Review

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Unlocking the gut-heart axis: exploring the role of gut microbiota in cardiovascular health and disease

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Introduction: Gut microbiota has emerged as a pivotal player in cardiovascular health and disease, extending its influence beyond the gut through intricate metabolic processes and interactions with the immune system. Accumulating evidence supports a significant association between gut microbiota and cardiovascular diseases such as atherosclerosis, hypertension, and heart failure. Dietary patterns have been identified as key factors shaping the composition of the gut microbiota and exerting notable impacts on cardiovascular health. Probiotics and prebiotics have shown promise in mitigating the risks of cardiovascular disease by modulating key cardiovascular parameters. Faecal microbiota transplantation (FMT) has recently emerged as a novel and intriguing therapeutic strategy.

Aim: This review paper aims to explore and elucidate the multifaceted role of gut microbiota in cardiovascular health. It will also address the prevailing challenges and limitations in gut microbiota studies, emphasizing the importance of future research in overcoming these obstacles to expand our understanding of the gut-heart axis.

Materials and methods: A comprehensive literature search was conducted using various databases including ClinicalTrials, Google Scholar, PubMed, ScienceDirect, MEDLINE, and Ovid Resources. The search strategy included utilizing keywords such as "Gut microbiota," "Randomized controlled trials (RCTs)," "Gut-heart axis," "Dysbiosis," "Diet," "Probiotics," "Prebiotics," "Faecal Microbiota transplantation," "cardiovascular disease," "Meta-analyses," and other compatible terms thereof. Only articles written in English were considered, and selection criteria included relevance to the research objectives, reasonable sample sizes, and robust methodology. In addition to the identified articles, meta-analyses, animal models and studies, and references from the selected articles were also examined to ensure a comprehensive review of the literature.

Results: Dietary patterns exert a significant influence on the composition of the gut microbiota, and certain diets, such as the Mediterranean diet, have been associated with a favourable gut microbiota profile and a reduced risk of cardiovascular disease (CVD). Probiotics and prebiotics have emerged as potential interventions to mitigate CVD risks by modulating blood pressure, glycemic control, lipid profiles, and gut dysbiosis. Another innovative therapeutic approach is FMT, which involves transferring faecal material from a healthy donor to restore a balanced gut microbiota. FMT holds promise for improving cardiometabolic parameters in individuals with CVD, although further research is needed to elucidate its precise mechanisms and assess its effectiveness.

Conclusion: The gut microbiota is emerging as a potential therapeutic target for CVD prevention and management. However, current research has limitations, including the need for larger and more diverse studies, the challenges of establishing causality, and concerns regarding the long-term consequences and safety of gut microbiota modulation. Despite these limitations, understanding the gut-heart axis holds promise for the development of personalized therapies and interventions for cardiovascular health. Further research is needed to expand our knowledge and address the ethical and safety issues associated with gut microbiota modification.

Keywords: gut-heart, cardiovascular, gut microbiota

Introduction

The gut microbiota, which consists of billions of organisms in the digestive tract, is a complex colony whose metabolic processes and interactions with the immune system extend well beyond the gut[1]. These bacteria's interactions involving inflammatory and metabolic mechanisms have showcased a role in the development of a variety of

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immune-mediated illnesses and metabolic disorders such as diabetes and obesity[2]. Cardiovascular diseases (CVDs) cause a substantial number of fatalities worldwide, killing more women than men. Atherosclerosis, a frequent cause of CVD development, is caused by a series of processes inside the artery wall that lead to necrosis, ischaemia, thromboembolic infarction, and arterial[3]. Evidence shows a relationship between gut microbiota and the development of CVDs because it impacts both direct and indirect risk factors for atherosclerosis[4]. Recent advances in our understanding of this connecting link inspired us to study the role of gut microbiota in the setting of CVD risk factors, extending the scope of research along the gut-heart axis in search of potential medicinal remedies[5]. Recent developments in our knowledge of this connecting connection prompted us to investigate the function of gut microbiota in relation to CVD risk factors, broadening the field of study along the gut-heart axis toward possible therapeutic approaches.

Gut microbiota and cardiovascular disease

Extensive study has indicated that the gut microbiota is crucial in CVD. CVD encompasses heart and blood vessel ailments such as coronary artery disease (CAD), heart failure, stroke, and other issues.[6]. It includes a variety of risk factors such as dyslipidemia, inflammation, and hypertension, the majority of which can harm the vascular structure and eventually lead to more direct processes such as atherosclerosis and thromboembolic events[7]. Aside from these physiological considerations, dietary nutrients have been identified as one of the key modifiable components that may interact with the gut microbiota, signalling a diet-microbiota-dependent route for CVD development[4].

More than 1000 bacterial species have been found in the human gut using high-throughput metagenomics sequencing methods, with around 160 species being shared by people[8]. Firmicutes and bacteroidetes are the two major phyla of bacteria, accounting for the majority of total bacteria, and their ratio is typically regarded as a crucial indicator of health conditions, but this is still debatable[9]. The phyla actinobacteria, proteobacteria, and verrucomicrobia are gut microbiota components, but in considerably lower numbers[10].

On the other hand, early research revealed that antibiotic therapy depleted gut microbiota, which elevated blood pressure in rats. These findings were verified in rats, indicating the important involvement of gut microbiota in the control of blood pressure[11]. Furthermore, as compared to regular diets, the lack of microbiota in ApoE/ mice models hastened the formation of atherosclerotic plaques in the aorta and the onset of heart disease. Surprisingly, animals injected with Angiotensin II showed the reverse impact of microbiota, with the lack of gut bacteria reducing arterial HT and vascular dysfunction[12]. Furthermore, the term dysbiosis has been revealed to have a connection with the incidence of CVD risk and to alter the development of CVD. A significant dysbiosis was identified in hypertensive animals, for example, with lower microbial richness and diversity, as well as an increased firmicutes/bacteroidetes (F/B) ratio[13]. Several metaorganism pathways (involving both microbes and the host) promote cardiovascular disease in animal models and show significant clinical associations in human studies. Trimethylamine N-oxide and, more recently, phenylacetylglutamine are gut microbiota-dependent metabolites whose blood levels have been associated with cardiovascular disease in large-scale clinical trials[14].

HIGHLIGHTS

- Probiotics and prebiotics have shown promise in mitigating the risks of cardiovascular disease (CVD) by modulating key cardiovascular parameters. Faecal microbiota transplantation has recently emerged as a novel and intriguing therapeutic strategy.
- Faecal microbiota transplantation holds promise for improving cardiometabolic parameters in individuals with CVD, although further research is needed to elucidate its precise mechanisms and assess its effectiveness.
- Cardiovascular risk factors and the development of atherosclerotic lesions have been linked to metabolites generated from the gut microbiota, such as trimethylamine N-oxide. Additionally, the development of atherosclerosis may be influenced by gut bacteria and mouth bacteria.
- The gut microbiota is emerging as a potential therapeutic target for CVD prevention and management. However, current research has limitations, including the need for larger and more diverse studies, the challenges of establishing causality, and concerns regarding the long-term consequences and safety of gut microbiota modulation.

Role of diet in shaping gut microbiota and its influence on cardiovascular health

Emerging evidence highlights the intricate interplay between dietary patterns and the gut microbiota's composition and diversity, with dysregulation of gut microbiota implicated in the pathogenesis and progression of CVD. Increasing dietary fibre intake enhances short-chain fatty acids (SCFAs) production by the gut microbiota, which has a positive influence on host metabolism, through its anti-inflammatory, anti-obesity, and anti-diabetic effects[15,16]. Mediterranean diets promote the growth of beneficial bacteria known for preserving gut barrier function and their anti-inflammatory properties[17,18]. Higher fibre intake is robustly associated with reduced risks of CVD, type 2 diabetes mellitus (T2DM), and obesity[19]. Conversely, Western diets rich in saturated fats and added sugars are linked to diminished microbial diversity and gut dysbiosis[20], increasing vulnerability to obesity, hypertension, and CVD[21–23]. Additionally, these diets contribute to atherosclerosis development through their impact on the integrity of the gut barrier[24,25]. Meanwhile, red meat overconsumption generates trimethylamine N-oxide (TMAO), a microbial metabolite emerging as a potential CVD biomarker, as it facilitates atherosclerosis progression through impairing cholesterol metabolism, inducing endothelial dysfunction and platelet hyperactivity[26,27].

Probiotics and their potential effects on cardiovascular disease prevention and management

Probiotics have displayed promising potential in mitigating cardiovascular disease risks, including improving blood pressure, glycemic and lipid profiles. Recent studies have provided support for these findings, with improved glycemic control seen in both obese and T2DM patients who were on probiotic supplementation, compared to diet-alone measures[28,29]. Another recent meta-analysis also demonstrated a significant decrease in total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C)

levels among hypercholesterolemic adults who consumed probiotics[30]. Recent studies have also highlighted the potential of probiotics as adjuncts to traditional weight loss interventions, yielding reductions in weight and BMI[31,32]. Furthermore, through their anti-hypertensive effects by modulating gut microbiota and balancing various factors that regulate the renin-angiotensin system[33], probiotic supplementations have led to significant blood pressure reduction in healthy, obese, diabetic, and even hypertensive patients[34,35]. Gut dysbiosis is linked to microbial translocation and the development of chronic inflammation in CAD through multiple mechanisms, one of them being metabolic endotoxemia which exacerbates the formation of atherosclerotic plaques[36]. Probiotics can have a protective role against CAD as selected strains have been shown to reduce inflammation and oxidative stress, enhance lipid profiles[37], and mitigate the effects of metabolic endotoxemia in individuals with CAD[38]. However, further research is still needed to explore the precise impact of probiotics on TMAO levels, which indirectly promote CVD[39]. (Fig. 1).

Prebiotics and their impact on gut microbiota composition and cardiovascular health

Prebiotics play a crucial role in promoting a healthy gut microbiome, with the majority of research focusing on its two specific types: inulin and fructooligosaccharides. Prebiotics stimulate the growth of beneficial bacteria and generate SCFAs, which maintain intestinal integrity, regulate glycemic levels, and manage body weight[40,41]. Prebiotics have demonstrated potential in ameliorating CVD symptoms through multiple mechanisms, including exerting anti-inflammation effects, rectifying intestinal dysbiosis and endotoxemia, as well as enhancing antioxidant capacities, and improving lipid profiles in CAD patients[42–44]. Moreover, they were found to have anti-obesogenic effects and contribute to lower serum cholesterol levels[45,46]. Prebiotic interventions have been found to significantly improve fasting blood glucose levels in patients with T2DM, contributing to cardiovascular disease prevention[47].

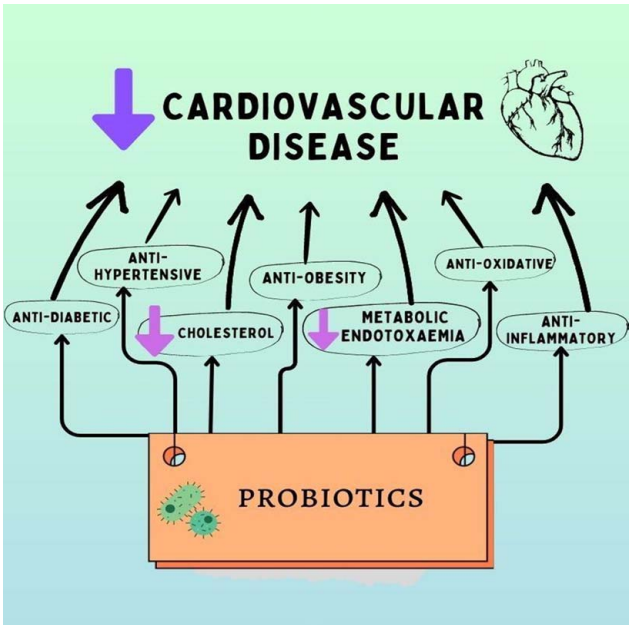

Figure 1. The potential benefits of probiotics for cardiovascular disease prevention and management.

Faecal microbiota transplantation and its therapeutic potential in cardiovascular disease

Faecal microbiota transplantation (FMT) is a novel therapeutic strategy used primarily for treating Clostridium difficile infection, involving the infusion of a faecal suspension from a healthy donor to restore a balanced gut microbiota and alter microbial composition[48,49]. There is growing interest in exploring its potential benefits in improving cardiometabolic parameters and mitigating CVD. While short-term improvements in insulin sensitivity in patients with obesity and metabolic syndrome have been observed, the overall impact on other metabolic parameters was uncertain[50,51]. A recent paper highlighted FMT's potential in improving BMI, blood glucose, HbA1c, and insulin resistance in T2DM patients[52]. Another recent trial found that repeated FMTs when combined with lifestyle interventions, led to increased microbiota engraftment, improved microbiota profile, and reduced LDL-C levels in obese and diabetic patients[53]. FMT holds potential as a therapy for metabolic syndrome and diabetes, but further research is needed to understand the underlying mechanisms and assess its effectiveness in CVD prevention and management. A study by Sayols-Baixeras and colleagues, gives proof of the relationship of the stomach microbiota organization portrayed by expanded wealth of Streptococcus spp and different species generally tracked down in the oral cavity with coronary atherosclerosis and fundamental irritation markers. Further longitudinal and trial studies are justified to investigate the expected ramifications of a bacterial part in atherogenesis[54].

Gut-heart axis in clinical settings

Various studies have investigated the connection between gut microbiota and several cardiovascular diseases, such as type 2 diabetes, hypertension, atherosclerosis, heart failure, and arrhythmia. Enrichment of some gut bacterial populations was seen in atherosclerotic cardiovascular disease patients compared to control people in a case-control study[55].

Numerous studies have shown a link between certain gut bacterial populations and atherosclerotic cardiovascular disease[56]. Cardiovascular risk factors and the development of atherosclerotic lesions have been linked to metabolites generated from the gut microbiota, such as TMAO[57]. Additionally, the development of atherosclerosis may be influenced by gut bacteria and mouth bacteria[58]. Pathways involving immunological control, host energy metabolism, oxidative stress, and programmed cell death, the makeup of the gut microbiota and metabolites, such as TMAO, SCFAs, and secondary bile acids (BA), are implicated in cardiovascular disorders. Targeting the gut microbiota and related metabolic pathways could offer potential treatment approaches for various cardiovascular diseases[59–61]. The development of hypertension may be influenced by gut microbial dysbiosis, according to research that links the gut microbiota with hypertension[62–64]. Attention has been drawn to the gut-brain-microbiota axis in the study of the aetiology of hypertension. Overall, coronary artery disease and

alterations in plasma metabolites in obese people are caused by the gut microbiota's production of bioactive metabolites and interaction with the immune system[65]. (Figure 2).

Growing evidence points to the gut microbiota as a possible therapeutic target for several illnesses, including cancer and inflammatory bowel disease. The gut microbiota can be modified by several therapies, including nutrition, probiotics, faecal microbiota transplant, and phage therapy, according to a study by McCarville *et al.*[66] from 2016. Prebiotics, dietary approaches, and dietary limits are examples of nutritional interventions that suggest opportunities to modify gut microbiota, which can have an immediate influence on cardiovascular health[67]. In 2020, Markey *et al.*[68] talked about the technical and clinical difficulties of developing and putting into practice methods to rebuild gut flora. These studies collectively imply that a variety of therapeutic approaches, including dietary changes, probiotics, antibiotics, and anti-inflammatory drugs, target the gut microbiota, but additional study is required to completely understand the mechanisms and make specific therapeutic recommendations.

The therapeutic importance of the gut-heart axis is being increasingly supported by studies, which reveal that imbalances in gut microbiota may be a factor in cardiac dysfunction and other diseases in patients with heart failure[69]. In their evaluation of the various processes, Forkosh *et al.*[70] identified the gut microbiome and bacterial translocation as prospective targets for novel treatment approaches to treat cardiac disorders. In 2013, Buglioni *et al.*[71] discovered a connection between the production of the gut hormone glucagon-like peptide-1 (GLP-1) and the heart hormone atrial natriuretic peptide, indicating the function of GLP-1 receptor agonists in overall cardiovascular homoeostasis.

Novel treatment strategies may result from a better understanding of the gut-heart axis's possible underlying mechanisms. There are difficulties in putting gut-heart axis research into therapeutic use, though. Although medicines that target the gut microbiota and some compounds, such as TMAO, are promising, there are still no clear-cut answers for how to deal with these problems[72]. To bridge the gap between gut-heart axis research and its practical use in the diagnosis and treatment of heart failure and other cardiac illnesses, including coeliac disease, more study is required.

Challenges and limitations in gut microbiota and cardiovascular health studies

Gut microbiota research has gotten a lot of interest recently because of the possible implications for cardiovascular health. Current research, however, has significant limitations that restrict our knowledge of the complicated link between gut microbiota and cardiovascular disease. The limits of existing studies, the variety in gut microbiota composition, and the ethical and safety problems associated with gut microbiota modification are all discussed in this article.

Limitations of current studies on gut microbiota and cardiovascular health

Observational nature: Although many observational studies have been established regarding the correlation between gut microbiota and cardiovascular health, they cannot prove a definite cause-and-effect link. Intervention studies are critical for determining the influence of gut microbiota modification on cardiovascular outcomes[73].

Sample size and diversity: Most gut microbiota studies have limited sample numbers, which limits their generalizability[74]. Furthermore, there is a lack of variety in research groups since most participants are frequently from a certain geographic place or have a specific health condition. To address these limitations and give more credible data, large-scale and diversified cohort studies are required.

Longitudinal studies and follow-up: Long-term longitudinal studies are required to better understand the dynamics and evolution of gut microbiota through time. Such studies, however, are challenging to conduct due to the need for extensive follow-up intervals, participant continuation, and the dynamic nature of gut microbiota composition.

Variability in gut microbiota composition and challenges in establishing causality

Interindividual variation: The makeup of the gut microbiota differs widely between people due to variables such as genetics,

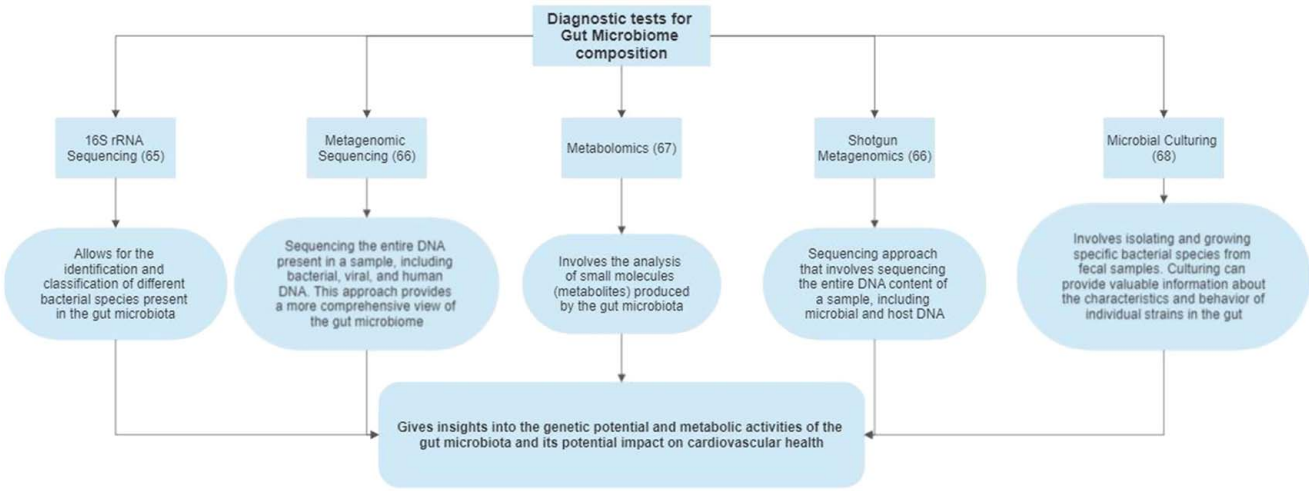

Figure 2. Organizes the different testing modalities available for gut microbiome composition.

food, lifestyle, and environmental exposures. Due to the considerable interindividual variability, identifying biomarkers related to cardiovascular health is difficult. Furthermore, the composition of the gut microbiota might vary rapidly in response to dietary or environmental changes, confounding the determination of causality[75].

Bidirectional relationship: There is a bidirectional relationship between gut microbiota and cardiovascular health. While gut microbiota can have an impact on cardiovascular health, cardiovascular illnesses, and related risk factors (e.g. obesity, hypertension) can also have an impact on gut microbiota composition. It is difficult to disentangle these intricate relationships and determine the main direct cause[76].

Concerns about the ethics and safety of gut microbiota modulation

Long-term consequences and unknown risks: The usage of some therapies and interventions like probiotics and prebiotics might have long-term impacts on cardiovascular health. But the long-term safety and possible dangers connected with these therapies are not completely established. Before gut microbiota modification techniques can be widely used, rigorous safety studies and monitoring are required.

Individualized methods and equity: Gut microbiota modification strategies need to be customized to an individual's particular microbial composition for optimal success. This personalized method increases ethical concerns about fair access to such therapies and the possibility of aggravating existing health inequities.[77].

Conclusion

This review emphasizes the importance of gut microbiota in cardiovascular health. The impact of dysbiosis on cardiovascular disease, the processes connecting gut microbiota to cardiovascular health, and the possibility of gut microbiota manipulation in improving cardiovascular outcomes are among the key discoveries. Current research challenges and limitations, such as limited sample numbers and ethical problems, have been recognized. Understanding the gut-heart axis has implications for the prevention and treatment of cardiovascular disease. To expand our understanding and provide individualized therapies for cardiovascular health, future research should focus on larger and more varied trials, demonstrating causation, and resolving safety issues.

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Author contribution

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References

[1] Sonnenburg JL, Bäckhed F. Diet–microbiota interactions as moderators of human metabolism. Nature 2016;535:56–64.
[2] Mensah GA, Roth GA, Fuster V. The global burden of cardiovascular diseases and risk factors: 2020 and beyond. J Am Coll Cardiol 2019;74:2529–32.
[3] Timmis A, Townsend N, Gale CP, *et al*. European Society of Cardiology: Cardiovascular Disease Statistics 2019. Eur Heart J 2020;41:12–85.
[4] Brown JM, Hazen SL. Microbial modulation of cardiovascular disease. Nat Rev Genet 2018;16:171–81.
[5] Jin L, Shi X, Yang J, *et al*. Gut microbes in cardiovascular diseases and their potential therapeutic applications. Protein Cell 2020;12:346–59.
[6] Mozaffarian D, Benjamin EJ, Go AS, *et al*. Executive summary: heart disease and stroke statistics-2016 update: a report from the American Heart Association. Circulation 2016;133:447–54.
[7] Zhou W, Cheng Y, Zhu P, *et al*. Implication of gut microbiota in cardiovascular diseases. Oxidat Med Cell Longevity 2020;2020:1–142020.
[8] Qin J, Li R, Raes J, *et al*. A human gut microbial gene catalogue established by metagenomic sequencing. Nature 2010;464:59–65.
[9] Eckburg PB, Bik EM, Bernstein CN, *et al*. Diversity of the human intestinal microbial flora. Science 2005;308:1635–8.
[10] Gill SR, Pop M, DeBoy RT, *et al*. Metagenomic analysis of the human distal gut microbiome. Science 2006;312:1355–9.
[11] Koeth RA, Wang Z, Levison BS, *et al*. Intestinal microbiota metabolism of L-carnitine, a nutrient in red meat, promotes atherosclerosis. Nat Med 2013;19:576–85.
[12] Karbach SH, Schönfelder T, Brandão I, *et al*. Gut microbiota promote angiotensin II–induced arterial hypertension and vascular dysfunction. J Am Heart Assoc 2016;5:e003698.
[13] Yang T, Santisteban MM, Rodriguez V, *et al*. Gut dysbiosis is linked to hypertension. Hypertension 2015;65:1331–40.
[14] Curtis LG, Jane FF. Gut microbiota and microbial metabolism in early risk of cardiometabolic disease. AHA J 2023. Accessed 9 November 2023. https://pubmed.ncbi.nlm.nih.gov/37289901/
[15] Xiong RG, Zhou DD, Wu SX, *et al*. Health benefits and side effects of short-chain fatty acids. Foods 2022;11:2863.

[16] Chen J, Zhao KN, Vitetta L. Effects of intestinal microbial-elaborated butyrate on oncogenic signaling pathways. Nutrients 2019;11:1026.
[17] Ghosh TS, Rampelli S, Jeffery IB, *et al*. Mediterranean diet intervention alters the gut microbiome in older people reducing frailty and improving health status: the NU-AGE 1-year dietary intervention across five European countries. Gut 2020;69:1218–28.
[18] Illescas O, Rodríguez-Sosa M, Gariboldi M. Mediterranean diet to prevent the development of colon diseases: a meta-analysis of gut microbiota studies [Internet]. U.S. National Library of Medicine; 2021. Accessed 29 May 2023.
[19] Veronese N, Solmi M, Caruso MG, *et al*. Dietary fiber and health outcomes: An umbrella review of systematic reviews and meta-analyses. Am J Clin Nutr 2018;107:436–44.
[20] Canale M, Noce A. Gut dysbiosis and western diet in the pathogenesis of essential arterial hypertension: a narrative review. Nutrients 2021;13: 1162.
[21] Li J, Zhao F, Wang Y, *et al*. Gut microbiota dysbiosis contributes to the development of hypertension. Microbiome 2017;5:14.
[22] Amabebe E, Robert FO, Agbalalah T, *et al*. Microbial dysbiosis-induced obesity: role of gut microbiota in homoeostasis of energy metabolism. British Journal of Nutrition [Internet]. Cambridge University Press; 2020. Accessed 29 May 2023.
[23] Tsai H-J, Tsai W-C, Hung W-C, *et al*. Gut microbiota and subclinical cardiovascular disease in patients with type 2 diabetes mellitus [Internet]. U.S. National Library of Medicine; 2021. Accessed 29 May 2023.
[24] Tang W, Hazen S. [Internet]. 2017. Accessed 29 May 2023. https://www.ahajournals.org/doi/10.1161/CIRCULATIONAHA.116.024251
[25] Jie Z, Xia H, Zhong SL, *et al*. The gut microbiome in atherosclerotic cardiovascular disease. Nat Commun 2017;8:845.
[26] Thogersen R, Rasmussen MK, Sundekilde UK, *et al*. Background diet influences TMAO concentrations associated with red meat intake without influencing apparent hepatic TMAO-related activity in a porcine model [Internet]. U.S. National Library of Medicine; 2020. Accessed 29 May 2023.
[27] Zhu W, Gregory JC, Org E, *et al*. Gut microbial metabolite TMAO enhances platelet hyperreactivity and thrombosis risk. Cell 2016;165: 111–24.
[28] Tenorio-Jiménez C, Martínez-Ramírez MJ, Tercero-Lozano M, *et al*. Evaluation of the effect of lactobacillus Reuteri V3401 on biomarkers of inflammation and cardiovascular risk in obese adults with metabolic syndrome: a randomized clinical trial (PROSIR). Clin Nutr 2018;37:S15.
[29] Rittiphairoj T, Pongpirul K. Probiotics contribute to glycemic control in patients with type 2 diabetes mellitus: a systematic review and meta-analysis [Internet]. U.S. National Library of Medicine; 2021. Accessed 29 May 2023.
[30] Mo R, Zhang X, Yang Y. Effect of probiotics on lipid profiles in hypercholesterolaemic adults: a meta-analysis of randomized controlled trials. Med Clín 2019;152:473–81.
[31] Othman R, Amor NB. A clinical trial about effects of prebiotic and probiotic supplementation on weight loss, psychological profile and metabolic parameters in obese subjects [Internet]. U.S. National Library of Medicine; 2023. Accessed 29 May 2023.
[32] Borgeraas H, Johnson LK, Skattebu J, *et al*. Effects of probiotics on body weight, body mass index, fat mass and fat percentage in subjects with overweight or obesity: a systematic review and meta-analysis of randomized controlled trials. Obes Rev 2021;22:e13199.
[33] Matsutomo T. Potential benefits of garlic and other dietary supplements for the management of hypertension (Review). Exp Ther Med 2019;19: 1479–84.
[34] Ejtahed H-S, Ardeshirlarijani E, Tabatabaei-Malazy O, *et al*. Effect of probiotic foods and supplements on blood pressure: a systematic review of meta-analyses studies of controlled trials. J Diabetes Metab Disord 2020;19:617–23.
[35] Zarezadeh M, Musazedeh V, Ghalichi F. Effects of probiotics supplementation on blood pressure: An umbrella meta-analysis of randomized controlled trials [Internet]. U.S. National Library of Medicine; 2023. Accessed 29 May 2023.
[36] Moludi J, Alizadeh M, Lotfi Yagin N, *et al*. New insights on atherosclerosis: a cross-talk between endocannabinoid systems with gut microbiota [Internet]. U.S. National Library of Medicine; 2018. Accessed 29 May 2023.
[37] Hofeld BC, Puppala VK, Tyagi S, *et al*. Lactobacillus Plantarum 299v probiotic supplementation in men with stable coronary artery disease suppresses systemic inflammation. Sci Rep 2021;11:3972.
[38] Moludi J, Kafil HS, Qaisar SA, *et al*. Effect of probiotic supplementation along with calorie restriction on metabolic endotoxemia and inflammation markers in coronary artery disease patients: a double-blind placebo-controlled randomized clinical trial. Nutr J 2021;20:47.
[39] Moludi J, Alizadeh M. Impact of probiotic supplementation on trimethylamine N-oxide (TMAO) in humans: a systematic review and meta-analysis of randomized controlled trials [Internet]. Elsevier; 2022. Accessed 29 May 2023.
[40] Farias DDP, de Araújo FF, Neri-Numa IA, *et al*. Prebiotics: trends in food, health and technological applications. Trends Food Sci Technol 2019;93: 23–35.
[41] Tan J, McKenzie C, Potamitis M, *et al*. The role of short-chain fatty acids in health and disease. Adv Immunol 2014;121:91–119.
[42] Moludi J, Khedmatgozar H, Nachvak SM, *et al*. The effects of co-administration of probiotics and prebiotics on chronic inflammation and depression symptoms in patients with coronary artery diseases: a randomized clinical trial. Nutr Neurosci 2021;10:1–10.
[43] Jiang T, Xing X, Zhang L, *et al*. Chitosan oligosaccharides show protective effects in coronary heart disease by improving antioxidant capacity via the increase in intestinal probiotics [Internet]. Hindawi; 2019. Accessed 29 May 2023.
[44] Vlasov AA, Shperling MI, Terkin DA, *et al*. Effect of prebiotic complex on gut microbiota and endotoxemia in female rats with modeled heart failure - bulletin of experimental biology and medicine [Internet]. Springer US; 2020. Accessed 29 May 2023.
[45] Kim B, Choi HN, Yim JE. Effect of diet on the gut microbiota associated with obesity. J Obesity Metab Synd 2019;28:216–24.
[46] Nicolucci AC, Hume MP, Martinez I, *et al*. Prebiotics reduce body fat and alter intestinal microbiota in children who are overweight or with obesity. Gastroenterology 2017;153:711–22.
[47] Gibb Ro, Russell DA, McRorie JW Jr. Psyllium fiber improves glycemic control proportional to loss of glycemic control: a meta-analysis of data in euglycemic subjects, patients at risk of type 2 diabetes mellitus, and patients being treated for type 2 diabetes mellitus [Internet]. U.S. National Library of Medicine; 2015. Accessed 29 May 2023.
[48] Wilson BC, Vatanen T, Cutfield WS, *et al*. The super-donor phenomenon in fecal microbiota transplantation. Front Cell Infect Microbiol 2019;9:2.
[49] Kriss M, Hazleton KZ, Nusbacher NM, *et al*. Low diversity gut microbiota dysbiosis: drivers, functional implications and recovery. Curr Opin Microbiol 2018;44:34–40.
[50] Kootte RS, Levin E, Salojarvi J, *et al*. Improvement of insulin sensitivity after lean donor feces in metabolic syndrome is driven by baseline intestinal microbiota composition. Cell Metab 2017;26:611–9.
[51] Vrieze A, Van Nood E, Holleman F, *et al*. Transfer of intestinal microbiota from lean donors increases insulin sensitivity in individuals with metabolic syndrome. Gastroenterology 2012;143:913–6.
[52] Wu Z, Zhang B, Chen F, *et al*. Fecal microbiota transplantation reverses insulin resistance in type 2 diabetes: a randomized, controlled, prospective study [Internet]. U.S. National Library of Medicine; 2023. Accessed 29 May 2023.
[53] Ng SC, Xu Z, Mak JWY, *et al*. Microbiota engraftment after faecal microbiota transplantation in obese subjects with type 2 diabetes: a 24-week, double-blind, randomised controlled trial. Gut 2022;71: 716–23.
[54] Sayols-Baixeras S, Dekkers KF. Streptococcus species abundance in the gut is linked to subclinical coronary atherosclerosis in 8973 participants from the SCAPIS cohort [Internet]. AHA journal 2023. Accessed 29 May 2023. https://pubmed.ncbi.nlm.nih.gov/37435755/
[55] Barrington WT, Lusis AJ. Association between the gut microbiome and atherosclerosis. Nat Rev Cardiol 2017;14:699–700.
[56] Zhu Y, Li Q, Jiang H. Gut microbiota in atherosclerosis: focus on trimethylamine N-oxide. APMIS 2020;128:353–66.
[57] Duttaroy AK. Role of gut microbiota and their metabolites on atherosclerosis, hypertension, and human blood platelet function: a review. Nutrients 2021;13:144.
[58] Koren O, Spor A, Felin J, *et al*. Human oral, gut, and plaque microbiota in patients with atherosclerosis. Proc Natl Acad Sci USA 2011;108 (suppl_1):4592–8.
[59] Peng J, Xiao X, Hu M, *et al*. Interaction between gut microbiome and cardiovascular disease. Life Sci 2018;214:153–7.
[60] Kitai T, Tang WHW. Gut microbiota in cardiovascular disease and heart failure. Clin Sci 2018;132:85–91.
[61] Moldovan DC, Ismaiel A, Fagoonee S, *et al*. Gut microbiota and cardiovascular diseases axis. Minerva Med [Internet] 2022;113 [cited 2023 May 28].

[62] Kang Y, Cai Y. Gut microbiota and hypertension: From pathogenesis to new therapeutic strategies. Clin Res Hepatol Gastroenterol 2018;42:110–7.
[63] Palmu J, Lahti L, Niiranen T. Targeting gut microbiota to treat hypertension: a systematic review. IJERPH 2021;18:1248.
[64] Pevsner-Fischer M, Blacher E, Tatirovsky E, *et al*. The gut microbiome and hypertension. Curr Opin Nephrol Hypertens 2017;26:1–8.
[65] Kurilshikov A, Van Den Munckhof ICL, Chen L, *et al*. Gut microbial associations to plasma metabolites linked to cardiovascular phenotypes and risk: a cross-sectional study. Circ Res 2019;124:1808–20.
[66] McCarville JL, Caminero A, Verdu EF. Novel perspectives on therapeutic modulation of the gut microbiota. Therap Adv Gastroenterol 2016;9:580–93.
[67] Rinninella E, Raoul P, Cintoni M, *et al*. Nutritional interventions targeting gut Microbiota during cancer therapies. Microorganisms 2021;9:1469.
[68] Markey KA, van den Brink MRM, Peled JU. Therapeutics targeting the gut microbiome: Rigorous pipelines for drug development. Cell Host Microbe 2020;27:169–72.
[69] Kamo T, Akazawa H, Suzuki J-I, *et al*. Novel concept of a heart-gut axis in the pathophysiology of heart failure. Korean Circ J 2017;47:663–9.
[70] Forkosh E, Ilan Y. The heart-gut axis: new target for atherosclerosis and congestive heart failure therapy. Open Heart 2019;6:e000993.
[71] Buglioni A, Burnett JC Jr. A gut-heart connection in cardiometabolic regulation. Nat Med 2013;19:534–6.
[72] Salzano A, Cassambai S, Yazaki Y, *et al*. The gut axis involvement in heart failure: Focus on Trimethylamine N-oxide. Heart Fail Clin 2020;16:23–31.
[73] Zhu W, Gregory JC, Org E, *et al*. Gut microbial metabolite TMAO enhances platelet hyperreactivity and thrombosis risk. Cell 2016;165:111–24.
[74] Lynch SV, Pedersen O. The human intestinal microbiome in health and disease. N Engl J Med 2016;375:2369–79.
[75] Falony G, Joossens M, Vieira-Silva S, *et al*. Population-level analysis of gut microbiome variation. Science 2016;352:560–4.
[76] Tang WH, Wang Z, Levison BS, *et al*. Intestinal microbial metabolism of phosphatidylcholine and cardiovascular risk. N Engl J Med 2013;368:1575–84.
[77] Haiser HJ, Turnbaugh PJ. Is it time for a metagenomic basis of therapeutics? Science 2012;336:1253–5.