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Diet and the gut microbiota profiles in individuals with at risk of chronic heart failure – A review on the Asian population

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ABSTRACT

Background and Objectives: Chronic Heart Failure (CHF) is one of the leading cardiovascular diseases (CVDs), particularly in the Asian population. Individuals with specific health risks, such as obesity, type 2 diabetes, hypertension, dyslipidemia, and coronary artery disease (CAD), are more susceptible to developing CHF. Current evidence is limited to understanding the link between gut microbiota dysbiosis and CHF. Therefore, this review aims to explore the potential connection between dietary patterns, gut microbiota, and its metabolites in individuals at risk of CHF in the Asian population. **Methods and Study Design:** A literature review of cross-sectional studies was conducted using primary keywords such as "Asian", "obesity", "type 2 diabetes", "hypertension", "dyslipidemia", "coronary artery disease", and "chronic heart failure". There was no restriction on sample size. **Results:** Several gut microbiotas were found to correlate with CHF risk factors. There were increased levels of *Prevotella*, *Klebsiella*, *Romboutsia*, *Catenibacterium*, *Clostridium*, *Holdemanella*, *Ruminococcus*, *Coprococcus*, *Parabacteroides*, *Bacteroides*, *Lachnoclostridium*, *Streptococcus*, and *Megamonas*, while decreased levels of *Oscillibacter*, *Bifidobacterium*, *Lactobacillus*, *Akkermansia*, *Roseburia*, *Faecalibacterium*, *Pseudobutyrvibrio*, and *Eubacterium* were reported. These microbiota shifts were linked to increased TMAO production and impaired short-chain fatty acids (SCFAs) production. Dietary intake and microbial metabolites were also identified as contributors to the gut microbiota associated with CHF. **Conclusions:** A potential link exists between the gut microbiota profile and CHF risk factors, possibly mediated by microbial metabolites. Dietary patterns may influence CHF-associated gut microbiota and metabolites. Future research is needed to investigate how dietary modifications can modulate gut microbiota and its metabolites in CHF patients.

Key Words: gut microbiota, cardiovascular diseases, chronic heart failure, Asian, risk factors

INTRODUCTION

Chronic Heart failure (CHF) is a syndrome defined by symptoms or signs due to structural or functional cardiac abnormalities, confirmed by elevated natriuretic peptides or objective evidence of pulmonary or systemic congestion. According to data from the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) 2019, there were 31.89 million prevalent cases of HF in Asia. Some countries in Asia such as China and Indonesia reporting among the highest age-standardized prevalence rates (1,032.84 and 900.90 per 100,000 population,

respectively), with one study from China in 2000 found the prevalence of CHF was 0,9%.¹ CHF is a complex clinical syndrome resulting from structural or functional abnormalities that impair the heart's ability to fill with or eject blood. The main symptoms of CHF include dyspnea (shortness of breath) and fatigue, which reduce the ability to exercise and fluid retention, leading to pulmonary, splanchnic, or peripheral congestion and edema.^{2,3}

The progression of HF into its chronic form can be attributed to four primary causes. First, ischemic heart disease occurs when the heart muscle does not receive adequate blood flow due to blocked arteries, leading to myocardial damage and heart failure. Second, chronic obstructive pulmonary disease (COPD), a lung condition that makes breathing difficult, can strain the heart over time, contributing to heart failure. Third, hypertensive heart disease results from long-term high blood pressure, which alters the heart's shape and function, leading to failure. Finally, rheumatic heart disease, caused by untreated strep throat or scarlet fever, can lead to heart damage and eventual heart failure.⁴⁻⁹

Individuals with specific health conditions, such as obesity, type 2 diabetes (T2D), hypertension, dyslipidemia (abnormal cholesterol levels), and coronary artery disease (CAD), are at increased risk of developing CHF. Obesity is a significant risk factor for CHF and is associated with other cardiovascular diseases, including atherosclerosis and hypertension, thereby exacerbating the risk of heart failure. It affects left ventricular structure and both systolic and diastolic function.¹⁰ Type 2 diabetes is also linked to an increased risk of heart failure, even in the absence of other heart-related issues.^{11,12} High blood pressure is another major risk factor that causes structural and functional changes in the heart, reducing its adaptability to blood volume, pressure, and stress levels.^{6,13} Dyslipidemia, which is a well-established risk factor for heart disease, has been associated with a higher likelihood of heart-related events.^{14,15} Lastly, CAD, which impairs the heart's ability to pump blood efficiently, either due to myocardial tissue loss from a heart attack or long-term structural changes, significantly raises the risk of CHF.^{16,17}

Several factors contribute to the development of CHF, with diet playing a critical role. Unhealthy dietary habits, such as consuming high-fat and refined carbohydrate-rich diets, are significant contributors. Long-term consumption of a high-carbohydrate diet has been linked to gut microbiota dysbiosis, characterized by increased *Prevotella* and decreased *Bacteroides*, along with elevated short-chain fatty acids (SCFAs) in individuals consuming high-fiber diets.¹⁸ This connection between diet and gut microbiota indicates that gut health may be central to developing diseases related to dietary habits. For instance, obese individuals often exhibit overgrowth of *Prevotella* and *Klebsiella*, with a reduction in *Bacteroides*,

Bifidobacterium, *Lactobacillus*, and *Akkermansia*.^{19,20} Similarly, individuals with T2D experience alterations in gut microbiota due to disruptions in glucose homeostasis,^{21,22} and diseases have been associated with gut microbial changes.^{23–26}

It is possible that the gut microbiota dysbiosis seen in these diseases increases the risk of CHF since the changes observed in CHF patients resemble those found in these conditions.²⁷ However, it is crucial to note that these studies may not fully generalize the impact of altered gut microbiota on CHF incidence. Factors such as diet, lifestyle, and genetics vary widely across populations and continents, influencing gut microbiota composition.²⁸

The relationship between gut microbiota profiles and disease progression in individuals at risk for CHF is a compelling area of research. There has been speculation about increased Prevotella and Proteobacteria in individuals with CHF, yet comprehensive studies conducted in Asia remain limited. This review aims to examine the gut microbiota profiles of Asian individuals with CHF risk factors, including CAD, T2D, hypertension, obesity, and dyslipidemia. It focuses on the Asian population due to the documented differences in gut microbiota composition between Asian and non-Asian populations. Previous research has shown a higher abundance of Firmicutes in Asian populations, while non-Asian populations have demonstrated greater enrichment of *Akkermansia muciniphila*. These variations are largely attributed to differences in geographical location and diet.²⁹

MATERIALS AND METHODS

A literature review was conducted from January to May 2024, with a search restriction of ten years (from 2015 to 2024). A set of primary keywords was used, including “Asian”, “Obesity”, “Type 2 Diabetes”, “Hypertension”, “Dyslipidemia”, “Coronary Artery Disease”, and “Chronic Heart Failure”. These keywords were applied individually and in various combinations to ensure a comprehensive search of relevant literature using Boolean operations. The final keyword combination included “Chronic Heart Failure” AND “Asian” AND (“Microbiota” OR “Microbiome”) AND (“Type 2 Diabetes” OR “Obesity” OR “Hypertension” OR “Dyslipidemia” OR “Coronary Artery Disease”). The databases used for the search included PubMed, Scopus, Cochrane Library, and EBSCO. The review process involved a thorough examination of databases and journals to identify studies that met the inclusion criteria. Studies were selected based on their alignment with the research objectives, as determined by all authors.

RESULTS

Epidemiology and etiology of CHF in the Asian population

The CHF manifests as a clinical syndrome with symptoms and signs related to cardiac dysfunction, supported by elevated levels of natriuretic peptides and/or clear evidence of pulmonary or systemic congestion. This progressive condition is classified into three groups based on left ventricular ejection fraction (LVEF): Heart Failure with reduced ejection fraction (HFrEF, LVEF \leq 40%), Heart Failure with mildly reduced ejection fraction (HFmrEF, LVEF 41-49%), and Heart Failure with preserved ejection fraction (HFpEF, LVEF \geq 50%).³⁰ The causes of CHF are complex and multifactorial. Typical signs and symptoms are often accompanied by diagnostic results indicating heart dysfunction. CHF can have a sudden onset, leading to symptoms such as acute pulmonary edema or cardiogenic shock when the heart fails to pump adequately before compensatory mechanisms can activate.^{3,31}

The prevalence of CHF in Asia is substantial, with estimates indicating that 0.4% to 6% of the population in various Asian countries is affected.³² The elderly population is particularly vulnerable to CHF due to age-related changes in vascular structure and function. Studies have also shown distinctions between elderly individuals and younger adults with CHF, where older patients frequently present with comorbidities like hypertension and diabetes.^{33,34} Common symptoms of CHF include shortness of breath, fatigue, and leg swelling, especially in patients with a history of myocardial infarction (MI), arterial hypertension, CAD, diabetes mellitus, or cardiotoxic chemotherapy.³⁵ Several risk factors for CHF, particularly in Southeast Asia, include obesity, type 2 diabetes, hypertension, and smoking. These risk factors can lead to dyslipidemia and CAD, further increasing the likelihood of developing CHF.³⁶

Role of diet and gut microbiota in CHF among the Asian population

Some dietary habits in Asian countries may contribute to CHF risk. For example, the typical Chinese diet, which often includes high monosodium glutamate (MSG) consumption, has been associated with increased blood pressure.³⁷ Studies have linked MSG consumption to changes in the gut microbiota, such as an increase in Proteobacteria and Bacteroidetes and a decrease in *Actinobacteria* and *Firmicutes*. This imbalance in gut microbiota has been connected to obesity, which can also be associated with other food intake habits like high consumption of ultra-processed foods (UPF). UPF consumption has been correlated with an increase in specific gut bacteria such as *Prevotella*.³⁸⁻⁴⁰

Another common diet consumed by the Asian population includes white rice and wheat flour, which contain resistant starch that is fermented by gut microbiota without being digested by amylase, producing SCFAs (like butyrate). When carbohydrate intake is reduced and substituted with a high-fat diet, as seen with increasing consumption in several Asian countries like China, Malaysia, and Indonesia, the reduction might alter gut microbial composition, such as *Faecalibacterium*, which is correlated with lower levels of butyrate. This may increase the risk of developing cardiovascular diseases, such as atherosclerosis and heart failure, and hypothetically result in an increased risk of hypertension.^{41–43}

However, it is important to know that a higher intake of carbohydrates has been associated with various metabolic disorders. For instance, diets high in starches are correlated with an increased risk of hyperlipidemia and hyperglycemia, while excessive fructose consumption has been linked to a greater risk of cardiovascular diseases, insulin resistance (which could lead to diabetes) and dyslipidemia. Additionally, a high intake of artificially sweetened beverages is also associated with an elevated risk of hypertension, a condition that is prevalent in several Asian countries, including South Korea.⁴⁴ Studies have shown that consumption of monosaccharides and disaccharides are correlated with an increase of *Bifidobacteria* and a decrease of *Bacteroides*, the latter are a contribution to the incidence of several risk factors such as T2D and hypertension.^{18,45}

Given that certain diseases are linked to alterations in gut microbiota associated with dietary intake, such as high-carbohydrate or high-fat diets, there is a potential connection between risk factors for CHF and CHF itself with the gut microbiota dysbiosis. Changes in the gut microbiome and its metabolites are associated with the severity of CAD, which can ultimately lead to CHF. For example, certain bacteria such as *Ruminococcaceae* have been implicated in atherosclerosis through alterations in the host's metabolic pathways, including taurine, sphingolipid, ceramide, and benzene metabolism. A disease classifier based on microbial and metabolite profiles has been able to distinguish between cases and controls, as well as between stable CAD and acute coronary syndrome, which can progress to CHF.²⁵ In a study conducted in Tibet, the dysbiosis of gut microbiota, particularly the prevalence of *Prevotella*, was found to be common among Tibetan highlanders with CAD.⁴⁶ In another study from China, a reduction in *Ruminococcaceae* was observed in patients with CAD, a finding that was similarly noted in individuals with CHF. This reduction in *Ruminococcaceae* may affect various biological functions, including cell cycle regulation, ion transport, metabolism, and ribosomal structure and biogenesis.^{25,47} Additionally, a decrease in *Faecalibacterium* has been noted in both CAD and CHF patients, although the specific

mechanism of action remains limited. These findings suggest that gut microbiota alterations, whether a cause or consequence of CAD, may correlate with CHF incidence in the Asian population.^{47,48}

In individuals with obesity, there's been a condition that leading to shift on gut microbiota composition correlated with the changes on dietary intake. The dysbiosis of gut microbiota can lead to a disruption of energy homeostasis, leading to increased energy extraction from non-digestible dietary carbohydrates. This results in an increase in intestinal absorption of both monosaccharides and SCFAs, and microbial regulation of host genes that promote deposition of lipids in adipocytes.^{49,50} One study conducted in Ukraine shown that there's a trend on increased *Bacillus*, *Clostridium*, *Prevotella*, and decreased *Lactobacillus*, *Bacteroides*, *Bifidobacterium*, and *Akkermansia* as a result of high-fat/carbohydrate diet.⁵¹ However, on one study conducted in Indonesia, there's increase on *Romboutsia* and decrease on *Bacteroides* and *Ruminococcaceae*, which is slightly different from the studies conducted in non-Asian population.⁵² This difference may be resulted from different dietary intake from both studies, however there is a similarity on the decrease of *Bacteroides* (and specifically *Ruminococcaceae* in the Indonesian study) that are also observed, previously, on individuals with CHF, showing that there is a potential link of gut microbiota involvement on obesity being risk factor of CHF.⁴⁵ There's been a development of understanding on how one of the risk factors of obesity, dyslipidemia, may also be linked to the dysbiosis of gut microbiota, as dysbiosis can modulate nutrient absorption and metabolite formation in the gut and can lead to systemic inflammation due to bacterial translocation across the gastrointestinal epithelial barrier, affecting mucosal and systemic immune regulation that can influence lipid metabolism. On the other hand, dysbiosis can result in altered production of metabolites, including short-chain fatty acids, bile acids, and trimethylamine N-oxide, which influence dyslipidemia by regulating cholesterol homeostasis.¹⁹ Dyslipidemia may enhance microbial fermentation of indigestible dietary polysaccharides, thereby elevating the production of pro-inflammatory metabolites, which contribute to systemic inflammation and insulin resistance. Consequently, there is increased absorption of monosaccharides and SCFAs in the intestines, alongside microbial modulation of host genes that facilitate lipid deposition in adipocytes.⁵³ In one study conducted in Japanese adults, linear non-Gaussian acyclic model study showed the higher abundance of *Lachnoclostridium* and *Streptococcus* on individuals with dyslipidemia, while the *Pseudobutyrvrio* and *Prevotella*⁹ were lower (These findings align with other studies conducted in Japan on patients with HF, where a decrease in *Prevotella* was associated with a reduced abundance of microbial genes involved in the biosynthesis of

essential amino acids in HF patients. This suggests a potential relationship between dyslipidemia and heart failure from the perspective of gut microbiota).^{54,55}

Key factors linking the gut microbiota and CHF among the Asian population

Several key factors contribute to the potential relationship between gut microbiota dysbiosis and heart failure, particularly CHF. Heart failure is correlated with gut dysbiosis, characterized by reduced bacterial diversity and the proliferation of potentially pathogenic bacteria. The principal pathological mechanisms of heart failure encompass myocardial fibrosis, microvascular dysfunction, and inflammation. These observations provide evidence for the significant association between gut microbiota dysbiosis, its derived metabolites, and the pathogenesis of heart failure.⁴⁵

There are several factors that influence the development of this disease, one of which is an unhealthy diet that begins with a lifestyle, such as consuming high fat diet and refined carbohydrate. Some regions in South Asia such as India have a diet with high sugar consumption (average adult consumption of 58 g per day) and have 67 million cases of metabolic diseases such as diabetes mellitus,⁵⁶ as well as the consumption of high-fat diets and using salty seasonings in some Southeast Asian dishes (such as Thailand) shows an increased risk of type 2 diabetes mellitus.⁵⁷ Long-term consumption of high-carbohydrate diets may affect gut microbiota dysbiosis such as increased *Prevotella* and decreased *Bacteroides*, as well as increased SCFAs for long-term consumption of high-fiber diets.¹⁸

Diets high in fats and low in fiber can negatively impact gut health by promoting leaky gut barriers and altering gut microbiota. High-fat diets are linked to increased intestinal permeability, which may allow harmful substances like lipopolysaccharides (LPS) to enter the bloodstream. Specific fatty acids in these diets, such as eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and gamma-linolenic acid, can modify the permeability of tight junctions, affecting the integrity of the intestinal barrier. In contrast, the metabolism of dietary fiber by gut bacteria produces SCFAs, such as acetate, propionate, and butyrate, which support the maintenance of intestinal barrier function and overall gut health. These findings highlight the crucial role of dietary fats and fiber in regulating intestinal barrier integrity and overall gastrointestinal health.⁵⁸

Gut microbiota can directly affect risk factors and CHF development via metabolite production such as trimethylamine N-oxide (TMAO), bile acids, LPS or endotoxin, and SCFAs. Dysbiosis of gut microbiota can elevate TMAO levels by altering gut bacteria composition (in this instance, gut microbiota metabolize L-carnitine into trimethylamine or

TMA), and production of TMAO is correlated with higher levels of *Firmicutes* and lower in *Bacteroidetes*.⁵⁹ Dysbiosis of gut microbiota can also decrease SCFAs production, leading to compromised gut integrity and increased inflammation, leading to increased intestinal permeability, which facilitates bacterial translocation and the entry of endotoxins.⁶⁰ Consequently, this multifaceted interplay culminates in systemic inflammation, potentially leading to heart failure. Alterations in gut microbiota further exacerbate dysbiosis, perpetuating inflammation and disease progression, thereby perpetuating a vicious cycle, as shown on Figure 1.⁶¹

It is worth noting about several gut microbiota that overlap in various disease conditions (and correlate with CHF disease) can be explained in a prediction, where one study explained that diet and environmental stressors are some of the variables that can affect the composition of gut microbiota.⁶² The overall findings can be summarized on Table 1 below, with further discussion followed shortly.

DISCUSSION

The rise in lifestyle-related diseases in Asia is closely linked to dietary changes that impact gut microbiota. The introduction of modern Western diets, characterized by higher fat content and lower fiber intake, is reshaping the gut microbiome in Asian populations. Comparative studies reveal that urban Asian children consuming modern diets tend to have a "*Bacteroides-Bifidobacterium* (BB) type" microbiome, while rural children with traditional plant-based diets retain a "*Prevotella* (P) type" microbiome. This shift from a *Prevotella*-dominant microbiome to a *Bacteroides*-dominant microbiome reflects the influence of Western diets on the Asian gut. The *Bacteroides* enterotype, especially *Bacteroides fragilis*, is associated with a higher risk of T2D in Asian populations due to its ability to alter bile acid signaling and metabolism through bile salt hydrolase activity. In contrast, the *Prevotella*-dominant microbiome is linked to positive metabolic outcomes. The transition from traditional plant-based diets to modern high-fat, low-fiber diets may contribute to the growing prevalence of metabolic diseases like T2D in Asia.⁶³

This review highlights the variation in gut microbiota among Asian individuals with risk factors for CHF, such as obesity, T2D, hypertension, and dyslipidemia, and how these variations may correlate with disease progression and an increased risk of CHF. The findings underscore the role of gut microbiota in these disease processes, although variations in gut microbiota composition can differ significantly across geographic regions and ethnic groups. For example, a study conducted in Tibet found distinct microbial profiles in Tibetan

highlanders with CAD compared to Han lowlanders with CAD.⁴⁶ This difference may be attributed to the unique dietary patterns of highlanders, who consume more dairy products, but fewer vegetables and fruits compared to lowlanders.⁶⁴ With these findings, the unique characteristics of Tibetan highlanders suffering from CAD were correlated with dysbiosis of gut microbiota, associated with CAD, with the difference between Tibetan and Han could be resulted in the different nutrient intake.

The role of gut microbiota in regulating platelet activity and the development of a pro-thrombotic state through the production of TMAO has been well-documented. Studies show that TMAO increases the risk of thrombosis and atherosclerosis by triggering platelet activation. Additionally, high TMAO levels are linked to oxidative stress, inflammation, and impaired cellular function, while lower levels have the opposite effect. For instance, patients with aortic stenosis have been found to have higher TMAO and TMA levels than controls, indicating that TMAO is an independent risk factor for cardiovascular diseases. In addition to TMAO, the dysbiosis of gut microbiota is associated with changes in SCFAs, bile acids, and endotoxins, which may also play a role in CHF development. For example, SCFAs production, which supports gut integrity and reduces inflammation, may decrease due to dysbiosis, leading to increased gut permeability and systemic inflammation. This inflammatory response could contribute to heart failure progression.⁵⁹

The gut microbiota and its metabolites may undergo changes during the progression of CAD, as elucidated in a study by Liu et al. (2019). For example, one study investigated alterations in gut microbiome composition and metabolism in relation to CAD severity. Notably, several co-abundance groups (CAGs) associated with the *Ruminococcaceae* family—known for its potential anti-inflammatory effects through butyric acid production—were found to be decreased during CAD development. Interestingly, another study revealed an increase in *Clostridium IV* (also part of the *Ruminococcaceae* family) based on data mining analysis. Additionally, CAGs containing *Proteobacteria*, such as *Klebsiella*, were more abundant in the group with more severe disease, while a CAG comprising *Faecalibacterium* and *Roseburia* was enriched in the control group. Given the extensive interaction between human gut microbiota and host metabolism, disruptions in body conditions during CAD progression could contribute to differential abundance patterns of gut microbiota.^{25,65} *Faecalibacterium* has been identified as a potential antiatherosclerosis microbe in the prevention of CAD by inhibiting atherosclerosis. This evidence comes from a study conducted by Yang Hai-Tao et al. (2024), which examined various CAD types and controls. Among several species analyzed (including *Faecalibacterium prausnitzii*, *Prevotella copri*,

Megamonas, *Escherichia coli*, and *Bacteroides fragilis*), *Faecalibacterium prausnitzii* was most frequently observed in patients within the control groups compared to the others. Subsequent analysis of the gut microbiota has unveiled the potential antiatherosclerotic effects of *Faecalibacterium prausnitzii*. Specifically, it demonstrates superior diagnostic efficacy when comparing varying degrees of CAD to the control group. These effects are attributed to its capacity to mitigate systemic inflammatory responses and inhibit local inflammation, primarily mediated by aortic macrophages.⁴⁸

The correlation between gut microbiota dysbiosis and the progression of dyslipidemia and obesity has been observed in two distinct studies. One study, conducted by Miyajima Yuna et al. (2022) in Japan, investigated the impact of gut microbiota on dyslipidemia. Another study, carried out by Therdtatha Phatthanaphong et al. (2021) in Indonesia, explored the influence of gut microbiota on obesity. When comparing individuals with dyslipidemia to those with normal lipid profiles, higher abundances of *Lachnoclostridium*, *Megamonas*, and *Streptococcus* were observed, while *Pseudobutyrvirio*, *Ruminococcus 2*, and *Prevotella 9* were found to be lower (note that these differences were significant only in females, as there was no significant difference in bacterial genus composition among males). Notably, linear discriminant analysis effect size (LefSe) revealed distinct compositions between males and females. Specifically, *Lachnoclostridium* and *Prevotella 9* were more abundant in females with dyslipidemia compared to *Pseudobutyrvirio*, while *Megamonas* and *Ruminococcus 2* were significantly higher in males (in the context of dyslipidemia versus non-dyslipidemia, respectively). Reports suggest that biological sex differences, hormonal factors, and lifestyle variables (such as alcohol consumption, which tends to be higher in males) may contribute to the observed variations in gut microbiota between males and females.⁵⁴

In the context of gut microbiota and lipid profiles, a significant correlation was observed between nine bacterial genera in males (*Bifidobacterium*, *Bacteroides*, *Megamonas*, *Prevotella 9*, *Phascolarctobacterium*, *Lachnoclostridium*, *Faecalibacterium*, *Anaerostipes*, *Ruminococcus*) and eight bacterial genera in females (*Pseudobutyrvibrio*, *Streptococcus*, *Lachnoclostridium*, *Romboutsia*, *Escherichia/Shigella* (E/S), *Bacteroides*, *Bifidobacterium*, *Faecalibacterium*). These correlations were examined in relation to four lipid profiles: low density lipoprotein-cholesterol (LDL-C), high density lipoprotein-cholesterol (HDL-C), triglycerides, and total cholesterol. The analysis revealed that *Bacteroides* and *Prevotella 9* in males may be associated with changes in HDL-C and LDL-C levels. These bacterial genera are abundant in the intestines of healthy adults and could potentially influence the activity of cholesteryl ester transfer protein (CETP). Notably, high CETP activity is known to decrease

HDL-C concentration. In females, *Akkermansia* and E/S were observed to have a relationship with lipid profiles. This association may be attributed to the impact of *Akkermansia*, especially *Akkermansia muciniphila*, on lipid metabolism.⁵⁴

The dysbiosis of gut microbiota has been observed in obese subjects, characterized by an increase in *Romboutsia* (an obesity-related genus that positively correlates with lipid profiles and liver lipogenesis) and a decrease in *Bacteroides* and *Ruminococcaceae*. Additionally, several other gut microbiotas, including *Faecalibacterium*, *Roseburia*, *Coprococcus*, and *Oscillibacter*, exhibit decreased abundance. The elevated levels of *Romboutsia* are associated with increased Bile Acids (BA), suggesting impaired BA metabolism within the intestinal microbiome. This impairment in obese individuals appears to adversely affect metabolic homeostasis. In subjects with T2D, there is an increase in *Ruminococcaceae* and *Bacteroides*, along with a decrease in *Prevotella*. The rise in *Ruminococcaceae* is linked to the depletion of ursodeoxycholic acid (UDCA), which exhibits anti-diabetic properties. The increase in *Bacteroides* (specifically *Bacteroides fragilis*) is associated with bile salt hydrolase (BSH) activity, leading to the loss of conjugated BAs. This BSH function acts as an antagonist to the Farnesoid X receptor (FXR), ultimately improving glucose homeostasis. The decrease in *Prevotella* is attributed to higher *Bacteroides*, which exhibit an antagonistic correlation. Furthermore, the study explains that *Prevotella* relies on dietary carbohydrates and serves as a potent propionate producer through indigestible carbohydrate fermentation. Consequently, the reduction in *Prevotella* abundance may lead to decreased glucose homeostasis via intestinal gluconeogenesis, potentially influenced by the scarcity of its intermediate product, succinate (although no direct positive correlation between *Prevotella* and succinate was observed in this study).⁵² It is not stated whenever the diet may influence the gut microbiota composition in relation to other studies already conducted or not.

Finally, recent research by Hayashi et al. (2021) has shown that the reduction of *Eubacterium* and *Prevotella* is linked to a decreased abundance of microbial genes involved in the biosynthesis of essential amino acids (EAAs) in patients with HF, which from the previous study, correlate with disease severity. The decrease in *Eubacterium* and *Prevotella* is specifically associated with a reduction in genes responsible for microbial EAA synthesis, particularly branched-chain amino acids (BCAAs) and histidine. These findings suggest that certain gut microbiota could be targeted therapeutically, in this case addressing systemic EAA metabolic abnormalities, to mitigate disturbance of systemic BCAA metabolic in HF patients. In the analysis of networks related to branched-chain amino acid BCAA biosynthesis, the genus *Eubacterium* emerges as pivotal in the reduced presence of microbial genes responsible

for histidine biosynthesis in patients with HF. Furthermore, low plasma concentrations of histidine have been linked to inflammation and oxidative stress. In summary, HF patients exhibit lower plasma EAA levels, a condition attributed to the depletion of *Eubacterium* and *Prevotella*.⁵⁵

Several gut microbiotas overlap in various diseases, including CHF, and may be influenced by environmental factors, diet, and lifestyle. These findings suggest that gut microbiota play a crucial role in disease development and progression, particularly in cardiovascular diseases. Table 1, Figures 2, and Figures 3 summarize the overall findings, highlighting the gut bacteria composition in both CHF patients and individuals with related risk factors. The literature review demonstrates a significant strength in its exploration of a novel area of interest—the role of gut microbiota in Asian populations at high risk of CHF. This focus on an underexplored population highlights the potential for new insights into the complex interactions between microbiota and CHF, particularly in a demographic with unique genetic and environmental risk factors. However, a key limitation is the lack of diverse regional studies, with much of the research centered on China. While the ethnicity across Asian populations shares some similarities, there may be regional variations that are not fully captured.

In the Asian population, emerging evidence suggests a potential association between gut microbiota profiles and specific risk factors, such as obesity, T2D, hypertension, dyslipidemia, and CAD, in individuals with CHF. While not all diseases exhibit direct interconnections through gut microbiota, this study adds to the growing body of knowledge about the molecular-level links between these conditions. Although these associations remain exploratory, they underscore the need for further research to understand the intricate relationship between CHF risk factors and gut microbiota composition. Future studies should explore the mechanisms, potential causality, and therapeutic implications of these interconnections, particularly by conducting observational studies on gut microbiota composition in the Asian population with CHF. Unraveling the gut-heart axis may reveal new therapeutic targets and strategies for improving outcomes in patients with CHF.

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CONFLICT OF INTEREST AND FUNDING DISCLOSURE

The authors declare no conflict of interest.

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fragment length polymorphism: gut microbiota could be a diagnostic marker of coronary artery disease.
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Table 1. Study characteristics that determine the association between gut microbiota profiles and chronic heart failure

No	Authors	Study design	Participants characteristics (n =)	Location	Microbiota analysis
1	Ma Y et al ⁴⁶	Observational studies	Adult Tibetan Highlander (n=42), Han Highlander (n=49) and Han Lowlander (n=49) (n=140) -Control=104 -CAD=36	Tibet	V3-V4 region of the 16S ribosomal RNA
2	Honghong Liu et al ²⁵	Cross sectional	Adult Chinese (n=201) -Control=40 -Stable CAD=44 -Unstable Angina=80 -Myocardial Infraction=37	China	V3-V4 region of the 16S ribosomal RNA
3	Yang Hai-Tao et al ⁴⁸	Cohort	Adult Chinese (n=215) -Control=156 -Stable CAD=56 -Unstable Angina=106 -Myocardial Infraction=53	China	Kruskal-Wallis test in conjunction with aldx2 and Bonferroni-Holm correction
Results					Microbiota(s) of interest
Tibetan highlanders suffering from CAD exhibit an enrichment of <i>Prevotella</i> compared to Han CAD patients. Additionally, several gut microbiota genera, including <i>Catenibacterium</i> , <i>Clostridium_sensu_stricto</i> , <i>Holdemanella</i> , and <i>Ruminococcus 2</i> , are more abundant in Tibetan Highlanders with CAD compared to both healthy Tibetan Highlanders and Han CAD patients.					Abundant in Tibetan Highlanders: - <i>Catenibacterium</i> - <i>Clostridium_sensu_stricto</i> - <i>Holdemanella</i> - <i>Ruminococcus 2</i> <i>Prevotella</i> (Specific for CAD)
Several gut microbiota exhibit differences based on the severity of CAD. Specifically, <i>Ruminococcaceae</i> are decreased, while <i>Klebsiella</i> are increased. Additionally, <i>Roseburia</i> and <i>Faecalibacterium</i> show enrichment in the control group					↓ <i>Ruminococcaceae</i> ↓ <i>Roseburia</i> ↓ <i>Faecalibacterium</i> ↑ <i>Klebsiella</i>
Person with high <i>Faecalibacterium prausnitzii</i> had the lowest incidence of CAD across the CAD and control groups. There's significant relationship between <i>Faecalibacterium prausnitzii</i> and incidence of CAD					↓ <i>Faecalibacterium prausnitzii</i>

Table 1. Study characteristics that determine the association between gut microbiota profiles and chronic heart failure (cont.)

No	Authors	Study design	Participants characteristics (n =)	Location	Microbiota analysis																
4	Therdthata Phatthanaphong et al ⁵²	Cross sectional	Adult Indonesian (n=75) - Non T2D, lean=25 - Non T2D, overweight=7 - Non T2D, obese=18 - T2D, lean=11 - T2D, overweight=11 - T2D, obese=3	Indonesia	V3-V4 region of the 16S ribosomal RNA																
5	Miyajima Yuna et al ⁵⁴	Cohort	Adult Japanese with dyslipidemia (n=234)	Japan (Shikamachi, Hakui-gun, Ishikawa Prefecture)	16S rRNA gene sequence by NGS																
6	Hayashi Tomohiro et al ⁵⁵	Cross Sectional	Elderly Japanese (n=33) - HF=22 - Control=11	Japan (Kobe)	Whole-genome shotgun sequencing																
Results					Microbiota(s) of interest																
There's an increase on <i>Romboutsia</i> and decrease on <i>Bacteroides</i> and <i>Ruminococcaceae</i> in obese subjects. Several gut microbiota such as <i>Faecalibacterium</i> , <i>Roseburia</i> , <i>Coprococcus</i> , <i>Oscillibacter</i> also decrease. In subjects with T2D, there is an increase on <i>Ruminococcaceae</i> and <i>Bacteroides</i> , and a decrease on <i>Prevotella</i>					<table border="0"> <tr> <td>Obese</td> <td>T2D</td> </tr> <tr> <td>↑ <i>Romboutsia</i></td> <td>↑ <i>Bacteroides</i></td> </tr> <tr> <td>↓ <i>Bacteroides</i></td> <td>↑ <i>Ruminococcaceae</i></td> </tr> <tr> <td>↓ <i>Ruminococcaceae</i></td> <td>↓ <i>Prevotella</i></td> </tr> <tr> <td>↓ <i>Faecalibacterium</i></td> <td></td> </tr> <tr> <td>↓ <i>Roseburia</i></td> <td></td> </tr> <tr> <td>↓ <i>Coprococcus</i></td> <td></td> </tr> <tr> <td>↓ <i>Oscillibacter</i></td> <td></td> </tr> </table>	Obese	T2D	↑ <i>Romboutsia</i>	↑ <i>Bacteroides</i>	↓ <i>Bacteroides</i>	↑ <i>Ruminococcaceae</i>	↓ <i>Ruminococcaceae</i>	↓ <i>Prevotella</i>	↓ <i>Faecalibacterium</i>		↓ <i>Roseburia</i>		↓ <i>Coprococcus</i>		↓ <i>Oscillibacter</i>	
Obese	T2D																				
↑ <i>Romboutsia</i>	↑ <i>Bacteroides</i>																				
↓ <i>Bacteroides</i>	↑ <i>Ruminococcaceae</i>																				
↓ <i>Ruminococcaceae</i>	↓ <i>Prevotella</i>																				
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↓ <i>Oscillibacter</i>																					
The higher abundance of <i>Lachnospirillum</i> , <i>Megamonas</i> , and <i>Streptococcus</i> on individuals with dyslipidemia, while the <i>Pseudobutyrvibrio</i> , <i>Ruminococcus 2</i> , and <i>Prevotella 9</i> were lower. <i>Bacteroides</i> , <i>Prevotella 9</i> (both in male), <i>Akkermansia</i> , and <i>Eschericia Coli/Shigella</i> (both in female) have causal relationship with serum lipid profile levels in relation with dyslipidemia.					<table border="0"> <tr> <td>↑ <i>Lachnospirillum</i></td> </tr> <tr> <td>↑ <i>Megamonas</i></td> </tr> <tr> <td>↑ <i>Streptococcus</i></td> </tr> <tr> <td>↓ <i>Pseudobutyrvibrio</i></td> </tr> <tr> <td>↓ <i>Prevotella 9</i></td> </tr> <tr> <td>↓ <i>Ruminococcus</i></td> </tr> </table>	↑ <i>Lachnospirillum</i>	↑ <i>Megamonas</i>	↑ <i>Streptococcus</i>	↓ <i>Pseudobutyrvibrio</i>	↓ <i>Prevotella 9</i>	↓ <i>Ruminococcus</i>										
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Genera such as <i>Bifidobacterium</i> , <i>Gordonibacter</i> , <i>Bilophila</i> , and <i>Pseudoflavonifractor</i> were abundant, whereas genera such as <i>Eubacterium</i> , <i>Prevotella</i> , <i>Finegoldia</i> , and <i>Succinatimonas</i> were significantly decreased in patients with HF. Decrease of <i>Eubacterium</i> and <i>Prevotella</i> contributed to decreased abundance of microbial genes involved in the biosynthesis of those essential amino acid in patients with HF					<table border="0"> <tr> <td>↑ <i>Bifidobacterium</i></td> </tr> <tr> <td>↑ <i>Gordonibacter</i></td> </tr> <tr> <td>↑ <i>Bilophila</i></td> </tr> <tr> <td>↑ <i>Pseudoflavonifractor</i></td> </tr> <tr> <td>↓ <i>Eubacterium</i></td> </tr> <tr> <td>↓ <i>Prevotella</i></td> </tr> <tr> <td>↓ <i>Finegoldia</i></td> </tr> <tr> <td>↓ <i>Succinatimonas</i></td> </tr> </table>	↑ <i>Bifidobacterium</i>	↑ <i>Gordonibacter</i>	↑ <i>Bilophila</i>	↑ <i>Pseudoflavonifractor</i>	↓ <i>Eubacterium</i>	↓ <i>Prevotella</i>	↓ <i>Finegoldia</i>	↓ <i>Succinatimonas</i>								
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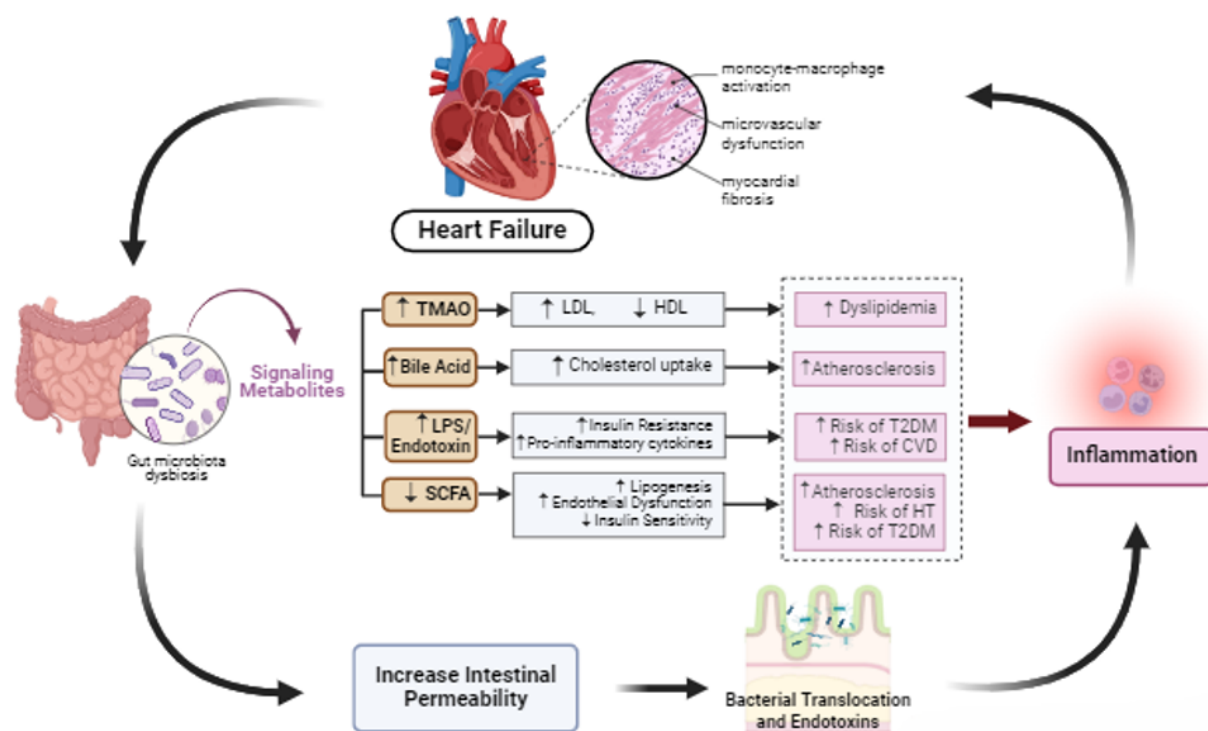


Figure 1. Role of gut microbiota on the pathogenesis of CHF. Gut microbiota influences cholesterol metabolism by regulating the enterohepatic circulation of bile acids. Elevated bile acid levels enhance cholesterol absorption, thereby increasing the risk of atherosclerosis.¹⁹ In the liver, TMAO reduces HDL levels, enhances macrophage activity, and promotes LDL uptake, disrupting lipid metabolic homeostasis. Elevated TMAO levels lead to increased cholesterol deposition from circulation, contributing to a heightened risk of atherosclerosis and dyslipidemia.²⁸ Additionally, lipopolysaccharides (LPS) entering the bloodstream cause metabolic endotoxemia. LPS binds to TLR-4 on circulating host cells, elevating pro-inflammatory cytokines and insulin resistance, which increases the risk of cardiovascular disease and type 2 diabetes. On the other hand, reduced uptake of SCFAs by colonocytes leads to decreased beta-oxidation and insulin sensitivity, increasing lipogenesis and endothelial dysfunction. Lower SCFAs production further increases the risk of atherosclerosis, type 2 diabetes, and hypertension.²⁰ This figure was created with BioRender.com.

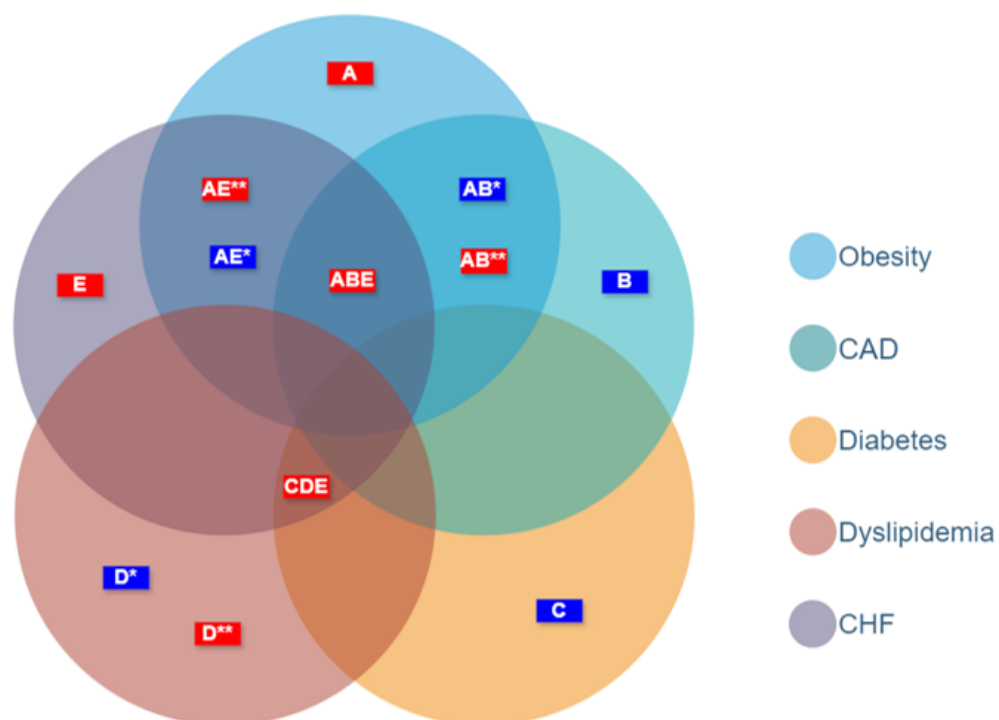


Figure 2. Comparative of gut microbiota composition in CHF patients and individuals with risk factors (overall data). A: *Coprococcus*, *Oscillibacter*, *Bifidobacterium*, *Lactobacillus*, *Akkermansia*; AB*: *Prevotella*, *Klebsiella*; AB**: *Roseburia*; ABE: *Ruminococcaceae*, *Faecalibacterium*; AE*: *Romboutsia*; AE**: *Bacteroides*; B: *Catenibacterium*, *Clostridium_sensu_stricto*, *Holdemanella*, *Ruminococcus*, *Coprococcus*, *Parabacteroides*, *Clostridium IV*; C: *Ruminococcaceae*, *Bacteroides*; CDE: *Prevotella*; D*: *Lachnoclostridium*, *Streptococcus*, *Megamonas*; D**: *Pseudobutyrvibrio*, *Ruminococcus*; E: *Eubacterium*; The presence of a blue hue on the labels signifies an abundance of bacteria, whereas the presence of a red hue suggests a diminished bacterial composition

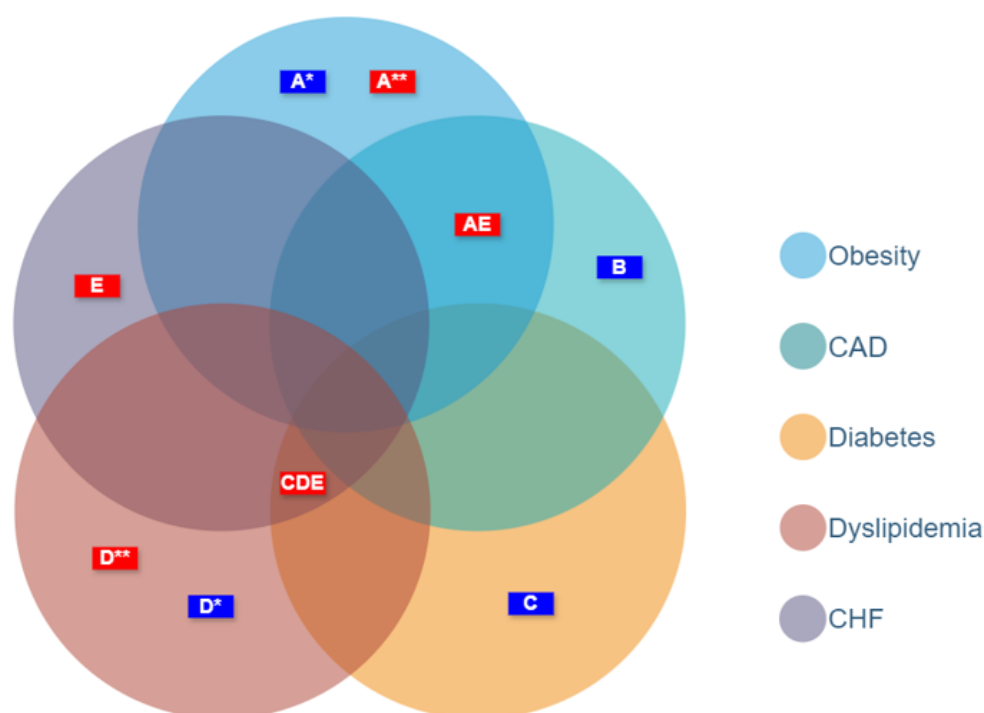


Figure 3. Comparative of gut microbiota composition in CHF patients and individuals with risk factors (cases from result table). A*: *Romboutsia*; A**: *Bacteroides*, *Coprococcus*, *Oscillibacter*; AE: *Ruminococcaceae*, *Roseburia*, *Faecalibacterium*; B: *Catenibacterium*, *Clostridium_sensu_stricto*, *Holdemanella*, *Ruminococcus*, *Coprococcus*, *Parabacteroides*, *Clostridium IV*, *Prevotella*, *Klebsiella*; C: *Ruminococcaceae*, *Bacteroides*; CDE: *Prevotella*; D*: *Lachnoclostridium*, *Megamonas*, *Streptococcus*; D**: *Pseudobutyrvirio*, *Ruminococcus*; E: *Eubacterium*; The presence of a blue hue on the labels signifies an abundance of bacteria, whereas the presence of a red hue suggests a diminished bacterial composition

$p < 0.05$ compared with Gp1; $^{\ddagger}p < 0.05$ compared with Gp2; $^{\S}p < 0.05$ compared with Gm1; $^{\P}p < 0.05$ compared with Gm2; $^{\ddagger\ddagger}p < 0.05$ compared with Gm3.