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Gut Microbiota and Microbial Metabolism in Early Risk of Cardiometabolic Disease

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Abstract

Cardiometabolic disease comprises cardiovascular and metabolic dysfunction, and underlies the leading causes of morbidity and mortality, both within the United States and worldwide. Commensal microbiota are implicated in the development of cardiometabolic disease. Evidence suggests that the microbiome is relatively variable during infancy and early childhood, becoming more fixed in later childhood and adulthood. Effects of microbiota, both during early development, and in later life, may induce changes in host metabolism that modulate risk mechanisms and predispose towards development of cardiometabolic disease. In this review, we summarize factors that influence gut microbiome composition and function during early life, and explore how changes in microbiota and microbial metabolism influence host metabolism and cardiometabolic risk throughout life. We highlight limitations in current methodology and approaches, and outline state of the art advances which are improving research, and building towards refined diagnosis and treatment options in microbiome-targeted therapies.

Keywords

Cardiovascular Disease; Metabolism

Introduction

Gut microbiota have been associated with a wide variety of diseases[1], with cardiometabolic diseases and their risk factors being repeatedly identified as having a microbial component. Exposure to commensal microbes and their products begins at or before birth, and microbial metabolism may modulate pathways that can initiate early metabolic reprograming that can be pathogenic or protective, depending on specific circumstances. While microbiota across

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various body sites have potential relevance to disease, the gut microbiome represent the most abundant and the most well-studied, and serves as the focus for this review. Within the following sections, we summarize the known determinants of gut microbiome composition (Figure 1), examine potential mechanisms linking microbial metabolism to disease (Figure 2), highlight known microbiome-disease relationships, and discuss developments in the field that may ultimately lead towards clinical utility.

Gut microbiome composition is highly variable during infancy and childhood.

Early life represents a highly variable period for microbial colonization. While some evidence has suggested that microbiota may be transferred to the developing fetus prior to delivery[2–4], the majority of current evidence points towards birth as the major event triggering large-scale microbial colonization[5–7]. Colonization of the infant gut occurs opportunistically, with initial contributions from vaginal, fecal, and skin microbiota, depending on delivery method, in addition to contributions from species present in the local environment[8–13]. Of these early strains, only a small subset are later found to successfully colonize[14], and it has not yet been firmly established whether the initial source of microbiota during delivery has a significant effect on any long-term outcomes[15–17]. Engraftment of specific microbes occurs during the months following birth, and is influenced by source of nutrition[18,19]. Infants who are fed human milk have been reported to have higher proportions of *Bifidobacterium*, *Actinobacteria* and *Firmicutes* compared to higher levels of *Atopobium*, *Proteobacteria*, and *Bacteroides* in infants fed with formula[18,19]. However, human milk feeding has also been associated with higher relative abundances of *Bacteroides* compared with formular feeding, in addition to lower proportions of *Clostridium, Lachnospiraceae, Streptococcus, Enterococcus*, and *Veillonella*[20]. These data highlight the challenges that remain in characterizing specific taxa that associate with environmental exposures, and suggest the need for more functional characterization. Human milk contains microbiota[21–23], and additionally contains prebiotics, oligosaccharides, and antibodies, which can preferentially support growth of specific microbiota, including *Bifidobacterium*, and protect against pathogens[24–30]. Further, there is some evidence of reciprocal interaction of oral microbiota and other signaling molecules which may occur during breastfeeding[31–35]. However the composition of human milk is highly variable[36–39], suggesting that effects of human milk feeding on infant microbiome composition and any long-term outcomes may not be uniform. Microbiome composition becomes more stable after age 3, resembling the composition seen in adults[14], with predominant representation by *Firmicutes* phylum, and *Prevotella* and *Bacteroides* genera[14,40]. Overall, this pattern of high variability suggests that infancy and early childhood is a critical period where sub-optimal colonization may determine later predisposition towards dysbiosis. There is some evidence linking early life microbiota to later inflammatory and immune-mediated disease, and to childhood obesity[41]. However, longitudinal studies are required to establish whether microbiome composition in childhood and early adulthood impacts long-term adult cardiometabolic health.

Bi-directional relationships between diet-derived nutrients and microbiota.

One of the most well-studied determinants of human microbiome composition is diet. Significant differences have been observed in gut microbiota from individuals consuming different diets based on geographical or traditional distinctions, such as hunter-gatherer, pastoralist, agriculture or urban[14,42–50]. However, even within local populations, microbiota differ between individuals based on dietary choices, such as vegetarian or vegan[51–55], low-carbohydrate “paleo”[56–58], low fat[59], or gluten free[60,61]. Non-digestible carbohydrates, including starches and fiber, are abundant in certain plant-based foods, and serve as a substrate for fermentation by colonic microbiota, leading to their designation as prebiotics. Prebiotics are generally defined as substances which are metabolized by commensal microbes and promote health[62], which contrasts with probiotics, defined as the beneficial microbes themselves[63]. Presence or absence of prebiotic nutrients provides a selective pressure which may favor specific microbes[64–67]. Further, metabolism of these nutrients produces short-chain fatty acids (SCFAs), which serve as a primary fuel source for colonic epithelial cells, and act as important signaling molecules[68], as discussed further in a later section. In the setting of sub-optimal diet, supplementation with pre- or probiotics may be an effective means of promoting microbial diversity. Supplementation with the prebiotic fiber inulin has been shown to lead to increases in *Bifidobacterium*, *Anaerostipes*, *Faecalibacterium* and *Lactobacilus*, with reduction in *Bacteroides*[69]. However, whether this leads to changes in SCFAs is unclear[69]. Further, given the complexity and inter-individual variability in microbiomes, there may be risks associated with probiotic and prebiotic supplementation, which remain to be fully explored[70]. Other dietary components with potentially large effects on microbiota include non-nutritive sweeteners[71,72], and probiotic-containing fermented foods[73–78].

In addition to host dietary intake influencing microbial abundance, the presence and action of specific microbes also modulates nutrient availability to the host[79]. This is one mechanism whereby microbiota can influence host health status, and may be of particular relevance to obesity. Many studies have identified differences in microbiome composition based on body weight or adiposity, starting in childhood[80–82], and fecal microbiota transplant (FMT) studies in animals and humans suggest that microbiota by themselves can promote obesity[83–85]. Because microbiota both consume and produce energy and nutrients within the intestines, there can be considerable variability in energy and nutrient availability to individuals consuming the same diet[79,84,86,87]. However, identifying effective strategies to reduce obesity through modulation of the gut microbiota have proven challenging[88,89], and considerable additional research is required to understand the complex host:microbe relationships modulating energy and nutrient metabolism.

Environmental determinants of microbiome composition and drug:microbe interactions.

Local environment plays an important role in determining microbiome composition, particularly during childhood, but also throughout the lifespan. Differences have been reported in microbiota within individuals in rural or urban environments[90–92]. Within

the home, exposure to older siblings[93], and to pets has been associated with increased bacterial diversity in children[94,95]. Use of antibiotics has a significant impact on commensal microbes, particularly in the case of broad-spectrum oral antibiotics, generally leading to a reduction in diversity and reduction in microbes through to be beneficial[96]. The gut microbiota generally recover following a course of antibiotics, however it can take several weeks, and may never completely restore to pre-antibiotic diversity[97]. Repeated courses of antibiotics, particularly in children, may have more long-standing effects[98], including increased risk of antibiotic resistance[99], in addition to obesity and cardiometabolic disease[100–107]. This is likely mediated by antibiotic-induced alterations in microbiota which alter the function of the microbiome, and may lead to altered production of metabolites, and persistent downstream host metabolic dysregulation[98,107–109]. Other medications also interact bidirectionally with the microbiome, and may alter microbiota, in addition to being differentially metabolized based on presence or absence of specific microbes[110–114]. These include commonly used anti-hypertensive and cardiometabolic drugs, including angiotensin II receptor blockers[115,116], statins[117], proton-pump inhibitors[118], and anti-diabetic medication[119], both individually and in combination[120], as well as neuropsychiatric[121] and gastrointestinal medications[122]. Microbiota may also alter vaccine responses in children and adults[123–126].

Genetic determinants of microbiome composition.

Several studies have investigated the impact of host genetic variation on gut microbial composition, primarily through genome-wide association studies (GWAS). These have identified close to 1,000 single nucleotide polymorphisms (SNPs) that associate with specific bacterial taxa[127–136]. However, given the inherent heterogeneity in metagenomic profiling between studies, and presence of confounding, robust replication and validation of suggested GWAS associations remains a challenge[137]. Several microbe-associated SNPs also associate with disease phenotypes, suggesting that one mechanisms linking human genetic variation with disease may be through modulation of commensal microbes[138–141]. Suggested associations include *Ruminococcus flavefaciens* and hypertension, *Clostridium* and platelet count[142], and *Lachnospiraceae and several autoimmune diseases*[138], however these associations require more validation, and remain to be proven experimentally. While human genetic variation may contribute to inter-individuality in gut microbiota, this may be relatively minor compared with other determinants of microbial composition[143].

Mechanisms linking gut microbiota to development of cardiometabolic disease.

Gut microbiome composition has been found to associate with numerous complex diseases, including cardiometabolic disease[144]. However, the potential pathways linking gut microbiota to cardiometabolic health are not fully understood. There are likely several distinct mechanisms whereby commensal microbes can influence disease pathogenesis, including through 1) modulation of nutrient and energy availability, as described above; 2) activation of immune responses; 3) modulation of gut barrier integrity; and 4) systemic effects via microbe-mediated signaling molecules.

Commensal microbiota and innate immune function:

The interaction between microbes and the host immune system is complex. In a healthy gut, multiple factors allow the intestinal immune system and commensal microbes to coexist in a mutually tolerant state[145]. Dysregulation of this balance, leading to uncontrolled immune activation, may partly underlie the chronic systemic low-grade inflammation associated with cardiometabolic diseases[146]. Immune activation occurs through direct interaction between host cells and microbes, and through microbe-generated signaling molecules. Intestinal host:microbe homeostasis is thought to be promoted through a balance of effector and suppressor arms of the adaptive immune system; commensal microbes target multiple antigen-presenting cells, promoting expansion of anti-inflammatory T regulatory cells (T_{reg}), or pro-inflammatory T helper 17 (T_H17) depending on the setting[147–149]. This is mediated through multiple mechanisms. Specific species, including segmented filamentous bacteria, activate T_H17 cells, which increases intestinal inflammation, and protects against intestinal pathogens[150]. However other species, including *Lactobacillus murinus*, have been suggested to inhibit pathogenic T_H17 cell activation, but are depleted in the setting of a high-salt diet[151]. While T_H17 activation in some settings may improve host immune responses and healing[152,153], there may also negative consequences on host immune function from pathogenic T_H17 activation, including hypertension, inflammatory and autoimmune disease[154,155]. Clostridium species have been found to induce T_{reg} cells[156,157]. The SCFA butyrate induces tolerogenic dendritic cells and promotes T_{reg} cells[158–161]. Other microbe-derived molecules may similarly affect T cell activity, including bile acids[162,163]. Innate immune system and T cell development during early life may have particular importance in establishing antigen tolerance[164–166], further highlighting the importance of early microbial colonization in infancy and childhood on lifelong health[167]. Changes in immune function occurring at subsequent life stages including pregnancy[168], may also disrupt the balance between microbes and the innate immune system. In addition, dietary factors, including intake of sodium, can affect host:microbe homeostasis, leading to activation of T_H17 cells, promoting formation of pro-inflammatory isolevuglandins and increased risk of hypertension[169,170].

Host:microbe interaction in gut barrier integrity:

In a healthy intestine, colonic goblet cells produce a thick mucus barrier which provides some separation between host cells and microbes[171]. The mechanisms determining mucus secretion remain incompletely defined, but are in part regulated by activation of autophagy and consequent reduction of endoplasmic reticulum (ER) stress, in a microbiota-dependent manner[172]. The presence of butyrate-producing bacteria promotes mucus production by goblet cells[173]. However, in the absence of sufficient SCFA availability, potentially due to low-fiber diet or dysbiosis, there is reduction in the mucosal barrier, linked both to reduced mucus production[173] and digestion of the mucosal barrier by commensal microbes[174]. While a certain amount of mucus digestion by microbes is expected and may even be beneficial to the microbial ecosystem and epithelial health[175], excessive degradation can promote inflammation within the intestinal wall, in addition to reduction in epithelial tight junctions, leading to a “leaky” gut barrier and increased risk of pathogenic infection and translocation of intestinal products[176–178]. The presence of bacteria or bacterial products such as lipopolysaccharide (LPS) entering through the portal vein then activates systemic

immune responses, leading to a pro-inflammatory state with altered LPS-responsiveness, and increased risk of cardiometabolic disease, heart failure, and adverse outcomes[179–182].

Microbial Metabolism:

Commensal microbes produce a large variety of metabolites, some of which have already been demonstrated to be of relevance to human health. However, our understanding of the specific pathophysiological relevance of the full spectrum of microbial-metabolites is still in its infancy. Several microbe-derived metabolites have been identified as being of particular importance to cardiometabolic health and disease[149,183,184]. Trimethylamine N-oxide (TMAO) is a metabolite produced collaboratively by the host and microbiota, where microbes generate trimethylamine (TMA) from dietary precursors (including choline, phosphatidylcholine, carnitine and betaine)[185], and the host then converts TMA into TMAO, which has been shown to increase atherosclerosis[186–188] and other cardiovascular diseases[183]. The production of TMA is dependent on the presence of microbial genes, collectively known as the gbu gene cluster, which catalyze intermediate steps, such as the conversion of carnitine to TMA via γ-butyrobetaine[189,190]. Another microbe-dependent metabolite, phenylacetylglutamine (PAG), which is derived from phenylalanine, has also been shown to associate with cardiovascular disease[191,192]. Production of this metabolite is dependent on the presence of microbial genes encoding enzymes in the phenylpyruvate:ferredoxin oxidoreductase (PPFOR) and phenylpyruvate decarboxylase (PPDC) pathways[191]. PAG has been shown to modulate adrenergic receptor signaling, and is linked to increased risk of thrombosis and heart failure[192,193]. Indole-3-propionic acid (IPA) is a microbe-derived metabolite of tryptophan, which acts as an antibiotic, and has been suggested to be protective in disease, exhibiting anti-inflammatory and antioxidant function[194,195], and modulation of cholesterol efflux[196]. Higher IPA has been associated with higher gut microbiome diversity[197]. Other tryptophan metabolites, including kynurenine, are also modulated by microbiota[198] and may associate with cardiometabolic disease[199,200] as well as with neuropsychiatric disease[201], highlighting potential mechanistic underpinnings of the known comorbidity of cardiovascular and neuropsychiatric disease[202]. The production and abundance of IPA and other indole-derived tryptophan metabolites is dependent on the presence of specific microbial genes[203]. Host-derived bile acids are important for nutrient metabolism within the digestive tract, but also alter microbial composition and function[204]. Bile acids are modified by microbiota into secondary bile acids[205], which can act as systemic signaling molecules modulating inflammation and metabolism[206,207]. The production of secondary bile acids, and potential downstream pathogenicity, are dependent on the presence of microbial species possessing bile salt hydrolase activity[208,209]. Several microbe-derived metabolites act as uremic toxins, including TMAO and IPA, in addition to other protein-derived metabolites[210,211]. Communication between the host and microbial metabolism can occur at any point throughout the lifetime, but may be particularly important during early life. As mentioned earlier, the evidence supporting pre-natal microbial colonization is limited. However, maternal microbes may affect fetal development through metabolic signaling that crosses the placenta[212]. SCFAs were shown to act on embryonic receptors (GPR41 and GPR43), altering cell differentiation and development across multiple tissues, with long-lasting effects on metabolism[212]. Other microbial metabolites, including amino acid-derived

metabolites may also cross the placenta, with potential effects on fetal development[213,214]. Further, there is growing evidence for a wide variety of other metabolites, produced through the action of microbiota on dietary nutrients, that may affect host health, including amino acids[215], soy-derived isoflavones[216–219], cannabinoids[220], and phenolic acids[221], in addition to a large number of pharmacological and host metabolites that may be modulated by microbiota[110,222–225].

Association between microbial metabolism and early development of cardiometabolic disease.

Effects of microbiota on gut barrier integrity and inflammation, both local and systemic, have the potential to alter cardiometabolic disease risk broadly, through modulation of body weight and energy metabolism, insulin and glucose homeostasis, hypertension, dyslipidemia, and vascular function. As described below, microbiota have been linked to multiple risk mechanisms underlying cardiometabolic disease[226], many of which likely precede overt CVD or diabetes. However, the relative importance of each mechanism remains to be further understood, and there may be considerable heterogeneity in effects, potentially linked to host genetic background or other factors.

The effects of gut microbiota on body weight regulation, inflammation, and insulin homeostasis:

Obesity and inflammation are recognized as important contributors to the development of subsequent cardiometabolic diseases, and may be one of the earliest symptoms of metabolic dysregulation[227]. Cross-sectional studies have identified differences in gut microbiota between lean and obese individuals across the lifespan[80,81,83,228,229], and in the setting of diabetes[230–232]. Further, FMT experiments suggest causality, with microbiota from obese individuals promoting obesity in recipients[84,85,233]. Fecal transplants have also been shown to modulate insulin sensitivity in humans, however whether these effects persist over the long-term is unknown[234,235]. As discussed, the mechanisms are incompletely understood, but may relate in part to the effects of microbiota on energy harvesting capacity[79,86,87,236]. Further, effects of microbiota on inflammation may, by itself, be sufficient to promote metabolic dysregulation and obesity[146,227,237]. In particular, interaction between microbes and the gut immune system during critical periods of development, including early life, may have long-lasting effects on immune programming[165–167,238–240].

Relationship between gut microbiota and hypertension:

Gut microbiota have been reported to modulate blood pressure through several potential mechanisms. Blood pressure elevation in response to dietary sodium has a contribution by gut microbiota, including *Lactobacillus* species, through modulation of T_H17 cells and production of isolevuglandins[151,169,170,241].Multiple bacterial species have been associated with hypertension, including *Lactobacillus*, *Klebsiella, Parabacteroides, Desulfovibrio, and Prevotella*[241,242], although more validation and functional work is needed to delineate causal associations. Specific microbiota, including *Romboutsia, Turicibacter, Ileibacterium, and Dubosiella*, have affinity to prompt host immunoglobulin A (IgA) binding, which may promote the development of hypertension, potentially through the gut-brain axis[243–245].

Many of the aforementioned diet-derived and microbe-mediated metabolites, including TMAO and SCFAs, also play a role in modulating blood pressure[246]. For example, microbe-derived SCFAs bind to olfactory and G protein-coupled receptors (Olfr78 and Gpr41) in the kidney and vascular endothelium to modulate vasodilation, heart rate and blood pressure[247–249].

Effects of gut microbiota on lipid metabolism:

Observational studies have identified potential relationships between gut microbiota and circulating lipids and lipoproteins[250–254], with microbiota accounting for an estimated 4–6% of the variation in TG and HDL cholesterol[255], and individual microbiota associating with specific lipoprotein subclasses in obese individuals[256]. Gut microbiota may affect lipid metabolism directly through modulation of lipids within the gut and systemically[257], with gut microbial production of SCFAs serving as the precursor for hepatic synthesis of longer-chain monounsaturated fatty acids and glycerophospholipids[258]. Microbiota have also been shown to mediate transformation of cholesterol[259]. Mendelian Randomization analysis has also been used to support a potential causal pathway between specific gut microbiota and dyslipidemia[260]. In contrast, a reverse relationship is not supported, and elevated plasma lipid levels may not significantly affect gut microbiota; however bile acids may mediate relationships between microbiota and lipids[261].

Gut microbial signaling modulates the development of hepatic steatosis:

Non-alcoholic fatty liver disease (NAFLD) accounts for a growing share of chronic liver disease in children and young adults[262]. NAFLD has been linked with atherosclerosis and left ventricular dysfunction in children and adolescents[263] and there is growing evidence that early-life NAFLD carries life-long cardiometabolic health implications. Maternal obesity is associated with the development of NAFLD in childhood and early adulthood, partly due to changes in the intestinal microbiota[264–267]. Offspring of obese mice had altered intestinal microbiota and a worsened NAFLD phenotype relative to offspring of lean mothers[266]. Mice that received fecal transplants from infants born of obese mothers had a higher intestinal Bacteroidetes-to-Firmicutes ratio and these intestinal microbiome changes were associated with higher hepatic expression of inflammatory genes and higher hepatic triglyceride accumulation[268]. Studies in later childhood showed that children with NAFLD had significantly different intestinal microbiota characterized by lower alpha diversity and higher Firmicutes-to-Bacteroidetes ratio, as well as higher abundance of *Bradyrhizobium*, *Peptoniphilus*, *Anaerococcus*, *Propionibacterium acnes*, *Dorea* and *Ruminococcus* and lower abundance of *Oscillospira*, *Gemmiger* and *Rikenellaceae*[269–271]. Additionally, *Oscillospira, Gemmiger*, and Bacteroidetes abundance as well as F/B ratio interact with *PNPLA3* polymorphisms to contribute to the severity of NAFLD in children and adolescents[270]. Similar pathogenic changes in microbiota are associated with obesity and high fat diet in later childhood[272]. Changes in intestinal microbiota contribute to NAFLD pathogenesis through a variety of mechanisms: increased intestinal permeability and translocation of proinflammatory bacterial products[268], changes in bile acid metabolism[273,274], endogenous alcohol production[275] and altered microbial metabolism of lipids, carbohydrates and amino acids[276–279].There are currently no FDA-approved treatments for pediatric NAFLD and dietary and lifestyle interventions remain the standard of care. Clinical trials targeting the

microbiome in children and adolescents with NAFLD have had promising results. Children with NAFLD treated with probiotics (VSL#3) for 4 months had significant improvement in hepatic steatosis compared to placebo controls[280]. Similarly, children with NAFLD treated with a probiotic containing Bifidobacterium and Lactobacillus spp. for 12 weeks had improvement in hepatic steatosis in addition to improvement in LDL and triglyceride levels and serum aspartate aminotransferase (AST)[281].

Gut microbial effects on cardiovascular disease:

Several studies have reported associations between microbiota and atherosclerosis[282,283]. As mentioned previously, TMAO associates with atherosclerosis and cardiovascular events, through mechanisms linked to atherothrombotic effects on platelet hyperreactivity and vascular function[284,285]. Down-regulation of IPA has been found to associate with coronary artery disease and atherosclerosis[196], as well as with peripheral artery disease[286]. However, in mice fed a Western Diet, supplementation with IPA did not ameliorate the development of cardiometabolic disease[287]. Beyond metabolites, microbial nucleic acids have been found within lipoproteins[288], suggesting that bacteria or their products may be carried within the circulation. Further, analysis of atherosclerotic plaque has identified microbial DNA within plaque[289], suggesting that translocation of microbiota or their products to the circulation, whether from intestinal or oral sources, may directly increase plaque formation. While intriguing, at present there is still limited evidence to suggest that live microbes themselves cause plaque formation directly[290], and atherosclerosis occurs even in the absence of live microbes[291,292]. However, plaque formation or expansion may be mediated by microbe-derived small RNAs, which can be carried by LDL cholesterol, and activate macrophages, potentiating development of atherosclerosis[293]. Microbiota, as assessed through microbiome composition, have been implicated in multiple cardiovascular diseases, including pulmonary arterial hypertension[294], abdominal aortic aneurysm[295], heart failure[296], heart failure with preserved ejection fraction (HFpEF)[297], heart failure with reduced ejection fraction (HFrEF)[298], and coronary artery disease[299]. However, most studies have included relatively small sample sizes, with little or no replication, leaving considerable uncertainty surrounding the clinical or mechanistic relevance of specific findings. While some of these associations are likely mediated by microbial metabolites, and effects on inflammation, lipid metabolism and vascular function, as previously discussed[179,196,284], the specific pathways linking microbiota to individual CVDs remain to be established. There is also some evidence that presence or absence of microbiota can alter gene expression in kidney and other tissues[300–302], which remains to be further characterized and explored. Much could be learned through increased efforts to characterize microbiome composition and function across disease development in robust metagenomic and metatranscriptomic studies with large sample sizes, including replication and validation of novel associations.

Interaction between the gut microbiome and viral infection in modulation of cardiometabolic risk.

There is evidence to suggest that the presence of viral pathogens may potentiate negative effects of gut microbiota on cardiometabolic disease. Persons with HIV (PWH) have a twofold greater risk of developing CVD relative to persons without HIV, independent

of Framingham cardiovascular risk factors[303]. HIV infection is associated with increased intestinal permeability[304,305] that permits translocation of pro-inflammatory bacterial products[306] that may increase systemic inflammation and cardiovascular disease risk. This may be due to lower production of microbiota-produced SCFA in PWH[307] which are integral for maintaining intestinal barrier function[308]. Additionally, levels of the microbial metabolite TMAO increase with antiretroviral therapy (ART) initiation and are associated with carotid plaque burden in PWH[309,310].

Following the emergence of SARS-CoV-2, several studies have focused on the role of the gut microbiota in COVID-19 and post-acute COVID-19 syndrome (PACS, or Long-COVID). The gut microbiota of COVID-19 patients has been reported to be altered when compared with uninfected individuals[311], and microbiota have been found to associate with severity of infection and outcomes within COVID-19 patients[312–314]. Specific microbes were reported to associated with PACS, and with various symptoms, including respiratory and neuropsychiatric[315]. Whether SARS-CoV-2 interacts with the gut microbiota to modulate COVID-19-related CVD risk remains unknown[316,317].

Best practices and state of the art methods for microbiome clinical translation.

Microbiome research has undergone rapid expansion over the past two decades, but many existing microbiome studies suffer from limitations which have impeded interpretability and clinical translation. Some of these inherent limitations are easier to address than others. Early issues in methods and study design, and in reporting of results, are now largely addressable through adherence to best practices such as the Strengthening The Organization and Reporting of Microbiome Studies' (STORMS) guidelines[318], including careful study design, consideration of confounders, standardized protocols, and well-selected controls[319]. While early studies mostly applied 16S rRNA sequencing to approximate taxa, the costs for whole metagenome sequencing are now broadly equivalent to 16S profiling, and offer considerable advantages including more precise taxonomical classification to the species level, and the possibility to infer functionality based on microbial genes[320,321]. However, it remains important to also use direct measurement of microbial gene expression through metatranscriptomics, and metabolite measurement to accurately assess microbiome function[322]. Sample sizes in many clinical studies are still relatively small, often including fewer than 100 individuals, which limits power and generalizability. However, this issue may be one of the easiest to address: sequencing costs continue to drop, removing some of the financial considerations that previously limited the size of studies. Further, stool is a highly accessible tissue, and several studies have demonstrated that previous barriers relating to sample collection, transportation, and cold storage, can be eliminated using convenient collection and preservation methods that allow for non-invasive sample collection and room temperature transportation and storage[323]. This also alleviates an additional limitation, which relates to the variability of samples obtained cross-sectionally. While there is relative stability in microbiome profiles over time, there are both stochastic and biological differences in gut microbiome samples obtained at different times. Inclusion of multiple samples over short and long-term follow-up can greatly improve the quality of a

study. While overall barriers relating to recruitment and cost of clinical and epidemiological studies remain, future studies can and should endeavor to maximize sample sizes and obtain repeated samples where possible for longitudinal analysis. However, some limitations are more difficult to overcome. As with other types of studies, there remains over-representation from certain population groups and geographical regions. Greater efforts are needed to ensure diversity in sampling and representation, including children and adolescents. Given the complexity of the relationships between microbiota and disease, there can be considerable confounding due to measured and unmeasured factors that affect microbial composition, and can lead to artifacts. These can be challenging to identify, but can be addressed in part through the strategies already discussed to maximize rigor and power, and by inclusion of external validation cohorts. Because microbes engage in horizontal gene transfer, there is a fundamental limitation in how accurately we can align sequence reads and define species, particularly when comparing across different studies[324]. Further, determining the relative importance of individual microbial species within the context of the holobiont remains a complex challenge. The use of complex synthetic microbiomes may be one way to bridge reductionist and holistic approaches[325,326], and to allow for better-defined FMT-based therapeutics. In addition to metagenomic sequencing, additional approaches including metatranscriptomics can shift focus from presence or absence of specific species or microbial genes, towards functional read-outs that may have more biological relevance. Large-scale metabolomic profiling of stool, or of microbial metabolites in circulation using NMR or Mass Spectrometry may also shed more light on microbiome function, but may require rapid processing and careful handling of samples[327–329]. While animal studies and basic mechanistic studies are very important, to further advance clinical translation, we will require a greater emphasis on studies that test microbiome-targeted interventions, including those using pre- and probiotics, FMT, and targeted therapeutics to alter microbiome composition or function[330–332]. Pharmacological manipulation of microbes, to “drug the bugs” is a promising avenue that may have advantages in providing host benefit, with fewer side effects than traditional pharmacological approaches[284,333,334]. Overall, the field would be strengthened by a greater focus on translational studies that combine observational findings with mechanistic interrogation, or clinical implementation.

In summary, the emerging wealth of literature on gut microbiota and microbial metabolism support clear roles for microbiota in early development of cardiometabolic disease. While much remains unknown, improvements in clinical trial design and increased focus on rigor and reproducibility in microbiome studies are likely to support significant advances in the field, leading towards improved clinical utility of microbiome-related biomarkers, and future therapeutic implementation of microbiome-targeted therapies.

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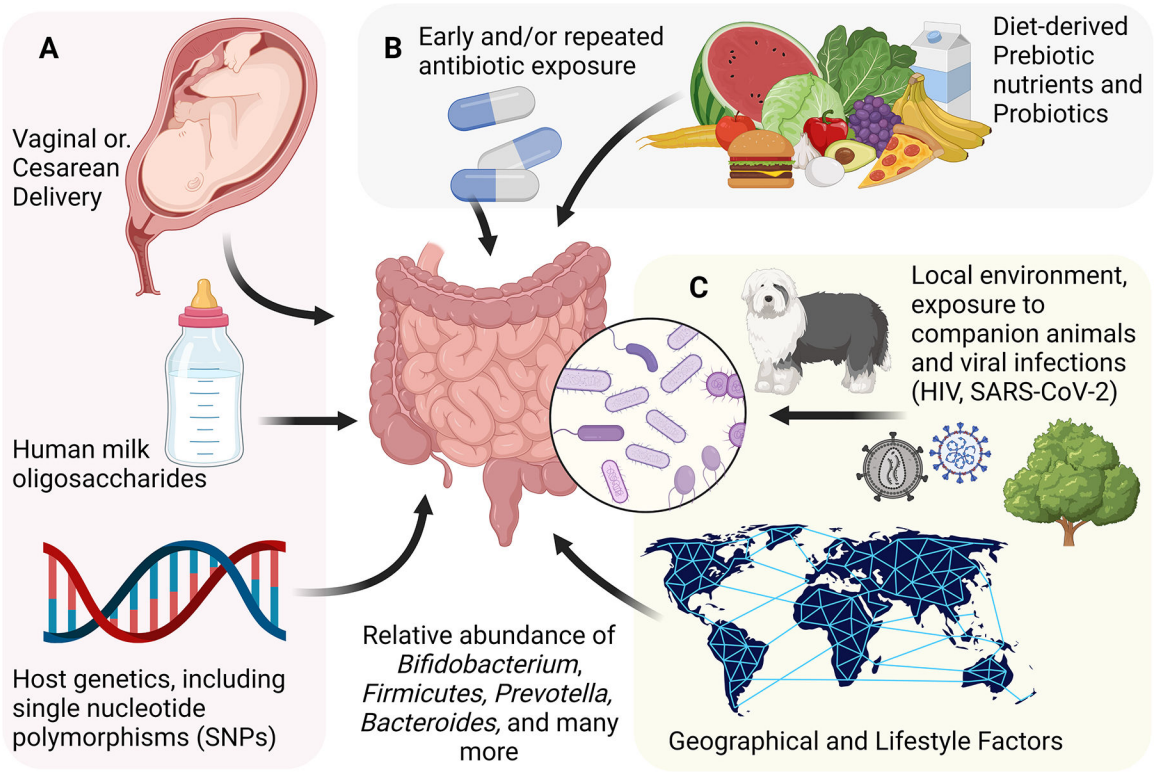

Figure 1. Determinants of Gut Microbiome Composition.

Many factors influence the composition of the gut microbiota. Some of these are determined very early in life, and are not modifiable later in life, including individual genetic background, delivery method, and early infant feeding method (**A**). Other determinants are variable throughout life, and potentially modifiable, including diet and use of medications (**B**). Other factors are similarly variable throughout life, but potentially more difficult to modify, including persistent viral infection, the local environment and broader geographical environment (**C**).

HIV: Human Immunodeficiency Virus; SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

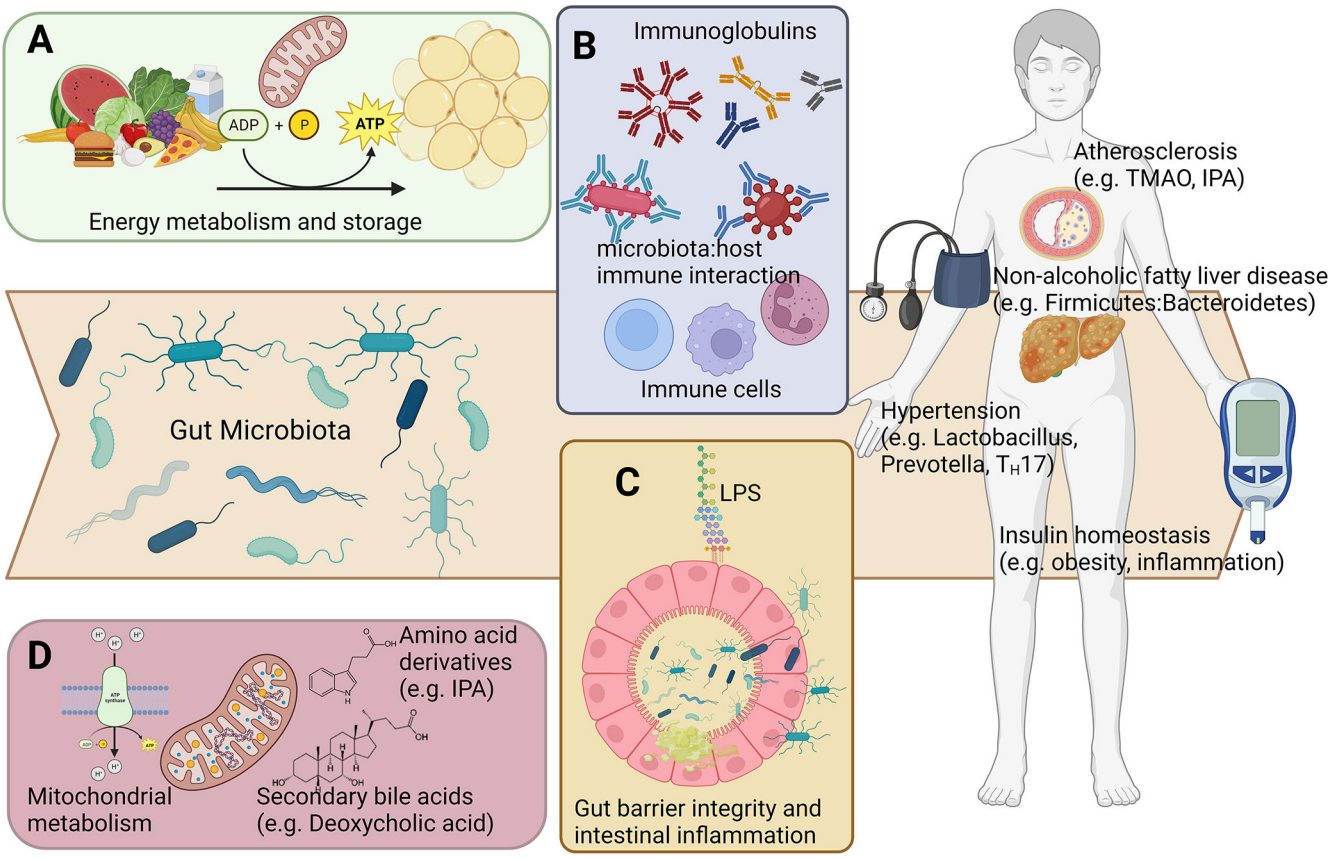

Figure 2. Mechanisms linking microbial metabolism to host physiology.

Gut microbiota may cause cardiometabolic disease through diverse mechanisms including A) modulation of energy and nutrient availability; B) activation of immune responses; C) modulation of gut barrier integrity; and D) systemic effects via microbe-mediated signaling molecules. TMAO: Trimethylamine N-oxide; IPA: Indole-3-propionic acid. T_H17: T helper 17 cells.