HHS Public Access

Author manuscript

*Clin Sci (Lond)*. Author manuscript; available in PMC 2019 March 12.

Published in final edited form as:

*Clin Sci (Lond)*. 2018 January 16; 132(1): 85–91. doi:10.1042/CS20171090.

# GUT MICROBIOTA IN CARDIOVASCULAR DISEASE AND HEART FAILURE

**Takeshi Kitai, MD, PhD**[1,2] and **W. H. Wilson Tang, MD**[1,3]

[1]Department of Cardiovascular Medicine, Heart and Vascular Institute, Cleveland Clinic, Cleveland, Ohio;

[2]Department of Cardiovascular Medicine, Kobe City Medical Center General Hospital, Kobe, Japan;

[3]Center for Clinical Genomics, Cleveland Clinic, Cleveland, Ohio.

## Abstract

Accumulating evidence supports a relationship between the complexity and diversity of the gut microbiota and host diseases. In addition to alterations in the gut microbial composition, the metabolic potential of gut microbiota has been identified as a contributing factor in the development of diseases. Recent technological developments of molecular and biochemical analyses enable us to detect and characterize the gut microbiota via assessment and classification of their genomes and corresponding metabolites. These advances have provided emerging data supporting the role of gut microbiota in various physiological activities including host metabolism, neurological development, energy homeostasis, and immune regulation. Although few human studies have looked into the causative associations and underlying pathophysiology of the gut microbiota and host disease, a growing body of preclinical and clinical evidence supports the theory that gut microbiota and its metabolites have the potential to be a novel therapeutic and preventative target for cardiovascular and metabolic diseases. In this review, we highlight the interplay between the gut microbiota and its metabolites, and the development and progression of hypertension, heart failure, and chronic kidney disease.

### Keywords

Gut microbiota; cardiovascular disease; metabolomics; heart failure; chronic kidney disease

## INTRODUCTION

The human gut harbors more than 100 trillion microbial cells, and majority of them being classified into the phyla *Firmicutes* and *Bacteroidetes.* Additionally, these microbes are responsible for various physiological activities including host metabolism, neurological development, energy homeostasis and immune regulation, and vitamin synthesis and

**Address for correspondence:** W. H. Wilson Tang, MD FACC, 9500 Euclid Avenue, Desk J3-4, Cleveland, OH 44195., Phone: (216) 444-212 / Fax: (216) 445-6165 / tangw@ccf.org.

DISCLOSURE

Drs. Tang and Kitai have no relationships to disclose.

digestion,(1) capable of regulating the normal function of intestinal epithelial mucosal barriers.(2,3) Disruption of intestinal epithelial barrier function can lead to increased gut permeability, increased bacterial translocation, and increased circulating endotoxins that can contribute to the underlying inflammation related to the progression of cardiovascular disease. Furthermore, accumulating evidence suggests that quantitative and qualitative alterations of the gut microbiota (so-called “dysbiosis”) can also play an important role in the pathogenesis of various cardiovascular and metabolic diseases.(4–7) Gut dysbiosis can induce significant changes in the gut immune system, leading to altered signals derived from the gut to the systemic immune system. Indeed, direct modulation of gut microbiota has been associated with alterations in host metabolism, mainly through immune systems and hormone secretion.(8–10) Furthermore, the metabolic potential of gut microbiota has been identified as a contributing factor in the development of diseases, with metabolites acting on distant target organs in a manner similar to the human host’s endocrine organ.(11–15) In addition to gut microbiota, many gut bacteriophages have been found in human gut.(16) Prokaryotic viruses, which are currently thought to be the most abundant in the gut, are associated with human health by affecting bacterial community structure and function.(17–19) However, the precise mechanisms of these pathways are yet to be fully clarified. In this review, we highlight the interplay between gut microbiota and its metabolites, and cardiovascular diseases, including hypertension, heart failure, and chronic kidney disease.

## GUT-BRAIN AXIS AND BLOOD PRESSURE REGULATION

The homeostatic regulation of blood pressure is a complex process, which is regulated by several factors, such as gene, environment and endocrine hormone secretion. Recent studies have revealed that the human gut had a significant connection with the central nervous system via complex signaling pathways, including bidirectional neuroendocrine signals and immunological factors. (20) This, so-called “gut–brain axis” consists of the gut microbiota, central nervous system, enteric nervous system, and parasympathetic and sympathetic nervous systems.(21) There has been also recognized that altered gut microbial composition is associated with the development of neuro-degeneration.(22,23) Besides regulating the microglia, manipulation of the gut microbiota has been thought to be able to modulate neuroimmune activation through the production of microbial-derived bioactive metabolites, such as short-chain fatty acids (SCFAs).(23–25)

Several studies have suggested a potential role of the gut microbiota in blood pressure regulation and the pathogenesis of hypertension.(26–29) A recent case report demonstrated a potent antihypertensive effect of gut microbiota in a patient with resistant hypertension that was treated with minocycline.(30) This effect was thought to be mainly due to the production of SCFAs, which are important signals generated by gut microbiota.(31–34) Gut dysbiosis was observed in patients with hypertension,(31–34) which was characterized by a reduction in SCFA production and a change in the *Firmicutes* to *Bacteroidetes* ratio. (26,27,29) An animal study of spontaneous hypertensive rats also demonstrated an increase in *Firmicutes* to *Bacteroidetes* ratio, while chronic administration of SCFA reversed this ratio and attenuated the hypertension.(27) Mechanistically, SCFAs can function to stimulate G-protein-coupled receptors 41 (GPR41) and 43 (GPR43), and these are expressed in the renal vasculature.(35) The other SCFA olfactory receptor 78 (Olf78) is also expressed in the

kidneys, where it regulates blood pressure.(32) However, the balance across these G-protein-coupled receptor activities is complex and likely dynamic. In a study using GPR41-deficient mice, administration of the SCFA propionate was associated with a significant increase in blood pressure, which suggested that GPR41 can negate a pressor response to SCFA.(32)

Gut microbial composition was found to be significantly different between spontaneously hypertensive rats and Wistar-Kyoto control rats, with hypertensive rats having reduced taxa richness and altered microbial composition compared to the control rats. (27) At the phylum level, the *Firmicutes* to *Bacteroidetes* ratio was significantly higher in the hypertensive rats than in the control rats. In addition, angiotensin II-treated rats showed a reduction in microbial species richness and an increased *Firmicutes* to *Bacteroidetes* ratio compared to control rats.(27) Another study have reported that the microbiota of Dahl S (salt sensitive) rats was significantly different from that of Dahl R (salt resistant) rats. The phylum *Bacteroidetes* and family *Veillonellaceae* were reported to be more abundant in Dahl S rats than in Dahl R rats.(29) Moreover, Dahl S rats showed a significant increase in blood pressure with a high salt diet, whereas the Dahl R rats did not respond to a high salt diet. (22,29) Furthermore, administration of an antibiotic to Dahl S rats did not affect their hypertensive responses to the high salt diet. Although fecal transplantation from Dahl R rats to Dahl S rats exacerbated the hypertensive responses of Dahl S rats and was associated with significantly elevated plasma levels of the SCFAs, fecal transplantation from Dahl S rats to Dahl R rats could not change hypertensive phenotype of the Dahl R rats.(29) These findings imply that the physiologic differences reside in the differences of gut microbial compositions and corresponding functions between the two rats.

## GUT MICROBIAL INTERACTION WITH HEART FAILURE AND ATHEROSCLEROSIS

Heart failure is a growing health problem and a main cause of mortality and morbidity worldwide. The gut has also been implicated in the pathophysiology and progression of heart failure, largely attributed to impaired perfusion to the intestines leading to intestinal barrier dysfunction. The Intestinal endothelial barrier is maintained by several mechanisms of a well-balanced gut microbiota.(36,37) In patients with heart failure, reduced blood flow into the intestinal endothelium due to reduced cardiac output leads to intestinal wall ischemia, leading to increased permeability due to structural disruption of the intestinal epithelial barrier function.(38) Further, systemic congestion in patients with heart failure can cause intestinal wall edema, which also results in increased intestinal permeability. This “leaky gut” is associated with translocation of endotoxins, microbial components, and microbial metabolites, such as lipopolysaccharides (LPS) produced by gram-negative bacteria, to enter the systemic circulation.(39,40) This process can further activate cytokines and generate systemic inflammation that, in turn, contributes to the progression of heart failure.(41–43) Indeed, gut microbial DNA has been detectable in the peripheral blood of patients with advanced kidney diseases, suggesting the leaky gut may serve as the primary source.(44)

In addition to hemodynamic deterioration in patients with heart failure, evidence showed that gut dysbiosis was associated with the production of several gut microbiota-derived metabolites, as well as promoting the disruption of gut endothelial barrier function. (7) In patients with heart failure, a significant interaction was observed between the amount of fecal gut microbiota and the intensity of intestinal permeability.(45) Furthermore, patients who had bacterial DNA in the peripheral blood had significantly higher plasma levels of inflammatory markers, including high-sensitive C-reactive protein and interleukin-6 levels, than those who did not have bacterial DNA in their peripheral blood.(46) A recent study has shown that heart failure patients had a significantly decreased diversity of gut microbiota and a depletion of core gut microbial groups.(47) These observations suggested that better understanding of the regulation of intestinal barrier function has the potential to develop intestinal barrier-directed heart failure therapy.

Trimethylamine N-oxide (TMAO), which is derived from metabolites of gut microbiota from specific dietary nutrients, is clearly linked to atherosclerotic cardiovascular risk. (44,48–50) Circulating TMAO levels are elevated and associated with disease severity in patients with atherosclerosis, CKD and peripheral artery diseases.(50–52) We found that elevated TMAO concentrations in animal models were associated with corresponding increases in renal tubulointerstitial fibrosis.(51) A recent study has shown that microbial taxa belonging to the clostridiaceae and peptostreptococcaceae families were positively associated with blood levels of TMAO in human.(53) Interestingly, patients with heart failure had significantly higher levels of TMAO than age-matched and sex-matched subjects without heart failure, irrespective of heart failure etiology.(50) Moreover, plasma TMAO levels were associated with adverse outcomes, and elevated plasma TMAO levels had a strong adverse prognostic value in addition to the traditional risk factors, cardio-renal indices and markers of systemic inflammation.(50) In a recent animal study using a transaortic constriction model of heart failure, high choline diet-fed mice had higher TMAO levels than those with standard choline diet.(54) In addition, high choline diet-fed mice showed adverse ventricular dilatation and wall thinning with a marked increase in fibrosis.(54) The profibrotic transforming growth factor (TGF)-B phosphor-Smad3 pathway has been shown to be enhanced in the choline diet-fed mice.(51) However, the causative effects of TMAO and the underlying mechanistic link that explains how TMAO might directly or indirectly promote heart failure is not well understood. In fact, although elevated TMAO levels have shown equivalent adverse prognostic value in patients with ischemic and non-ischemic etiologies, (50) a recent report has reported a conflicting result that TMAO levels were elevated in ischemic heart failure compared to non-ischemic dilated cardiomyopathy.(55) Furthermore, there is a lack of understanding of the relationship between TMAO or other gut microbial metabolites in altered intestinal permeability and hemodynamic status in the context of heart failure. Additional studies are needed to investigate whether manipulation of the gut microbial TMAO pathway can attenuate the progression of heart failure, and improve outcomes, even though early animal studies have shown promise with direct microbial enzyme inhibitors of TMA/TMAO synthesis in attenuating cardiac dysfunction.(49)

## GUT-RENAL AXIS AND UREMIC TOXINS

A complex interplay between the kidney and the gut microbiota has long been observed.(37) Several mechanisms were suggested to underlie the interaction between the gut microbiota and pathogenesis of CKD.(56) Gut microbiota has been shown to contribute to the generation of several uremic toxins, such as advanced glycation end products (AGEs), phenols, and indoles.(57) These are absorbed into the systemic circulation and are normally cleared by the kidneys. However, in states of impaired renal function, they accumulate and become toxic and induce an inflammatory response in the host, resulting in the progression of CKD.(38,56) The presence of uremic toxins has justified a wide range of innovative and/or obscure colonic cleansing practices or resection procedures to remove colonic uremic toxins over the century. Nevertheless, several contemporary studies have suggested that blood levels of uremic toxins have been associated with mortality and cardiovascular risks.(58–60) Circulating LPS levels increase with the stages of CKD and were an independent predictor of mortality.(61) Elevated indoxyl sulfate levels (microbial product of tryptophan metabolism) were associated with aortic calcification, increased vascular stiffness, and the risk of cardiovascular mortality in patients with CKD.(62) In uremic rats, the administration of indoxyl sulfate mediates the renal gene expression of TGFbeta-1, which is related to tubulointerstitial fibrosis.(60) Indoxyl sulfate has been suggested to be responsible for vascular disease through an induction of oxidative stress. Indoxyl sulfate induced the production of reactive oxygen species in human umbilical vein endothelial cells.(58) Treatment with the oral adsorbent AST-120 resulted in a significant decrease in indoxyl sulfate with a corresponding increase in flow-mediated, endothelium-dependent vasodilatation.(63) Meanwhile, another tryptophan metabolite, *p*-cresyl sulfate, may cause inflammation in blood vessels in experimental models.(64) Elevated *p*-cresyl sulfate levels were also associated with all-cause mortality.(65) Furthermore, in a partial nephrectomized mice model, indoxyl sulfate or *p*-cresyl sulfate activated the intrarenal renin-angiotensin-aldosterone system and interstitial fibrosis and glomerulosclerosis.(65)

In humans and animals with advanced CKD, extensive change in the structure and function of the gut microbiota has been reported.(66) Gut dysbiosis in patients with CKD has been implicated in an increased production of indoxyl sulfate and *p*-cresyl sulfate, and as a promoter for increasing inflammation and contributing to the progression of their disease.(38) Patients with CKD also showed significant changes in SCFA-producing microbiota, which are known to have beneficial effects. These observations suggested that gut dysbiosis and uremic toxins can cause endothelial dysfunction, aggravate inflammation and oxidative stress, and impair the normal physiological repair process of the endothelium.(58)

Patients with CKD has consistently high TMAO levels that are associated with higher mortality, accelerated atherosclerosis and progressive loss of kidney function in patients with CKD.(50,51,67,68) Dietary induced elevation of TMAO concentrations in mouse models has been associated with greater degree of tubulointerstitial fibrosis.(51) Animals with increased TMAO levels also had increased fibrosis and phosphorylation of Smad3, an important regulator of fibrosis.(65) However, there was only a modest correlation between TMAO levels and either the estimated glomerular filtration ratio.(51,69) Since TMAO is predominately excreted in urine and its clearance is largely dependent on renal function,

(49,70) decreased renal function in patients with CKD can confound the association of high TMAO levels in CKD.(71) A recent meta-analysis clearly showed that TMAO and its precursors were associated with an increased risk of mortality and major adverse cardiac event independently of traditional risk factors, such as diabetes mellitus, obesity, and CKD.(72) Further studies exploring the physiology of TMAO generation and metabolism are warranted to more thoroughly define the etiology of TMAO elevations in CKD.

## DIET INTERVENTION

Several studies have shown that dietary interventions were effective strategy in reducing cardiovascular risks.(73,74) It has been reported that adherence to the Mediterranean diet leads to a decrease in all the causes of mortality and in the incidence of cardiovascular diseases.(75) Moreover, dietary interventions can modify the microbiota composition by inducing rapid changes in certain nutrients.(76,77) A high level of variability in microbiota significantly correlated with dietary habits, confirming the shaping effect of long-term dietary patterns on gut microbiota.(78) A recent study has shown that fiber-rich diets promote the growth of beneficial commensal bacteria and limit the growth of known opportunistic pathogens.(79) Thus, modulation of gut microbiota composition through dietary intervention represents a promising therapeutic target. However, little is known about the mechanistic interplay between the diet intervention and the relevant gut microbial metabolism.

## CONCLUSIONS AND FUTURE PERSPECTIVE

Gut microbiota is an exciting new research field with enormous possibilities for human health, and holds great promises for novel diagnostic and therapeutic approaches with lasting and preventive impact. Nevertheless, few human studies have looked into causative associations of gut microbiota and its metabolites to host disease, and their putative mechanisms. Recent novel molecular biochemical analyses are expected to enable to detect and classify the diverse microorganisms, and to assess all genomes of these microbiota and their metabolites. In particular, since the diversity of gut microbiota in different individuals may lead to different responses to treatment and ultimately different outcomes, genome-scale metabolic models have the potential to be used as a key in understanding the role of individual species in the gut microbiota as well as the role of the microbiota as a whole. Genome-scale metabolic models are mathematical representations of the knowledge of a microbiota’s metabolic capacity and can predict how metabolic system functions differently in different species by integrating knowledge of the metabolism of the gut microbiota. These technological developments are expected to facilitate the move from correlation studies to a gain in mechanistic insights, and to result in new diagnostic tests and therapeutics in the near future. Additional studies are needed to investigate the exact mechanisms underlying interactions between the host and microbiota to better understand the impact of direct or indirect manipulations of the gut microbiota on their biological functions.

## Acknowledgments

FUNDING

Dr. Tang is supported by grants from the National Institutes of Health (NIH) and the Office of Dietary Supplements (P20HL113452, R01DK106000, R01HL126827).

## REFERENCES

1. Everard A, Cani PD. Gut microbiota and GLP-1. Reviews in endocrine & metabolic disorders 2014;15:189–96. [PubMed: 24789701]
2. Power SE, O'Toole PW, Stanton C, Ross RP, Fitzgerald GF. Intestinal microbiota, diet and health. The British journal of nutrition 2014;111:387–402. [PubMed: 23931069]
3. Vitetta L, Gobe G. Uremia and chronic kidney disease: the role of the gut microflora and therapies with pro- and prebiotics. Molecular nutrition & food research 2013;57:824–32. [PubMed: 23450842]
4. Festi D, Schiumerini R, Eusebi LH, Marasco G, Taddia M, Colecchia A. Gut microbiota and metabolic syndrome. World journal of gastroenterology 2014;20:16079–94. [PubMed: 25473159]
5. Gomez-Hurtado I, Such J, Sanz Y, Frances R. Gut microbiota-related complications in cirrhosis. World journal of gastroenterology 2014;20:15624–31. [PubMed: 25400446]
6. Ilan Y Leaky gut and the liver: a role for bacterial translocation in nonalcoholic steatohepatitis. World journal of gastroenterology 2012;18:2609–18. [PubMed: 22690069]
7. Winslow MM, Gallo EM, Neilson JR, Crabtree GR. The calcineurin phosphatase complex modulates immunogenic B cell responses. Immunity 2006;24:141–52. [PubMed: 16473827]
8. Burcelin R Gut microbiota and immune crosstalk in metabolic disease. Molecular metabolism 2016;5:771–81. [PubMed: 27617200]
9. Perry RJ, Peng L, Barry NA et al. Acetate mediates a microbiome-brain-beta-cell axis to promote metabolic syndrome. Nature 2016;534:213–7. [PubMed: 27279214]
10. Thaiss CA, Zmora N, Levy M, Elinav E. The microbiome and innate immunity. Nature 2016;535:65–74. [PubMed: 27383981]
11. Schroeder BO, Backhed F. Signals from the gut microbiota to distant organs in physiology and disease. Nature medicine 2016;22:1079–1089.
12. Tang WH, Kitai T, Hazen SL. Gut Microbiota in Cardiovascular Health and Disease. Circulation research 2017;120:1183–1196. [PubMed: 28360349]
13. Tang WH, Hazen SL. The contributory role of gut microbiota in cardiovascular disease. The Journal of clinical investigation 2014;124:4204–11. [PubMed: 25271725]
14. Kitai T, Tang WW. Recent advances in treatment of heart failure. F1000Research 2015;4.
15. Kitai T, Tang WHW. The Role and Impact of Gut Microbiota in Cardiovascular Disease. Revista espanola de cardiologia 2017.
16. Virgin HW. The virome in mammalian physiology and disease. Cell 2014;157:142–50. [PubMed: 24679532]
17. Reyes A, Haynes M, Hanson N et al. Viruses in the faecal microbiota of monozygotic twins and their mothers. Nature 2010;466:334–8. [PubMed: 20631792]
18. Cadwell K, Patel KK, Maloney NS et al. Virus-plus-susceptibility gene interaction determines Crohn's disease gene Atg16L1 phenotypes in intestine. Cell 2010;141:1135–45. [PubMed: 20602997]
19. Minot S, Bryson A, Chehoud C, Wu GD, Lewis JD, Bushman FD. Rapid evolution of the human gut virome. Proceedings of the National Academy of Sciences of the United States of America 2013;110:12450–5. [PubMed: 23836644]
20. Bauer KC, Huus KE, Finlay BB. Microbes and the mind: emerging hallmarks of the gut microbiota-brain axis. Cellular microbiology 2016;18:632–44. [PubMed: 26918908]
21. O'Mahony SM, Clarke G, Borre YE, Dinan TG, Cryan JF. Serotonin, tryptophan metabolism and the brain-gut-microbiome axis. Behavioural brain research 2015;277:32–48. [PubMed: 25078296]
22. Kohler CA, Maes M, Slyepchenko A et al. The Gut-Brain Axis, Including the Microbiome, Leaky Gut and Bacterial Translocation: Mechanisms and Pathophysiological Role in Alzheimer's Disease. Current pharmaceutical design 2016;22:6152–6166. [PubMed: 27604604]

23. Dinan TG, Cryan JF. Gut instincts: microbiota as a key regulator of brain development, ageing and neurodegeneration. The Journal of physiology 2017;595:489–503. [PubMed: 27641441]
24. Sampson TR, Debelius JW, Thron T et al. Gut Microbiota Regulate Motor Deficits and Neuroinflammation in a Model of Parkinson's Disease. Cell 2016;167:1469–1480 e12. [PubMed: 27912057]
25. Erny D, Hrabe de Angelis AL, Jaitin D et al. Host microbiota constantly control maturation and function of microglia in the CNS. Nature neuroscience 2015;18:965–77. [PubMed: 26030851]
26. Durgan DJ, Ganesh BP, Cope JL et al. Role of the Gut Microbiome in Obstructive Sleep Apnea-Induced Hypertension. Hypertension 2016;67:469–74. [PubMed: 26711739]
27. Yang T, Santisteban MM, Rodriguez V et al. Gut dysbiosis is linked to hypertension. Hypertension 2015;65:1331–40. [PubMed: 25870193]
28. Holmes E, Loo RL, Stamler J et al. Human metabolic phenotype diversity and its association with diet and blood pressure. Nature 2008;453:396–400. [PubMed: 18425110]
29. Mell B, Jala VR, Mathew AV et al. Evidence for a link between gut microbiota and hypertension in the Dahl rat. Physiological genomics 2015;47:187–97. [PubMed: 25829393]
30. Qi Y, Aranda JM, Rodriguez V, Raizada MK, Pepine CJ. Impact of antibiotics on arterial blood pressure in a patient with resistant hypertension - A case report. International journal of cardiology 2015;201:157–8. [PubMed: 26301638]
31. Nutting CW, Islam S, Daugirdas JT. Vasorelaxant effects of short chain fatty acid salts in rat caudal artery. The American journal of physiology 1991;261:H561–7. [PubMed: 1877681]
32. Pluznick JL. Renal and cardiovascular sensory receptors and blood pressure regulation. American journal of physiology Renal physiology 2013;305:F439–44. [PubMed: 23761671]
33. Mortensen FV, Nielsen H, Mulvany MJ, Hessov I. Short chain fatty acids dilate isolated human colonic resistance arteries. Gut 1990;31:1391–4. [PubMed: 2265780]
34. Pluznick JL, Zou DJ, Zhang X et al. Functional expression of the olfactory signaling system in the kidney. Proceedings of the National Academy of Sciences of the United States of America 2009;106:2059–64. [PubMed: 19174512]
35. Pluznick JL, Protzko RJ, Gevorgyan H et al. Olfactory receptor responding to gut microbiota-derived signals plays a role in renin secretion and blood pressure regulation. Proceedings of the National Academy of Sciences of the United States of America 2013;110:4410–5. [PubMed: 23401498]
36. Vaziri ND, Goshtasbi N, Yuan J et al. Uremic plasma impairs barrier function and depletes the tight junction protein constituents of intestinal epithelium. American journal of nephrology 2012;36:438–43. [PubMed: 23128155]
37. Sabatino A, Regolisti G, Brusasco I, Cabassi A, Morabito S, Fiaccadori E. Alterations of intestinal barrier and microbiota in chronic kidney disease. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 2015;30:924–33.
38. Ramezani A, Raj DS. The gut microbiome, kidney disease, and targeted interventions. Journal of the American Society of Nephrology : JASN 2014;25:657–70. [PubMed: 24231662]
39. Krack A, Richartz BM, Gastmann A et al. Studies on intragastric PCO2 at rest and during exercise as a marker of intestinal perfusion in patients with chronic heart failure. European journal of heart failure 2004;6:403–7. [PubMed: 15182764]
40. Sandek A, Bauditz J, Swidsinski A et al. Altered intestinal function in patients with chronic heart failure. Journal of the American College of Cardiology 2007;50:1561–9. [PubMed: 17936155]
41. Sandek A, Bjarnason I, Volk HD et al. Studies on bacterial endotoxin and intestinal absorption function in patients with chronic heart failure. International journal of cardiology 2012;157:80–5. [PubMed: 21190739]
42. Verbrugge FH, Dupont M, Steels P et al. Abdominal contributions to cardiorenal dysfunction in congestive heart failure. Journal of the American College of Cardiology 2013;62:485–95. [PubMed: 23747781]
43. Niebauer J, Volk HD, Kemp M et al. Endotoxin and immune activation in chronic heart failure: a prospective cohort study. Lancet 1999;353:1838–42. [PubMed: 10359409]

44. Shi K, Wang F, Jiang H et al. Gut bacterial translocation may aggravate microinflammation in hemodialysis patients. Digestive diseases and sciences 2014;59:2109–17. [PubMed: 24828917]
45. Pasini E, Aquilani R, Testa C et al. Pathogenic Gut Flora in Patients With Chronic Heart Failure. JACC Heart failure 2016;4:220–7. [PubMed: 26682791]
46. Wang F, Jiang H, Shi K, Ren Y, Zhang P, Cheng S. Gut bacterial translocation is associated with microinflammation in end-stage renal disease patients. Nephrology 2012;17:733–8. [PubMed: 22817644]
47. Luedde M, Winkler T, Heinsen FA et al. Heart failure is associated with depletion of core intestinal microbiota. ESC heart failure 2017;4:282–290. [PubMed: 28772054]
48. Tang WH, Wang Z, Levison BS et al. Intestinal microbial metabolism of phosphatidylcholine and cardiovascular risk. The New England journal of medicine 2013;368:1575–84. [PubMed: 23614584]
49. Wang Z, Klipfell E, Bennett BJ et al. Gut flora metabolism of phosphatidylcholine promotes cardiovascular disease. Nature 2011;472:57–63. [PubMed: 21475195]
50. Tang WH, Wang Z, Fan Y et al. Prognostic value of elevated levels of intestinal microbe-generated metabolite trimethylamine-N-oxide in patients with heart failure: refining the gut hypothesis. Journal of the American College of Cardiology 2014;64:1908–14. [PubMed: 25444145]
51. Tang WH, Wang Z, Kennedy DJ et al. Gut microbiota-dependent trimethylamine N-oxide (TMAO) pathway contributes to both development of renal insufficiency and mortality risk in chronic kidney disease. Circulation research 2015;116:448–55. [PubMed: 25599331]
52. Senthong V, Wang Z, Fan Y, Wu Y, Hazen SL, Tang WH. Trimethylamine N-Oxide and Mortality Risk in Patients With Peripheral Artery Disease. Journal of the American Heart Association 2016;5.
53. Backhed F Meat-metabolizing bacteria in atherosclerosis. Nature medicine 2013;19:533–4.
54. Organ CL, Otsuka H, Bhushan S et al. Choline Diet and Its Gut Microbe-Derived Metabolite, Trimethylamine N-Oxide, Exacerbate Pressure Overload-Induced Heart Failure. Circulation Heart failure 2016;9:e002314. [PubMed: 26699388]
55. Troseid M, Ueland T, Hov JR et al. Microbiota-dependent metabolite trimethylamine-N-oxide is associated with disease severity and survival of patients with chronic heart failure. Journal of internal medicine 2015;277:717–26. [PubMed: 25382824]
56. Goncalves S, Pecoits-Filho R, Perreto S et al. Associations between renal function, volume status and endotoxaemia in chronic kidney disease patients. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 2006;21:2788–94.
57. Wikoff WR, Anfora AT, Liu J et al. Metabolomics analysis reveals large effects of gut microflora on mammalian blood metabolites. Proceedings of the National Academy of Sciences of the United States of America 2009;106:3698–703. [PubMed: 19234110]
58. Yu M, Kim YJ, Kang DH. Indoxyl sulfate-induced endothelial dysfunction in patients with chronic kidney disease via an induction of oxidative stress. Clinical journal of the American Society of Nephrology : CJASN 2011;6:30–9. [PubMed: 20876676]
59. Liabeuf S, Barreto DV, Barreto FC et al. Free p-cresylsulphate is a predictor of mortality in patients at different stages of chronic kidney disease. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 2010;25:1183–91.
60. Miyazaki T, Ise M, Seo H, Niwa T. Indoxyl sulfate increases the gene expressions of TGF-beta 1, TIMP-1 and pro-alpha 1(I) collagen in uremic rat kidneys. Kidney international Supplement 1997;62:S15–22. [PubMed: 9350672]
61. Mak RH, Cheung W. Adipokines and gut hormones in end-stage renal disease. Peritoneal dialysis international : journal of the International Society for Peritoneal Dialysis 2007;27 Suppl 2:S298–302. [PubMed: 17556323]
62. Lin CJ, Wu V, Wu PC, Wu CJ. Meta-Analysis of the Associations of p-Cresyl Sulfate (PCS) and Indoxyl Sulfate (IS) with Cardiovascular Events and All-Cause Mortality in Patients with Chronic Renal Failure. PloS one 2015;10:e0132589. [PubMed: 26173073]

63. Niwa T, Nomura T, Sugiyama S, Miyazaki T, Tsukushi S, Tsutsui S. The protein metabolite hypothesis, a model for the progression of renal failure: an oral adsorbent lowers indoxyl sulfate levels in undialyzed uremic patients. Kidney international Supplement 1997;62:S23–8. [PubMed: 9350673]
64. Massy ZA, Barreto DV, Barreto FC, Vanholder R. Uraemic toxins for consideration by the cardiologist-Beyond traditional and non-traditional cardiovascular risk factors. Atherosclerosis 2010;211:381–3. [PubMed: 20471651]
65. Sun CY, Chang SC, Wu MS. Uremic toxins induce kidney fibrosis by activating intrarenal renin-angiotensin-aldosterone system associated epithelial-to-mesenchymal transition. PloS one 2012;7:e34026. [PubMed: 22479508]
66. Vaziri ND, Wong J, Pahl M et al. Chronic kidney disease alters intestinal microbial flora. Kidney international 2013;83:308–15. [PubMed: 22992469]
67. Rhee EP, Souza A, Farrell L et al. Metabolite profiling identifies markers of uremia. Journal of the American Society of Nephrology : JASN 2010;21:1041–1051. [PubMed: 20378825]
68. Tang WH, Wang Z, Shrestha K et al. Intestinal microbiota-dependent phosphatidylcholine metabolites, diastolic dysfunction, and adverse clinical outcomes in chronic systolic heart failure. Journal of cardiac failure 2015;21:91–6. [PubMed: 25459686]
69. Stubbs JR, House JA, Ocque AJ et al. Serum Trimethylamine-N-Oxide is Elevated in CKD and Correlates with Coronary Atherosclerosis Burden. Journal of the American Society of Nephrology : JASN 2016;27:305–13. [PubMed: 26229137]
70. Al-Waiz M, Mitchell SC, Idle JR, Smith RL. The metabolism of 14C-labelled trimethylamine and its N-oxide in man. Xenobiotica; the fate of foreign compounds in biological systems 1987;17:551–8. [PubMed: 3604260]
71. Mueller DM, Allenspach M, Othman A et al. Plasma levels of trimethylamine-N-oxide are confounded by impaired kidney function and poor metabolic control. Atherosclerosis 2015;243:638–44. [PubMed: 26554714]
72. Heianza Y, Ma W, Manson JE, Rexrode KM, Qi L. Gut Microbiota Metabolites and Risk of Major Adverse Cardiovascular Disease Events and Death: A Systematic Review and Meta-Analysis of Prospective Studies. Journal of the American Heart Association 2017;6.
73. Estruch R, Ros E, Salas-Salvado J et al. Primary prevention of cardiovascular disease with a Mediterranean diet. The New England journal of medicine 2013;368:1279–90. [PubMed: 23432189]
74. Appel LJ, Moore TJ, Obarzanek E et al. A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. The New England journal of medicine 1997;336:1117–24. [PubMed: 9099655]
75. Mekki K, Bouzidi-bekada N, Kaddous A, Bouchenak M. Mediterranean diet improves dyslipidemia and biomarkers in chronic renal failure patients. Food & function 2010;1:110–5. [PubMed: 21776461]
76. David LA, Maurice CF, Carmody RN et al. Diet rapidly and reproducibly alters the human gut microbiome. Nature 2014;505:559–63. [PubMed: 24336217]
77. Ravussin Y, Koren O, Spor A et al. Responses of gut microbiota to diet composition and weight loss in lean and obese mice. Obesity 2012;20:738–47. [PubMed: 21593810]
78. Almoosawi S, Winter J, Prynne CJ, Hardy R, Stephen AM. Daily profiles of energy and nutrient intakes: are eating profiles changing over time? European journal of clinical nutrition 2012;66:678–86. [PubMed: 22190135]
79. Foye OT, Huang IF, Chiou CC, Walker WA, Shi HN. Early administration of probiotic Lactobacillus acidophilus and/or prebiotic inulin attenuates pathogen-mediated intestinal inflammation and Smad 7 cell signaling. FEMS immunology and medical microbiology 2012;65:467–80. [PubMed: 22524476]

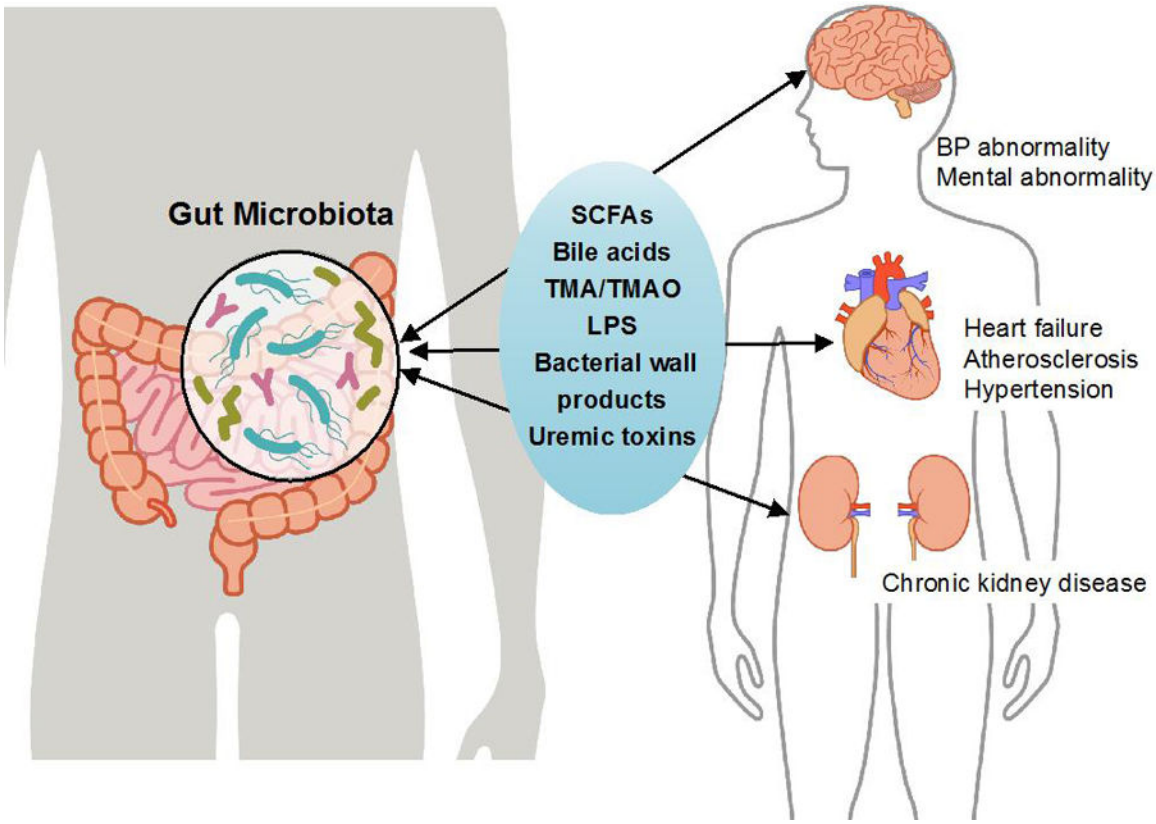


**FIGURE.**
Interplay between the gut and the brain, the heart and the kidneys.