspects of health have established the groundwork for recognition of the microbiome as a component of human biology. However, the challenge now lies in elucidating the mechanisms underlying the associations between our microbes and health. Metabolic phenotyping and identification of the microbial metabolites interacting with the host will be pivotal to this challenge. With such knowledge, progress can be made in the development of defined microbial cultures (for example, probiotics) and substrates conducive to selective growth or function of microbes (for example, prebiotics) for health enhancement. In short, there is need and opportunity for the innovative deployment of metabolic phenotyping of the human microbiome to develop a new generation of interventions to improve health.

Abbreviations

BA, bile acid; BSH, bile salt hydrolase; BV, bacterial vaginosis; CBA, conjugated bile acid; DCA, deoxycholic acid; EGFR, epidermal growth factor receptor; GI, gastrointestinal; HDAC, histone deacetylase; MAPK, mitogen-activated protein kinase; NO, nitric oxide; SASP, senescence-associated secretory phenotype; SCFA, short-chain fatty acid; T2-high, type 2-high; TMAO, trimethylamine-N-oxide

References



- Xie W, Wang F, Guo L, *et al.*: **Comparative metagenomics of microbial communities inhabiting deep-sea hydrothermal vent chimneys with contrasting chemistries.** *ISME J.* 2011; 5(3): 414–26.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Afshinekoo E, Meydan C, Chowdhury S, *et al.*: **Geospatial Resolution of Human and Bacterial Diversity with City-Scale Metagenomics.** *Cell Syst.* 2015; 1(1): 72–87.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Ruiz-Calderon JF, Cavallin H, Song SJ, *et al.*: **Walls talk: Microbial biogeography of homes spanning urbanization.** *Sci Adv.* 2016; 2(2): e1501061.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Coughlan LM, Cotter PD, Hill C, *et al.*: **New Weapons to Fight Old Enemies: Novel Strategies for the (Bio)control of Bacterial Biofilms in the Food Industry.** *Front Microbiol.* 2016; 7: 1641.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Bourrie BC, Willing BP, Cotter PD: **The Microbiota and Health Promoting Characteristics of the Fermented Beverage Kefir.** *Front Microbiol.* 2016; 7: 647.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Doyle CJ, Gleeson D, O'Toole PW, *et al.*: **High-throughput metatranscriptomic characterization of the raw milk microbiota identifies changes reflecting lactation stage and storage conditions.** *Int J Food Microbiol.* 2017; 255: 1–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Walsh AM, Crispie F, Daari K, *et al.*: **Strain-Level Metagenomic Analysis of the Fermented Dairy Beverage Nunu Highlights Potential Food Safety Risks.** *Appl Environ Microbiol.* 2017; 83(16): pii: e01144–17.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- McHugh AJ, Feehily C, Hill C, *et al.*: **Detection and Enumeration of Spore-Forming Bacteria in Powdered Dairy Products.** *Front Microbiol.* 2017; 8: 109.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Venkateswaran K, Vaishampayan P, Cisneros J, *et al.*: **International Space Station environmental microbiome - microbial inventories of ISS filter debris.** *Appl Microbiol Biotechnol.* 2014; 98(14): 6453–66.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Be NA, Avila-Herrera A, Allen JE, *et al.*: **Whole metagenome profiles of particulates collected from the International Space Station.** *Microbiome.* 2017; 5(1): 81.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Scanlan PD: **Blastocystis: past pitfalls and future perspectives.** *Trends Parasitol.* 2012; 28(8): 327–34.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Scanlan PD, Knight R, Song SJ, *et al.*: **Prevalence and genetic diversity of Blastocystis in family units living in the United States.** *Infect Genet Evol.* 2016; 45: 95–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Scanlan PD, Stensvold CR, Rajilic-Stojanovic M, *et al.*: **The microbial eukaryote Blastocystis is a prevalent and diverse member of the healthy human gut microbiota.** *FEMS Microbiol Ecol.* 2014; 90(1): 326–30.
[PubMed Abstract](#) | [Publisher Full Text](#)
- Burgess SL, Gilchrist CA, Lynn TC, *et al.*: **Parasitic Protozoa and Interactions with the Host Intestinal Microbiota.** *Infect Immun.* 2017; 85(8): pii: e00101–17.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Chudnovskiy A, Mortha A, Kana V, *et al.*: **Host-Protozoan Interactions Protect from Mucosal Infections through Activation of the Inflammasome.** *Cell.* 2016; 167(2): 444–456.e14.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
- Hanevik K, Dizdar V, Langeland N, *et al.*: **Development of functional gastrointestinal disorders after Giardia lamblia infection.** *BMC Gastroenterol.* 2009; 9: 27.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | **F1000 Recommendation**
- Ghannoum MA, Jurevic RJ, Mukherjee PK, *et al.*: **Characterization of the oral fungal microbiome (mycobiome) in healthy individuals.** *PLoS Pathog.* 2010; 6(1): e1000713.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | **F1000 Recommendation**
- Huffnagle GB, Noverr MC: **The emerging world of the fungal microbiome.** *Trends Microbiol.* 2013; 21(7): 334–41.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

19. Huseyin CE, O'Toole PW, Cotter PD, *et al.*: **Forgotten fungi-the gut mycobiome in human health and disease.** *FEMS Microbiol Rev.* 2017; **41**(4): 479–511.
[PubMed Abstract](#) | [Publisher Full Text](#)
20. Nguyen LD, Viscogliosi E, Delhaes L: **The lung mycobiome: an emerging field of the human respiratory microbiome.** *Front Microbiol.* 2015; **6**: 89.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
21. Minot S, Sinha R, Chen J, *et al.*: **The human gut virome: inter-individual variation and dynamic response to diet.** *Genome Res.* 2011; **21**(10): 1616–25.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
22. Hannigan GD, Zheng Q, Meisel JS, *et al.*: **Evolutionary and functional implications of hypervariable loci within the skin virome.** *PeerJ.* 2017; **5**: e2959.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
23. Virgin HW: **The virome in mammalian physiology and disease.** *Cell.* 2014; **157**(1): 142–50.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
24. **F** Norman JM, Handley SA, Baldrige MT, *et al.*: **Disease-specific alterations in the enteric virome in inflammatory bowel disease.** *Cell.* 2015; **160**(3): 447–60.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
25. **F** Human Microbiome Project Consortium: **Structure, function and diversity of the healthy human microbiome.** *Nature.* 2012; **486**(7402): 207–14.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
26. **F** Costello EK, Lauber CL, Hamady M, *et al.*: **Bacterial community variation in human body habitats across space and time.** *Science.* 2009; **326**(5960): 1694–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
27. **F** Gill SR, Pop M, DeBoy RT, *et al.*: **Metagenomic analysis of the human distal gut microbiome.** *Science.* 2006; **312**(5778): 1355–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
28. **F** Turnbaugh PJ, Hamady M, Yatsunenko T, *et al.*: **A core gut microbiome in obese and lean twins.** *Nature.* 2009; **457**(7228): 480–4.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
29. Zhernakova A, Kurilshikov A, Bonder MJ, *et al.*: **Population-based metagenomics analysis reveals markers for gut microbiome composition and diversity.** *Science.* 2016; **352**(6285): 565–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
30. **F** Scanlan PD: **Bacteria-Bacteriophage Coevolution in the Human Gut: Implications for Microbial Diversity and Functionality.** *Trends Microbiol.* 2017; **25**(8): 614–23.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
31. Coyte KZ, Schluter J, Foster KR: **The ecology of the microbiome: Networks, competition, and stability.** *Science.* 2015; **350**(6261): 663–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
32. Kennedy MJ, Volz PA: **Ecology of *Candida albicans* gut colonization: inhibition of *Candida* adhesion, colonization, and dissemination from the gastrointestinal tract by bacterial antagonism.** *Infect Immun.* 1985; **49**(3): 654–63.
[PubMed Abstract](#) | [Free Full Text](#)
33. **F** Smillie CS, Smith MB, Friedman J, *et al.*: **Ecology drives a global network of gene exchange connecting the human microbiome.** *Nature.* 2011; **480**(7376): 241–4.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
34. Walter J, Ley R: **The human gut microbiome: ecology and recent evolutionary changes.** *Annu Rev Microbiol.* 2011; **65**: 411–29.
[PubMed Abstract](#) | [Publisher Full Text](#)
35. **F** Clarke G, Stilling RM, Kennedy PJ, *et al.*: **Minireview: Gut microbiota: the neglected endocrine organ.** *Mol Endocrinol.* 2014; **28**(8): 1221–38.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
36. Evans JM, Morris LS, Marchesi JR: **The gut microbiome: the role of a virtual organ in the endocrinology of the host.** *J Endocrinol.* 2013; **218**(3): R37–R47.
[PubMed Abstract](#) | [Publisher Full Text](#)
37. Possemiers S, Bolca S, Verstraete W, *et al.*: **The intestinal microbiome: a separate organ inside the body with the metabolic potential to influence the bioactivity of botanicals.** *Fitoterapia.* 2011; **82**(1): 53–66.
[PubMed Abstract](#) | [Publisher Full Text](#)
38. **F** Eckburg PB, Bik EM, Bernstein CN, *et al.*: **Diversity of the human intestinal microbial flora.** *Science.* 2005; **308**(5728): 1635–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
39. **F** Dominguez-Bello MG, Costello EK, Contreras M, *et al.*: **Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns.** *Proc Natl Acad Sci U S A.* 2010; **107**(26): 11971–5.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
40. Bäckhed F, Roswall J, Peng Y, *et al.*: **Dynamics and Stabilization of the Human Gut Microbiome during the First Year of Life.** *Cell Host Microbe.* 2015; **17**(5): 690–703.
[PubMed Abstract](#) | [Publisher Full Text](#)
41. Chu DM, Ma J, Prince AL, *et al.*: **Maturation of the infant microbiome community structure and function across multiple body sites and in relation to mode of delivery.** *Nat Med.* 2017; **23**(3): 314–26.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
42. Nuriel-Ohayon M, Neuman H, Koren O: **Microbial Changes during Pregnancy, Birth, and Infancy.** *Front Microbiol.* 2016; **7**: 1031.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
43. Korpela K, Costea P, Coelho LP, *et al.*: **Selective maternal seeding and environment shape the human gut microbiome.** *Genome Res.* 2018; **28**(4): 561–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
44. Mueller NT, Whyatt R, Hoepner L, *et al.*: **Prenatal exposure to antibiotics, cesarean section and risk of childhood obesity.** *Int J Obes (Lond).* 2015; **39**(4): 665–70.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
45. Sevelsted A, Stokholm J, Bønnelykke K, *et al.*: **Cesarean section and chronic immune disorders.** *Pediatrics.* 2015; **135**(1): e92–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
46. Bager P, Wohlfahrt J, Westergaard T: **Caesarean delivery and risk of atopy and allergic disease: meta-analyses.** *Clin Exp Allergy.* 2008; **38**(4): 634–42.
[PubMed Abstract](#) | [Publisher Full Text](#)
47. Negele K, Heinrich J, Borte M, *et al.*: **Mode of delivery and development of atopic disease during the first 2 years of life.** *Pediatr Allergy Immunol.* 2004; **15**(1): 48–54.
[PubMed Abstract](#) | [Publisher Full Text](#)
48. Goedert JJ, Hua X, Yu G, *et al.*: **Diversity and composition of the adult fecal microbiome associated with history of cesarean birth or appendectomy: Analysis of the American Gut Project.** *eBioMedicine.* 2014; **1**(2–3): 167–72.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
49. **F** Dominguez-Bello MG, de Jesus-Laboy KM, Shen N, *et al.*: **Partial restoration of the microbiota of cesarean-born infants via vaginal microbial transfer.** *Nat Med.* 2016; **22**(3): 250–3.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
50. Haahr T, Glavind J, Axelsson P, *et al.*: **Vaginal seeding or vaginal microbial transfer from the mother to the caesarean-born neonate: a commentary regarding clinical management.** *BJOG.* 2018; **125**(5): 533–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
51. Cunnington AJ, Sim K, Deierl A, *et al.*: **“Vaginal seeding” of infants born by caesarean section.** *BMJ.* 2016; **352**: i227.
[PubMed Abstract](#) | [Publisher Full Text](#)
52. Cabrera-Rubio R, Collado MC, Laitinen K, *et al.*: **The human milk microbiome changes over lactation and is shaped by maternal weight and mode of delivery.** *Am J Clin Nutr.* 2012; **96**(3): 544–51.
[PubMed Abstract](#) | [Publisher Full Text](#)
53. Mueller NT, Bakacs E, Combellick J, *et al.*: **The infant microbiome development: Mom matters.** *Trends Mol Med.* 2015; **21**(2): 109–17.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
54. Vangay P, Ward T, Gerber JS, *et al.*: **Antibiotics, pediatric dysbiosis, and disease.** *Cell Host Microbe.* 2015; **17**(5): 553–64.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
55. **F** Bokulich NA, Chung J, Battaglia T, *et al.*: **Antibiotics, birth mode, and diet shape microbiome maturation during early life.** *Sci Transl Med.* 2016; **8**(343): 343ra82.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
56. Clooney AG, Bernstein CN, Leslie WD, *et al.*: **A comparison of the gut microbiome between long-term users and non-users of proton pump inhibitors.** *Aliment Pharmacol Ther.* 2016; **43**(9): 974–84.
[PubMed Abstract](#) | [Publisher Full Text](#)
57. Imhann F, Bonder MJ, Vich Vila A, *et al.*: **Proton pump inhibitors affect the gut microbiome.** *Gut.* 2016; **65**(5): 740–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
58. Korpela K, Salonen A, Virta LJ, *et al.*: **Intestinal microbiome is related to lifetime antibiotic use in Finnish pre-school children.** *Nat Commun.* 2016; **7**: 10410.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
59. Peterson VL, Jury NJ, Cabrera-Rubio R, *et al.*: **Drunk bugs: Chronic vapour alcohol exposure induces marked changes in the gut microbiome in mice.** *Behav Brain Res.* 2017; **323**: 172–176.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
60. **F** Barton W, Penney NC, Cronin O, *et al.*: **The microbiome of professional athletes differs from that of more sedentary subjects in composition and particularly at the functional metabolic level.** *Gut.* 2018; **67**(4): 625–633.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
61. Campbell SC, Wisniewski PJ 2nd: **Exercise is a Novel Promoter of Intestinal Health and Microbial Diversity.** *Exerc Sport Sci Rev.* 2017; **45**(1): 41–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
62. Cerdá B, Pérez M, Pérez-Santiago JD, *et al.*: **Gut Microbiota Modification: Another Piece in the Puzzle of the Benefits of Physical Exercise in Health?** *Front Physiol.* 2016; **7**: 51.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
63. Clarke SF, Murphy EF, O'Sullivan O, *et al.*: **Exercise and associated dietary extremes impact on gut microbial diversity.** *Gut.* 2014; **63**(12): 1913–20.
[PubMed Abstract](#) | [Publisher Full Text](#)
64. Cronin O, Molloy MG, Shanahan F: **Exercise, fitness, and the gut.** *Curr Opin Gastroenterol.* 2016; **32**(2): 67–73.
[PubMed Abstract](#) | [Publisher Full Text](#)
65. Mika A, Fleshner M: **Early-life exercise may promote lasting brain and metabolic health through gut bacterial metabolites.** *Immunol Cell Biol.* 2016; **94**(2): 151–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
66. O'Sullivan O, Cronin O, Clarke SF, *et al.*: **Exercise and the microbiota.** *Gut*

- Microbes*. 2015; 6(2): 131–6.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
67. **F** Paulsen JA, Ptacek TS, Carter SJ, *et al.*: **Gut microbiota composition associated with alterations in cardiorespiratory fitness and psychosocial outcomes among breast cancer survivors.** *Support Care Cancer*. 2017; 25(5): 1563–70.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
68. **F** Petersen LM, Bautista EJ, Nguyen H, *et al.*: **Community characteristics of the gut microbiomes of competitive cyclists.** *Microbiome*. 2017; 5(1): 98.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
69. Cronin O, Barton W, Skuse P, *et al.*: **A Prospective Metagenomic and Metabolomic Analysis of the Impact of Exercise and/or Whey Protein Supplementation on the Gut Microbiome of Sedentary Adults.** *mSystems*. 2018; 3(3): pii: e00044-18.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
70. **F** Zhao X, Zhang Z, Hu B, *et al.*: **Response of Gut Microbiota to Metabolite Changes Induced by Endurance Exercise.** *Front Microbiol*. 2018; 9: 765.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
71. Walsh CJ, Guinane CM, O'Toole PW, *et al.*: **Beneficial modulation of the gut microbiota.** *FEBS Lett*. 2014; 588(22): 4120–30.
[PubMed Abstract](#) | [Publisher Full Text](#)
72. **F** David LA, Maurice CF, Carmody RN, *et al.*: **Diet rapidly and reproducibly alters the human gut microbiome.** *Nature*. 2014; 505(7484): 559–63.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
73. **F** Yatsunenko T, Rey FE, Manary MJ, *et al.*: **Human gut microbiome viewed across age and geography.** *Nature*. 2012; 486(7402): 222–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
74. Spor A, Koren O, Ley R: **Unravelling the effects of the environment and host genotype on the gut microbiome.** *Nat Rev Microbiol*. 2011; 9(4): 279–90.
[PubMed Abstract](#) | [Publisher Full Text](#)
75. Claesson MJ, Cusack S, O'Sullivan O, *et al.*: **Composition, variability, and temporal stability of the intestinal microbiota of the elderly.** *Proc Natl Acad Sci U S A*. 2011; 108 Suppl 1: 4586–91.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
76. Claesson MJ, Jeffery IB, Conde S, *et al.*: **Gut microbiota composition correlates with diet and health in the elderly.** *Nature*. 2012; 488(7410): 178–84.
[PubMed Abstract](#) | [Publisher Full Text](#)
77. Salazar N, Arboleya S, Valdés L, *et al.*: **The human intestinal microbiome at extreme ages of life. Dietary intervention as a way to counteract alterations.** *Front Genet*. 2014; 5: 406.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
78. Javan GT, Finley SJ, Abidin Z, *et al.*: **The Thanatomiobiome: A Missing Piece of the Microbial Puzzle of Death.** *Front Microbiol*. 2016; 7: 225.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
79. Javan GT, Finley SJ, Can I, *et al.*: **Human Thanatomiobiome Succession and Time Since Death.** *Sci Rep*. 2016; 6: 29598.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
80. Metcalf JL, Xu ZZ, Weiss S, *et al.*: **Microbial community assembly and metabolic function during mammalian corpse decomposition.** *Science*. 2016; 351(6269): 158–62.
[PubMed Abstract](#) | [Publisher Full Text](#)
81. Lloyd CM, Marsland BJ: **Lung Homeostasis: Influence of Age, Microbes, and the Immune System.** *Immunity*. 2017; 46(4): 549–561.
[PubMed Abstract](#) | [Publisher Full Text](#)
82. Madan JC, Koestler DC, Stanton BA, *et al.*: **Serial analysis of the gut and respiratory microbiome in cystic fibrosis in infancy: interaction between intestinal and respiratory tracts and impact of nutritional exposures.** *mBio*. 2012; 3(4): pii: e00251-12 91.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
83. Millares L, Bermudo G, Pérez-Brocá V, *et al.*: **The respiratory microbiome in bronchial mucosa and secretions from severe IgE-mediated asthma patients.** *BMC Microbiol*. 2017; 17(1): 20.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
84. Morris A, Beck JM, Schloss PD, *et al.*: **Comparison of the respiratory microbiome in healthy nonsmokers and smokers.** *Am J Respir Crit Care Med*. 2013; 187(10): 1067–75.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
85. Wilson MT, Hamilos DL: **The nasal and sinus microbiome in health and disease.** *Curr Allergy Asthma Rep*. 2014; 14(12): 485.
[PubMed Abstract](#) | [Publisher Full Text](#)
86. Liu CM, Price LB, Hungate BA, *et al.*: **Staphylococcus aureus and the ecology of the nasal microbiome.** *Sci Adv*. 2015; 1(5): e1400216.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
87. Wu J, Peters BA, Dominianni C, *et al.*: **Cigarette smoking and the oral microbiome in a large study of American adults.** *ISME J*. 2016; 10(10): 2435–46.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
88. Bjerre RD, Bandier J, Skov L, *et al.*: **The role of the skin microbiome in atopic dermatitis: A systematic review.** *Br J Dermatol*. 2017; 177(5): 1272–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
89. **F** Grice EA, Kong HH, Conlan S, *et al.*: **Topographical and Temporal Diversity of the Human Skin Microbiome.** *Science*. 2009; 324(5931): 1190–2.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
90. Kong HH, Andersson B, Clavel T, *et al.*: **Performing Skin Microbiome Research: A Method to the Madness.** *J Invest Dermatol*. 2017; 137(37): 561–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
91. Kong HH, Oh J, Deming C, *et al.*: **Temporal shifts in the skin microbiome associated with disease flares and treatment in children with atopic dermatitis.** *Genome Res*. 2012; 22(5): 850–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
92. Meadow JF, Bateman AC, Herkert KM, *et al.*: **Significant changes in the skin microbiome mediated by the sport of roller derby.** *PeerJ*. 2013; 1: e53.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
93. **F** Wang Y, Zhang L, Yu J, *et al.*: **A Co-Drug of Butyric Acid Derived from Fermentation Metabolites of the Human Skin Microbiome Stimulates Adipogenic Differentiation of Adipose-Derived Stem Cells: Implications in Tissue Augmentation.** *J Invest Dermatol*. 2017; 137(1): 46–56.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
94. **F** Klatt NR, Cheu R, Birse K, *et al.*: **Vaginal bacteria modify HIV tenofovir microbicide efficacy in African women.** *Science*. 2017; 356(6341): 938–945.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
95. Lamont RF, Sobel JD, Akins RA, *et al.*: **The vaginal microbiome: new information about genital tract flora using molecular based techniques.** *BJOG*. 2011; 118(5): 533–49.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
96. **F** Ravel J, Gajer P, Abdo Z, *et al.*: **Vaginal microbiome of reproductive-age women.** *Proc Natl Acad Sci U S A*. 2011; 108 Suppl 1: 4680–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
97. **F** Arumugam M, Raes J, Pelletier E, *et al.*: **Enterotypes of the human gut microbiome.** *Nature*. 2011; 473(7346): 174–180.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
98. Ying S, Zeng DN, Chi L, *et al.*: **The Influence of Age and Gender on Skin-Associated Microbial Communities in Urban and Rural Human Populations.** *PLoS One*. 2015; 10(10): e0141842.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
99. Kong HH, Segre JA: **Skin microbiome: looking back to move forward.** *J Invest Dermatol*. 2012; 132(3 Pt 2): 933–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
100. **F** Ross AA, Doxey AC, Neufeld JD: **The Skin Microbiome of Cohabiting Couples.** *mSystems*. 2017; 2(4): pii: e00043-17.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
101. Fierer N, Hamady M, Lauber CL, *et al.*: **The influence of sex, handedness, and washing on the diversity of hand surface bacteria.** *Proc Natl Acad Sci U S A*. 2008; 105(46): 17994–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
102. Perez Perez GI, Gao Z, Jourdain R, *et al.*: **Body Site Is a More Determinant Factor than Human Population Diversity in the Healthy Skin Microbiome.** *PLoS One*. 2016; 11(4): e0151990.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
103. Si J, Lee S, Park JM, *et al.*: **Genetic associations and shared environmental effects on the skin microbiome of Korean twins.** *BMC Genomics*. 2015; 16: 992.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
104. **F** Rothschild D, Weissbrod O, Barkan E, *et al.*: **Environment dominates over host genetics in shaping human gut microbiota.** *Nature*. 2018; 555(7695): 210–5.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
105. Urban J, Fergus DJ, Savage AM, *et al.*: **The effect of habitual and experimental antiperspirant and deodorant product use on the armpit microbiome.** *PeerJ*. 2016; 4: e1605.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
106. Oh J, Byrd AL, Park M, *et al.*: **Temporal Stability of the Human Skin Microbiome.** *Cell*. 2016; 165(4): 854–66.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
107. Wang Y, Dai A, Huang S, *et al.*: **Propionic acid and its esterified derivative suppress the growth of methicillin-resistant Staphylococcus aureus USA300.** *Benef Microbes*. 2014; 5(2): 161–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
108. Grice EA, Segre JA: **The skin microbiome.** *Nat Rev Micro*. 2011; 9(4): 244–53.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
109. SanMiguel A, Grice EA: **Interactions between host factors and the skin microbiome.** *Cell Mol Life Sci*. 2015; 72(8): 1499–515.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
110. **F** Findley K, Oh J, Yang J, *et al.*: **Topographic diversity of fungal and bacterial communities in human skin.** *Nature*. 2013; 498(7454): 367–70.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
111. Gribbon EM, Cunliffe WJ, Holland KT: **Interaction of Propionibacterium acnes with skin lipids in vitro.** *J Gen Microbiol*. 1993; 139(8): 1745–51.
[PubMed Abstract](#) | [Publisher Full Text](#)
112. **F** Francuzik W, Franke K, Schumann RR, *et al.*: **Propionibacterium acnes Abundance Correlates Inversely with Staphylococcus aureus: Data from Atopic Dermatitis Skin Microbiome.** *Acta Derm Venereol*. 2018; 98(5): 490–495.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
113. **F** Noverr MC, Huffnagle GB: **Regulation of Candida albicans morphogenesis by fatty acid metabolites.** *Infect Immun*. 2004; 72(11): 6206–10.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)

114. Struzycka I: **The oral microbiome in dental caries.** *Pol J Microbiol.* 2014; **63**(2): 127–35.
[PubMed Abstract](#)
115. Krishnan K, Chen T, Paster BJ: **A practical guide to the oral microbiome and its relation to health and disease.** *Oral Dis.* 2017; **23**(3): 276–286.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
116. Kilian M, Chapple IL, Hannig M, *et al.*: **The oral microbiome - an update for oral healthcare professionals.** *Br Dent J.* 2016; **221**(10): 657–666.
[PubMed Abstract](#) | [Publisher Full Text](#)
117. Liu B, Faller LL, Klitgord N, *et al.*: **Deep sequencing of the oral microbiome reveals signatures of periodontal disease.** *PLoS One.* 2012; **7**(6): e37919.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
118. Edlund A, Garg N, Mohimani H, *et al.*: **Metabolic Fingerprints from the Human Oral Microbiome Reveal a Vast Knowledge Gap of Secreted Small Peptidic Molecules.** *mSystems.* 2017; **2**(4): pii: e00058-17.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
119. Gomez A, Nelson KE: **The Oral Microbiome of Children: Development, Disease, and Implications Beyond Oral Health.** *Microb Ecol.* 2017; **73**(2): 492–503.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
120. Walsh CJ, Guinane CM, O' Toole PW, *et al.*: **A Profile Hidden Markov Model to investigate the distribution and frequency of LanB-encoding lantibiotic modification genes in the human oral and gut microbiome.** *PeerJ.* 2017; **5**: e3254.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
121. van 't Hof W, Veerman EC, Nieuw Amerongen AV, *et al.*: **Antimicrobial defense systems in saliva.** *Monogr Oral Sci.* 2014; **24**: 40–51.
[PubMed Abstract](#) | [Publisher Full Text](#)
122. Takahashi N: **Oral Microbiome Metabolism: From “Who Are They?” to “What Are They Doing?”.** *J Dent Res.* 2015; **94**(12): 1628–37.
[PubMed Abstract](#) | [Publisher Full Text](#)
123. Hezel MP, Weitzberg E: **The oral microbiome and nitric oxide homeostasis.** *Oral Dis.* 2015; **21**(1): 7–16.
[PubMed Abstract](#) | [Publisher Full Text](#)
124. Charlson ES, Bittinger K, Haas AR, *et al.*: **Topographical continuity of bacterial populations in the healthy human respiratory tract.** *Am J Respir Crit Care Med.* 2011; **184**(8): 957–63.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
125. Yu G, Gail MH, Consonni D, *et al.*: **Characterizing human lung tissue microbiota and its relationship to epidemiological and clinical features.** *Genome Biol.* 2016; **17**(1): 163.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
126. Dickson RP, Huffnagle GB: **The Lung Microbiome: New Principles for Respiratory Bacteriology in Health and Disease.** *PLoS Pathog.* 2015; **11**(7): e1004923.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
127. Dickson RP, Erb-Downward JR, Freeman CM, *et al.*: **Bacterial Topography of the Healthy Human Lower Respiratory Tract.** *MBio.* 2017; **8**(1).
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
128. Lozupone CA, Stombaugh JI, Gordon JI, *et al.*: **Diversity, stability and resilience of the human gut microbiota.** *Nature.* 2012; **489**(7415): 220–30.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
129. Legatzki A, Rösler B, von Mutius E: **Microbiome diversity and asthma and allergy risk.** *Curr Allergy Asthma Rep.* 2014; **14**(10): 466.
[PubMed Abstract](#) | [Publisher Full Text](#)
130. Ramakrishnan VR, Hauser LJ, Feazel LM, *et al.*: **Sinus microbiota varies among chronic rhinosinusitis phenotypes and predicts surgical outcome.** *J Allergy Clin Immunol.* 2015; **136**(2): 334–342.e1.
[PubMed Abstract](#) | [Publisher Full Text](#)
131. Goleva E, Jackson LP, Harris JK, *et al.*: **The effects of airway microbiome on corticosteroid responsiveness in asthma.** *Am J Respir Crit Care Med.* 2013; **188**(10): 1193–201.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
132. Sharma A, Laxman B, Naureckas ET, *et al.*: **Associations between fungal and bacterial microbiota of airways and asthma endotypes.** *J Allergy Clin Immunol.* 2019; **144**(5): 1214–1227.e7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
133. Ege MJ, Mayer M, Normand AC, *et al.*: **Exposure to environmental microorganisms and childhood asthma.** *N Engl J Med.* 2011; **364**(8): 701–9.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
134. Stein MM, Hrusch CL, Gozdz J, *et al.*: **Innate Immunity and Asthma Risk in Amish and Hutterite Farm Children.** *N Engl J Med.* 2016; **375**(5): 411–421.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
135. Arrieta MC, Stiemsma LT, Dimitriu PA, *et al.*: **Early infancy microbial and metabolic alterations affect risk of childhood asthma.** *Sci Transl Med.* 2015; **7**(307): 307ra152.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
136. Hilty M, Burke C, Pedro H, *et al.*: **Disordered microbial communities in asthmatic airways.** *PLoS One.* 2010; **5**(1): e8578.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
137. Durack J, Lynch SV, Nariya S, *et al.*: **Features of the bronchial bacterial microbiome associated with atopy, asthma, and responsiveness to inhaled corticosteroid treatment.** *J Allergy Clin Immunol.* 2017; **140**(1): 63–75.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
138. van Woerden HC, Gregory C, Brown R, *et al.*: **Differences in fungi present in induced sputum samples from asthma patients and non-atopic controls: a community based case control study.** *BMC Infect Dis.* 2013; **13**: 69.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
139. Salam MT, Margolis HG, McConnell R, *et al.*: **Mode of delivery is associated with asthma and allergy occurrences in children.** *Ann Epidemiol.* 2006; **16**(5): 341–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
140. Kero J, Gissler M, Grönlund M-M, *et al.*: **Mode of delivery and asthma -- is there a connection?** *Pediatr Res.* 2002; **52**(1): 6–11.
[PubMed Abstract](#) | [Publisher Full Text](#)
141. Yip BHK, Leonard H, Stock S, *et al.*: **Caesarean section and risk of autism across gestational age: A multi-national cohort study of 5 million births.** *Int J Epidemiol.* 2017; **46**(2): 429–39.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
142. Whiteside SA, Razvi H, Dave S, *et al.*: **The microbiome of the urinary tract—a role beyond infection.** *Nat Rev Urol.* 2015; **12**(2): 81–90.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
143. Hillier SL, Nugent RP, Eschenbach DA, *et al.*: **Association between bacterial vaginosis and preterm delivery of a low-birth-weight infant. The Vaginal Infections and Prematurity Study Group.** *N Engl J Med.* 1995; **333**(26): 1737–42.
[PubMed Abstract](#) | [Publisher Full Text](#)
144. Mitra A, MacIntyre DA, Lee YS, *et al.*: **Cervical intraepithelial neoplasia disease progression is associated with increased vaginal microbiome diversity.** *Sci Rep.* 2015; **5**: 16865.
[Publisher Full Text](#) | [F1000 Recommendation](#)
145. Ness RB, Kip KE, Hillier SL, *et al.*: **A cluster analysis of bacterial vaginosis-associated microflora and pelvic inflammatory disease.** *Am J Epidemiol.* 2005; **162**(6): 585–90.
[PubMed Abstract](#) | [Publisher Full Text](#)
146. Sewankambo N, Gray RH, Wawer MJ, *et al.*: **HIV-1 infection associated with abnormal vaginal flora morphology and bacterial vaginosis.** *Lancet.* 1997; **350**(9077): 546–50.
[PubMed Abstract](#) | [Publisher Full Text](#)
147. Gravett MG: **Independent associations of bacterial vaginosis and Chlamydia trachomatis infection with adverse pregnancy outcome.** *JAMA.* 1986; **256**(14): 1899–903.
[PubMed Abstract](#)
148. Ma B, Forney LJ, Ravel J: **Vaginal microbiome: rethinking health and disease.** *Annu Rev Microbiol.* 2012; **66**: 371–89.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
149. Miller EA, Beasley DE, Dunn RR, *et al.*: **Lactobacilli Dominance and Vaginal pH: Why Is the Human Vaginal Microbiome Unique?** *Front Microbiol.* 2016; **7**: 1936.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
150. Boris S, Suárez JE, Vázquez F, *et al.*: **Adherence of human vaginal lactobacilli to vaginal epithelial cells and interaction with uropathogens.** *Infect Immun.* 1998; **66**: 1985–9.
[PubMed Abstract](#) | [Free Full Text](#)
151. Moncla BJ, Chappell CA, Debo BM, *et al.*: **The Effects of Hormones and Vaginal Microflora on the Glycome of the Female Genital Tract: Cervical-Vaginal Fluid.** *PLoS One.* 2016; **11**(7): e0158687.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
152. Gorodeski GI, Hopfer U, Liu CC, *et al.*: **Estrogen acidifies vaginal pH by up-regulation of proton secretion via the apical membrane of vaginal-ectocervical epithelial cells.** *Endocrinology.* 2005; **146**(2): 816–24.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
153. Boskey ER, Telsch KM, Whaley KJ, *et al.*: **Acid production by vaginal flora in vitro is consistent with the rate and extent of vaginal acidification.** *Infect Immun.* 1999; **67**(10): 5170–5.
[PubMed Abstract](#) | [Free Full Text](#)
154. Gorodeski GI: **Effects of estrogen on proton secretion via the apical membrane in vaginal-ectocervical epithelial cells of postmenopausal women.** *Menopause.* 2005; **12**(6): 679–84.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
155. Aldunate M, Srinovski D, Hearps AC, *et al.*: **Antimicrobial and immune modulatory effects of lactic acid and short chain fatty acids produced by vaginal microbiota associated with eubiosis and bacterial vaginosis.** *Front Physiol.* 2015; **6**: 164.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
156. Linhares IM, Summers PR, Larsen B, *et al.*: **Contemporary perspectives on vaginal pH and lactobacilli.** *Am J Obstet Gynecol.* 2011; **204**(2): 120.e1-5.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
157. O'Hanlon DE, Moench TR, Cone RA: **Vaginal pH and microbicidal lactic acid when lactobacilli dominate the microbiota.** *PLoS One.* 2013; **8**(11): e80074.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
158. Mirmonsef P, Zariffard MR, Gilbert D, *et al.*: **Short-chain fatty acids induce pro-inflammatory cytokine production alone and in combination with toll-like**

- receptor ligands. *Am J Reprod Immunol.* 2012; **67**(5): 391–400.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
159. Koh A, De Vadder F, Kovatcheva-Datchary P, *et al.*: From Dietary Fiber to Host Physiology: Short-Chain Fatty Acids as Key Bacterial Metabolites. *Cell.* 2016; **165**(6): 1332–45.
[PubMed Abstract](#) | [Publisher Full Text](#)
160. Price LB, Liu CM, Johnson KE, *et al.*: The effects of circumcision on the penis microbiome. *PLoS One.* 2010; **5**(1): e8422.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
161. Liu CM, Hungate BA, Tobian AA, *et al.*: Male circumcision significantly reduces prevalence and load of genital anaerobic bacteria. *mBio.* 2013; **4**(2): e00076.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
162. Prodder JL, Kaul R: The biology of how circumcision reduces HIV susceptibility: broader implications for the prevention field. *AIDS Res Ther.* 2017; **14**(1): 49.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
163. Yasuda K, Oh K, Ren B, *et al.*: Biogeography of the intestinal mucosal and luminal microbiome in the rhesus macaque. *Cell Host Microbe.* 2015; **17**(3): 385–91.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
164. Tropini C, Earle KA, Huang KC, *et al.*: The Gut Microbiome: Connecting Spatial Organization to Function. *Cell Host Microbe.* 2017; **21**(4): 433–42.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
165. Bik EM, Eckburg PB, Gill SR, *et al.*: Molecular analysis of the bacterial microbiota in the human stomach. *Proc Natl Acad Sci U S A.* 2006; **103**(3): 732–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
166. Lang JM, Eisen JA, Zivkovic AM: The microbes we eat: abundance and taxonomy of microbes consumed in a day's worth of meals for three diet types. *PeerJ.* 2014; **2**: e659.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
167. Sonnenburg JL, Bäckhed F: Diet-microbiota interactions as moderators of human metabolism. *Nature.* 2016; **535**(7610): 56–64.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
168. Martens EC, Kelly AG, Tauzin AS, *et al.*: The devil lies in the details: how variations in polysaccharide fine-structure impact the physiology and evolution of gut microbes. *J Mol Biol.* 2014; **426**(23): 3851–65.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
169. Jones BV, Begley M, Hill C, *et al.*: Functional and comparative metagenomic analysis of bile salt hydrolase activity in the human gut microbiome. *Proc Natl Acad Sci U S A.* 2008; **105**(36): 13580–5.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
170. Joyce SA, MacSharry J, Casey PG, *et al.*: Regulation of host weight gain and lipid metabolism by bacterial bile acid modification in the gut. *Proc Natl Acad Sci U S A.* 2014; **111**(20): 7421–6.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
171. Nicholson JK, Holmes E, Kinross J, *et al.*: Host-gut microbiota metabolic interactions. *Science.* 2012; **336**(6086): 1262–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
172. van Passel MW, Kant R, Zoetendal EG, *et al.*: The genome of *Akkermansia muciniphila*, a dedicated intestinal mucin degrader, and its use in exploring intestinal metagenomes. *PLoS One.* 2011; **6**(3): e16876.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
173. Belzer C, Chia LW, Aalvink S, *et al.*: Microbial Metabolic Networks at the Mucus Layer Lead to Diet-Independent Butyrate and Vitamin B₁₂ Production by Intestinal Symbionts. *mBio.* 2017; **8**(5): pii: e00770-17.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
174. Vrieze A, Out C, Fuentes S, *et al.*: Impact of oral vancomycin on gut microbiota, bile acid metabolism, and insulin sensitivity. *J Hepatol.* 2014; **60**(4): 824–31.
[PubMed Abstract](#) | [Publisher Full Text](#)
175. Enright EF, Gahan CG, Joyce SA, *et al.*: The Impact of the Gut Microbiota on Drug Metabolism and Clinical Outcome. *Yale J Biol Med.* 2016; **89**(3): 375–82.
[PubMed Abstract](#) | [Free Full Text](#)
176. Wu H, Esteve E, Tremaroli V, *et al.*: Metformin alters the gut microbiome of individuals with treatment-naïve type 2 diabetes, contributing to the therapeutic effects of the drug. *Nat Med.* 2017; **23**(7): 850–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
177. Maier L, Pruteanu M, Kuhn M, *et al.*: Extensive impact of non-antibiotic drugs on human gut bacteria. *Nature.* 2018; **555**(7698): 623–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
178. Cluny NL, Keenan CM, Reimer RA, *et al.*: Prevention of Diet-Induced Obesity Effects on Body Weight and Gut Microbiota in Mice Treated Chronically with Δ⁹-Tetrahydrocannabinol. *PLoS One.* 2015; **10**(12): e0144270.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
179. Mutlu EA, Gillevet PM, Rangwala H, *et al.*: Colonic microbiome is altered in alcoholism. *Am J Physiol Gastrointest Liver Physiol.* 2012; **302**(9): G966–78.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
180. Wilson ID, Nicholson JK: Gut microbiome interactions with drug metabolism, efficacy, and toxicity. *Transl Res.* 2017; **179**: 204–22.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
181. Panee J, Gerschenson M, Chang L: Associations Between Microbiota, Mitochondrial Function, and Cognition in Chronic Marijuana Users. *J Neuroimmune Pharmacol.* 2018; **13**(1): 113–22.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
182. Fulcher JA, Hussain SK, Cook R, *et al.*: Effects of Substance Use and Sex Practices on the Intestinal Microbiome During HIV-1 Infection. *J Infect Dis.* 2018; **218**(10): 1560–70.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
183. Hamer HM, Jonkers DM, Bast A, *et al.*: Butyrate modulates oxidative stress in the colonic mucosa of healthy humans. *Clin Nutr.* 2009; **28**(1): 88–93.
[PubMed Abstract](#) | [Publisher Full Text](#)
184. Holmes E, Loo RL, Stampler J, *et al.*: Human metabolic phenotype diversity and its association with diet and blood pressure. *Nature.* 2008; **453**(7193): 396–400.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
185. Allen JM, Mailing LJ, Niemi GM, *et al.*: Exercise Alters Gut Microbiota Composition and Function in Lean and Obese Humans. *Med Sci Sports Exerc.* 2018; **50**(4): 747–57.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
186. Zoetendal EG, von Wright A, Vilpponen-Salmela T, *et al.*: Mucosa-associated bacteria in the human gastrointestinal tract are uniformly distributed along the colon and differ from the community recovered from feces. *Appl Environ Microbiol.* 2002; **68**(7): 3401–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
187. Postler TS, Ghosh S: Understanding the Holobiont: How Microbial Metabolites Affect Human Health and Shape the Immune System. *Cell Metab.* 2017; **26**(1): 110–30.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
188. Louis P, Flint HJ: Formation of propionate and butyrate by the human colonic microbiota. *Environ Microbiol.* 2016; **19**(1): 29–41.
[PubMed Abstract](#) | [Publisher Full Text](#)
189. Le Poul E, Loison C, Struyf S, *et al.*: Functional characterization of human receptors for short chain fatty acids and their role in polymorphonuclear cell activation. *J Biol Chem.* 2003; **278**(28): 25481–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
190. Frost G, Sleeth ML, Sahuri-Arisoylu M, *et al.*: The short-chain fatty acid acetate reduces appetite via a central homeostatic mechanism. *Nat Commun.* 2014; **5**: 3611.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
191. De Vadder F, Kovatcheva-Datchary P, Goncalves D, *et al.*: Microbiota-generated metabolites promote metabolic benefits via gut-brain neural circuits. *Cell.* 2014; **156**(1–2): 84–96.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
192. Smith PM, Howitt MR, Panikov N, *et al.*: The microbial metabolites, short-chain fatty acids, regulate colonic T_H17 cell homeostasis. *Science.* 2013; **341**(6145): 569–73.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
193. Bui TP, Ritari J, Boeren S, *et al.*: Production of butyrate from lysine and the Amadori product fructoselysine by a human gut commensal. *Nat Commun.* 2015; **6**: 10062.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
194. Macfarlane GT, Gibson GR, Beatty E, *et al.*: Estimation of short-chain fatty acid production from protein by human intestinal bacteria based on branched-chain fatty acid measurements. *FEMS Microbiol Lett.* 1992; **101**(2): 81–8.
[Publisher Full Text](#)
195. Vital M, Howe AC, Tiedje JM: Revealing the bacterial butyrate synthesis pathways by analyzing (meta)genomic data. *mBio.* 2014; **5**(2): e00889.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
196. Thangaraju M, Cresci G, Itagaki S, *et al.*: Sodium-coupled transport of the short chain fatty acid butyrate by SLC5A8 and its relevance to colon cancer. *J Gastrointest Surg.* 2008; **12**(10): 1773–82.
[PubMed Abstract](#) | [Publisher Full Text](#)
197. Donohoe DR, Collins LB, Wali A, *et al.*: The Warburg effect dictates the mechanism of butyrate-mediated histone acetylation and cell proliferation. *Mol Cell.* 2012; **48**(4): 612–26.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
198. Trompette A, Gollwitzer ES, Yadava K, *et al.*: Gut microbiota metabolism of dietary fiber influences allergic airway disease and hematopoiesis. *Nat Med.* 2014; **20**(2): 159–66.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
199. Thorburn AN, McKenzie CL, Shen S, *et al.*: Evidence that asthma is a developmental origin disease influenced by maternal diet and bacterial metabolites. *Nat Commun.* 2015; **6**: 7320.
[PubMed Abstract](#) | [Publisher Full Text](#)
200. Lloyd CM, Hawrylowicz CM: Regulatory T cells in asthma. *Immunity.* 2009; **31**(3): 438–49.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
201. Labbé A, Ganopolsky JG, Martoni CJ, *et al.*: Bacterial bile metabolising gene abundance in Crohn's, ulcerative colitis and type 2 diabetes metagenomes. *PLoS One.* 2014; **9**(12): e115175.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

202. Ridlon JM, Kang DJ, Hylemon PB, *et al.*: **Bile acids and the gut microbiome.** *Curr Opin Gastroenterol.* 2014; **30**: 332–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
203. Lefebvre P, Cariou B, Lien F, *et al.*: **Role of bile acids and bile acid receptors in metabolic regulation.** *Physiol Rev.* 2009; **89**(1): 147–91.
[PubMed Abstract](#) | [Publisher Full Text](#)
204. Ridlon JM, Harris SC, Bhowmik S, *et al.*: **Consequences of bile salt biotransformations by intestinal bacteria.** *Gut Microbes.* 2016; **7**(1): 22–39.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
205. Hartstra AV, Bouter KE, Bäckhed F, *et al.*: **Insights into the role of the microbiome in obesity and type 2 diabetes.** *Diabetes Care.* 2015; **38**(1): 159–65.
[PubMed Abstract](#) | [Publisher Full Text](#)
206. **F** Turnbaugh PJ, Ley RE, Mahowald MA, *et al.*: **An obesity-associated gut microbiome with increased capacity for energy harvest.** *Nature.* 2006; **444**(7122): 1027–31.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
207. Kobayashi M, Ikegami H, Fujisawa T, *et al.*: **Prevention and treatment of obesity, insulin resistance, and diabetes by bile acid-binding resin.** *Diabetes.* 2007; **56**(1): 239–47.
[PubMed Abstract](#) | [Publisher Full Text](#)
208. Penney NC, Kinross J, Newton RC, *et al.*: **The role of bile acids in reducing the metabolic complications of obesity after bariatric surgery: A systematic review.** *Int J Obes (Lond).* 2015; **39**(11): 1565–74.
[PubMed Abstract](#) | [Publisher Full Text](#)
209. **F** Patti ME, Houten SM, Bianco AC, *et al.*: **Serum bile acids are higher in humans with prior gastric bypass: potential contribution to improved glucose and lipid metabolism.** *Obesity (Silver Spring).* 2009; **17**(9): 1671–7.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#) | [F1000 Recommendation](#)
210. Centuori SM, Gomes CJ, Trujillo J, *et al.*: **Deoxycholic acid mediates non-canonical EGFR-MAPK activation through the induction of calcium signaling in colon cancer cells.** *Biochim Biophys Acta.* 2016; **1861**(7): 663–70.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
211. **F** Yoshimoto S, Loo TM, Atarashi K, *et al.*: **Obesity-induced gut microbial metabolite promotes liver cancer through senescence secretome.** *Nature.* 2013; **499**(7456): 97–101.
[PubMed Abstract](#) | [Publisher Full Text](#) | [F1000 Recommendation](#)
212. Bayerdörffer E, Mannes GA, Ochsenkühn T, *et al.*: **Unconjugated secondary bile acids in the serum of patients with colorectal adenomas.** *Gut.* 1995; **36**(2): 268–73.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
213. Coppé JP, Desprez PY, Krtolica A, *et al.*: **The senescence-associated secretory phenotype: the dark side of tumor suppression.** *Annu Rev Pathol.* 2010; **5**: 99–118.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

Open Peer Review

Current Peer Review Status:  

Editorial Note on the Review Process

F1000 Faculty Reviews are written by members of the prestigious F1000 Faculty. They are commissioned and are peer reviewed before publication to ensure that the final, published version is comprehensive and accessible. The reviewers who approved the final version are listed with their names and affiliations.

The reviewers who approved this article are:

Version 1

1 **Jack A Gilbert**

Department of Pediatrics and Scripps Institution of Oceanography, University of California San Diego, La Jolla, CA, 92037, USA

Competing Interests: Jack A Gilbert is an Editor-in-Chief for MSystems

2 **Robert E Brown**

Department of Biology, George Mason University, Manassas, VA, USA

Competing Interests: No competing interests were disclosed.

The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com

F1000Research