

PubMed/Web of Science Research query:

("Gastrointestinal microbiome"[Title/Abstract] OR "Microbiome, Gastrointestinal"[Title/Abstract] OR "Gastrointestinal Microbial Community"[Title/Abstract] OR "Gastrointestinal Microbial Communities"[Title/Abstract] OR "Microbial Community, Gastrointestinal"[Title/Abstract] OR "Gut Microbiome"[Title/Abstract] OR "Gut Microbiomes"[Title/Abstract] OR "Microbiome, Gut"[Title/Abstract] OR "Gut Microflora"[Title/Abstract] OR "Microflora, Gut"[Title/Abstract] OR "Gastrointestinal Microflora"[Title/Abstract] OR "Microflora, Gastrointestinal"[Title/Abstract] OR "Gastrointestinal Flora"[Title/Abstract] OR "Flora, Gastrointestinal"[Title/Abstract] OR "Gut Flora"[Title/Abstract] OR "Flora, Gut"[Title/Abstract] OR "Gastrointestinal Microbiota"[Title/Abstract] OR "Gastrointestinal Microbiotas"[Title/Abstract] OR "Microbiota, Gastrointestinal"[Title/Abstract] OR "Gut Microbiota"[Title/Abstract] OR "Gut Microbiotas"[Title/Abstract] OR "Microbiota, Gut"[Title/Abstract] OR "Intestinal Microbiome"[Title/Abstract] OR "Intestinal Microbiomes"[Title/Abstract] OR "Microbiome, Intestinal"[Title/Abstract] OR "Intestinal Flora"[Title/Abstract] OR "Flora, Intestinal"[Title/Abstract] OR "Intestinal Microbiota"[Title/Abstract] OR "Intestinal Microbiotas"[Title/Abstract] OR "Microbiota, Intestinal"[Title/Abstract] OR "Intestinal Microflora"[Title/Abstract] OR "Microflora, Intestinal"[Title/Abstract] OR "Enteric Bacteria"[Title/Abstract] OR "Bacteria, Enteric"[Title/Abstract] OR "Gastric Microbiome"[Title/Abstract] OR "Gastric Microbiomes"[Title/Abstract] OR "Microbiome, Gastric") AND ("Cardiovascular Disease"[Title/Abstract] OR "Disease, Cardiovascular"[Title/Abstract] OR "Cardiac Events"[Title/Abstract] OR "Cardiac Event"[Title/Abstract] OR "Event, Cardiac"[Title/Abstract] OR "Adverse Cardiac Event"[Title/Abstract] OR "Adverse Cardiac Events"[Title/Abstract] OR "Cardiac Event, Adverse"[Title/Abstract] OR "Cardiac Events, Adverse"[Title/Abstract] OR "Major Adverse Cardiac Events"[Title/Abstract] OR "Cardiovascular Abnormalities"[Title/Abstract] OR "Heart Defects, Congenital"[Title/Abstract] OR "Vascular Malformations"[Title/Abstract] OR "Cardiovascular Infections"[Title/Abstract] OR "Endocarditis, Bacterial"[Title/Abstract] OR "Syphilis, Cardiovascular"[Title/Abstract] OR "Tuberculosis, Cardiovascular"[Title/Abstract] OR "Heart Diseases"[Title/Abstract] OR "Arrhythmias, Cardiac"[Title/Abstract] OR "Carcinoid Heart Disease"[Title/Abstract] OR "Cardiac Conduction System Disease"[Title/Abstract] OR "Cardiac Output, High"[Title/Abstract] OR "Cardiac Output, Low"[Title/Abstract] OR "Cardiac Tamponade"[Title/Abstract] OR "Cardiomegaly"[Title/Abstract] OR "Cardiomyopathies"[Title/Abstract] OR "Cardiotoxicity"[Title/Abstract] OR "Endocarditis"[Title/Abstract] OR "Heart Aneurysm"[Title/Abstract] OR "Heart Arrest"[Title/Abstract] OR "Heart Failure"[Title/Abstract] OR "Heart Neoplasms"[Title/Abstract] OR "Heart Rupture"[Title/Abstract] OR "Heart Valve Diseases"[Title/Abstract] OR "Myocardial Ischemia"[Title/Abstract] OR "Myocardial Stunning"[Title/Abstract] OR "Pericardial Effusion"[Title/Abstract] OR "Pericarditis"[Title/Abstract] OR "Pneumopericardium"[Title/Abstract] OR "Post-Cardiac Arrest Syndrome"[Title/Abstract] OR "Postpericardiotomy Syndrome"[Title/Abstract] OR "Pulmonary Heart Disease"[Title/Abstract] OR "Rheumatic Heart Disease"[Title/Abstract] OR "Ventricular Dysfunction"[Title/Abstract] OR "Ventricular Outflow Obstruction"[Title/Abstract] OR "Pregnancy Complications, Cardiovascular"[Title/Abstract] OR "Embolism, Amniotic Fluid"[Title/Abstract] OR "Vascular Diseases"[Title/Abstract] OR "Aneurysm"[Title/Abstract] OR "Aneurysm, False"[Title/Abstract] OR "Angiodysplasia"[Title/Abstract] OR "Angioedema"[Title/Abstract] OR "Angiomatosis"[Title/Abstract] OR "Aortic Diseases"[Title/Abstract] OR "Arterial Occlusive Diseases"[Title/Abstract] OR "Arteriovenous Malformations"[Title/Abstract] OR "Capillary Leak Syndrome"[Title/Abstract] OR "Cerebrovascular Disorders"[Title/Abstract] OR "Colitis, Ischemic"[Title/Abstract] OR "Compartment Syndromes"[Title/Abstract] OR "Diabetic Angiopathies"[Title/Abstract] OR "Embolism and Thrombosis"[Title/Abstract] OR "Hand-Arm Vibration Syndrome"[Title/Abstract] OR "Hemorrhoids"[Title/Abstract] OR "Hemostatic Disorders"[Title/Abstract] OR "Hepatic Veno-Occlusive Disease"[Title/Abstract] OR "Hyperemia"[Title/Abstract] OR "Hypertension"[Title/Abstract] OR "Hypotension"[Title/Abstract] OR "Mesenteric Ischemia"[Title/Abstract] OR "Myocardial Ischemia"[Title/Abstract] OR "Optic Neuropathy, Ischemic"[Title/Abstract] OR "Peliosis Hepatis"[Title/Abstract] OR "Penetrating Atherosclerotic Ulcer"[Title/Abstract] OR "Peripheral Vascular Diseases"[Title/Abstract] OR "Prehypertension"[Title/Abstract] OR "Pulmonary Veno-Occlusive Disease"[Title/Abstract] OR "Reperfusion Injury"[Title/Abstract] OR "Retinal Vein Occlusion"[Title/Abstract] OR "Scimitar Syndrome"[Title/Abstract] OR "Spinal Cord Vascular Diseases"[Title/Abstract] OR "Splenic Infarction"[Title/Abstract] OR "Stenosis, Pulmonary Vein"[Title/Abstract] OR "Superior Vena Cava Syndrome"[Title/Abstract] OR "Telangiectasis"[Title/Abstract] OR "Thoracic Outlet Syndrome"[Title/Abstract] OR "Varicocele"[Title/Abstract] OR "Varicose Veins"[Title/Abstract] OR "Vascular Fistula"[Title/Abstract] OR "Vascular Neoplasms"[Title/Abstract] OR "Vascular System Injuries"[Title/Abstract] OR "Vasculitis"[Title/Abstract] OR "Vasoplegia"[Title/Abstract] OR "Venous Insufficiency"[Title/Abstract]) NOT "Review"[Publication Type] NOT "Systematic Review"[Publication Type]

Scopus Research Query:

("Gastrointestinal Microbiome" OR "Microbiome, Gastrointestinal" OR "Gastrointestinal Microbial Community" OR "Gastrointestinal Microbial Communities" OR "Microbial Community, Gastrointestinal" OR "Gut Microbiome" OR "Gut Microbiomes" OR "Microbiome, Gut" OR "Gut Microflora" OR "Microflora, Gut" OR "Gastrointestinal Microflora" OR "Microflora, Gastrointestinal" OR "Gastrointestinal Flora" OR "Flora, Gastrointestinal" OR "Gut Flora" OR "Flora, Gut" OR "Gastrointestinal Microbiota" OR "Gastrointestinal Microbiotas" OR "Microbiota, Gastrointestinal" OR "Gut Microbiota" OR "Gut Microbiotas" OR "Microbiota, Gut" OR "Intestinal Microbiome" OR "Intestinal Microbiomes" OR "Microbiome, Intestinal" OR "Intestinal Flora" OR "Flora, Intestinal" OR "Intestinal Microbiota" OR "Intestinal Microbiotas" OR "Microbiota, Intestinal" OR "Intestinal Microflora" OR "Microflora, Intestinal" OR "Enteric Bacteria" OR "Bacteria, Enteric" OR "Gastric Microbiome" OR "Gastric Microbiomes" OR "Microbiome, Gastric") AND ("Cardiovascular Disease" OR "Disease, Cardiovascular" OR "Cardiac Events" OR "Cardiac Event" OR "Event, Cardiac" OR "Adverse Cardiac Event" OR "Adverse Cardiac Events" OR "Cardiac Event, Adverse" OR "Cardiac Events, Adverse" OR "Major Adverse Cardiac Events" OR "Cardiovascular Abnormalities" OR "Heart Defects, Congenital" OR "Vascular Malformations" OR "Cardiovascular Infections" OR "Endocarditis, Bacterial" OR "Syphilis, Cardiovascular" OR "Tuberculosis, Cardiovascular" OR "Heart Diseases" OR "Arrhythmias, Cardiac" OR "Carcinoid Heart Disease" OR "Cardiac Conduction System Disease" OR "Cardiac Output, High" OR "Cardiac Output, Low" OR "Cardiac Tamponade" OR "Cardiomegaly" OR "Cardiomyopathies" OR "Cardiotoxicity" OR "Endocarditis" OR "Heart Aneurysm" OR "Heart Arrest" OR "Heart Failure" OR "Heart Neoplasms" OR "Heart Rupture" OR "Heart Valve Diseases" OR "Myocardial Ischemia" OR "Myocardial Stunning" OR "Pericardial Effusion" OR "Pericarditis" OR "Pneumopericardium" OR "Post-Cardiac Arrest Syndrome" OR "Postpericardiotomy Syndrome" OR "Pulmonary Heart Disease" OR "Rheumatic Heart Disease" OR "Ventricular Dysfunction" OR "Ventricular Outflow Obstruction" OR "Pregnancy Complications, Cardiovascular" OR "Embolism, Amniotic Fluid" OR "Vascular Diseases" OR "Aneurysm" OR "Aneurysm, False" OR "Angiodysplasia" OR "Angioedema" OR "Angiomatosis" OR "Aortic Diseases" OR "Arterial Occlusive Diseases" OR "Arteriovenous Malformations" OR "Capillary Leak Syndrome" OR "Cerebrovascular Disorders" OR "Colitis, Ischemic" OR "Compartment Syndromes" OR "Diabetic Angiopathies" OR "Embolism and Thrombosis" OR "Hand-Arm Vibration Syndrome" OR "Hemorrhoids" OR "Hemostatic Disorders" OR "Hepatic Veno-Occlusive Disease" OR "Hyperemia" OR "Hypertension" OR "Hypotension" OR "Mesenteric Ischemia" OR "Myocardial Ischemia" OR "Optic Neuropathy, Ischemic" OR "Peliosis Hepatis" OR "Penetrating Atherosclerotic Ulcer" OR "Peripheral Vascular Diseases" OR "Prehypertension" OR "Pulmonary Veno-Occlusive Disease" OR "Reperfusion Injury" OR "Retinal

Vein Occlusion" OR "Scimitar Syndrome" OR "Spinal Cord Vascular Diseases" OR "Splenic Infarction" OR "Stenosis, Pulmonary Vein" OR "Superior Vena Cava Syndrome" OR "Telangiectasis" OR "Thoracic Outlet Syndrome" OR "Varicocele" OR "Varicose Veins" OR "Vascular Fistula" OR "Vascular Neoplasms" OR "Vascular System Injuries" OR "Vasculitis" OR "Vasoplegia" OR "Venous Insufficiency")

| Author                  | Year | Study type      | Clearly stated aim | Inclusion of consecutive patients | Prospective collection of data | End points appropriate to study aim | Unbiased assessment of Study end point | Follow-Up Period Appropriate to Study Aim | Less Than 5% Lost to Follow Up | Prospective Calculation of the Study Size | Adequate control group | Contemporary Groups | Baseline equivalence of Groups | Adequate Statistical analysis | Total MINORS score |
|-------------------------|------|-----------------|--------------------|-----------------------------------|--------------------------------|-------------------------------------|----------------------------------------|-------------------------------------------|--------------------------------|-------------------------------------------|------------------------|---------------------|--------------------------------|-------------------------------|--------------------|
| Beale et al[1]          | 2021 | Comparative     | 1                  | 1                                 | 2                              | 2                                   | 0                                      | 2                                         | 2                              | 0                                         | 2                      | 2                   | 1                              | 2                             | 17                 |
| Peng et al[2]           | 2023 | Comparative     | 2                  | 1                                 | 2                              | 2                                   | 0                                      | 0                                         | 2                              | 0                                         | 2                      | 2                   | 2                              | 2                             | 17                 |
| Sun et al[3]            | 2022 | Comparative     | 2                  | 1                                 | 2                              | 2                                   | 2                                      | 1                                         | 2                              | 0                                         | 2                      | 2                   | 2                              | 2                             | 20                 |
| Luedde et al[4]         | 2017 | Comparative     | 2                  | 1                                 | 2                              | 2                                   | 2                                      | 0                                         | 2                              | 0                                         | 2                      | 2                   | 2                              | 2                             | 19                 |
| Katsimichas et al[5]    | 2018 | Comparative     | 2                  | 2                                 | 2                              | 2                                   | 0                                      | 2                                         | 2                              | 0                                         | 2                      | 2                   | 1                              | 2                             | 19                 |
| Drapkina et al[6]       | 2022 | Comparative     | 2                  | 1                                 | 2                              | 2                                   | 0                                      | 2                                         | 2                              | 1                                         | 2                      | 2                   | 1                              | 2                             | 19                 |
| Yuzefpolskaya et al[7]  | 2020 | Non-comparative | 2                  | 1                                 | 2                              | 2                                   | 2                                      | 2                                         | 2                              | 0                                         | -                      | -                   | -                              | -                             | 13                 |
| Huang et al [8]         | 2022 | Comparative     | 2                  | 1                                 | 2                              | 2                                   | 0                                      | 1                                         | 2                              | 0                                         | 2                      | 2                   | 2                              | 2                             | 18                 |
| Kamo et al [9]          | 2017 | Comparative     | 2                  | 1                                 | 2                              | 2                                   | 0                                      | 0                                         | 2                              | 0                                         | 2                      | 2                   | 1                              | 2                             | 16                 |
| Pasini et al[10]        | 2016 | Comparative     | 2                  | 1                                 | 2                              | 2                                   | 2                                      | 0                                         | 2                              | 0                                         | 2                      | 2                   | 2                              | 2                             | 19                 |
| Yang et al [11]         | 2024 | Comparative     | 2                  | 1                                 | 2                              | 2                                   | 1                                      | 1                                         | 2                              | 0                                         | 2                      | 2                   | 2                              | 2                             | 19                 |
| Zhang et al[12]         | 2023 | Comparative     | 1                  | 1                                 | 2                              | 2                                   | 0                                      | 1                                         | 2                              | 0                                         | 2                      | 2                   | 2                              | 2                             | 17                 |
| Hayashi et al[13]       | 2018 | comparative     | 1                  | 1                                 | 2                              | 2                                   | 0                                      | 1                                         | 2                              | 0                                         | 2                      | 2                   | 2                              | 2                             | 17                 |
| Cui et al[14]           | 2018 | Comparative     | 2                  | 2                                 | 2                              | 1                                   | 0                                      | 0                                         | 2                              | 0                                         | 2                      | 2                   | 2                              | 2                             | 17                 |
| Modrego et al [15]      | 2023 | Non-comparative | 2                  | 2                                 | 2                              | 2                                   | 0                                      | 1                                         | 2                              | 0                                         | -                      | -                   | -                              | -                             | 11                 |
| Ahmad et al[16]         | 2023 | Comparative     | 2                  | 1                                 | 2                              | 2                                   | 0                                      | 1                                         | 2                              | 0                                         | 2                      | 2                   | 1                              | 2                             | 17                 |
| Wang et al [17]         | 2021 | Comparative     | 2                  | 1                                 | 2                              | 2                                   | 0                                      | 0                                         | 2                              | 0                                         | 2                      | 2                   | 2                              | 2                             | 17                 |
| Raju et al[18]          | 2024 | Comparative     | 2                  | 1                                 | 1                              | 2                                   | 0                                      | 0                                         | 2                              | 0                                         | 2                      | 2                   | 1                              | 2                             | 15                 |
| Kummen et al[19]        | 2018 | Comparative     | 1                  | 1                                 | 1                              | 1                                   | 0                                      | 0                                         | 2                              | 0                                         | 2                      | 2                   | 1                              | 2                             | 13                 |
| Romano et al[20]        | 2023 | Comparative     | 2                  | 1                                 | 2                              | 2                                   | 0                                      | 0                                         | 2                              | 0                                         | 2                      | 2                   | 1                              | 2                             | 16                 |
| Kinugasa et al [21]     | 2023 | Non-comparative | 2                  | 2                                 | 2                              | 2                                   | 0                                      | 2                                         | 2                              | 0                                         | -                      | -                   | -                              | -                             | 12                 |
| Zhou et al[22]          | 2022 | Non-comparative | 2                  | 2                                 | 2                              | 2                                   | 0                                      | 2                                         | 1                              | 0                                         | -                      | -                   | -                              | -                             | 11                 |
| Trøseid et al[23]       | 2014 | Comparative     | 2                  | 2                                 | 2                              | 2                                   | 0                                      | 2                                         | 1                              | 0                                         | 2                      | 2                   | 2                              | 2                             | 19                 |
| Mayerhofer et al[24]    | 2017 | Comparative     | 2                  | 2                                 | 2                              | 2                                   | 0                                      | 2                                         | 1                              | 0                                         | 2                      | 2                   | 2                              | 2                             | 19                 |
| Tang et al[25]          | 2014 | Non-comparative | 2                  | 1                                 | 2                              | 2                                   | 0                                      | 2                                         | 1                              | 0                                         | -                      | -                   | -                              | -                             | 10                 |
| Dong et al [26]         | 2021 | Comparative     | 2                  | 1                                 | 2                              | 2                                   | 1                                      | 1                                         | 2                              | 0                                         | 2                      | 2                   | 2                              | 2                             | 19                 |
| Tang et al [27]         | 2015 | Non-comparative | 2                  | 1                                 | 2                              | 2                                   | 0                                      | 2                                         | 2                              | 0                                         | -                      | -                   | -                              | -                             | 11                 |
| Yuzefpolskaya et al[28] | 2021 | Non-comparative | 2                  | 1                                 | 2                              | 2                                   | 0                                      | 2                                         | 1                              | 0                                         | -                      | -                   | -                              | -                             | 10                 |
| Zong et al [29]         | 2022 | Comparative     | 2                  | 2                                 | 2                              | 2                                   | 1                                      | 2                                         | 1                              | 0                                         | 2                      | 2                   | 1                              | 2                             | 19                 |
| Li et al [30]           | 2025 | Comparative     | 2                  | 2                                 | 2                              | 2                                   | 1                                      | 2                                         | 1                              | 0                                         | 2                      | 2                   | 1                              | 2                             | 19                 |
| Yafarova et al [31]     | 2024 | Comparative     | 2                  | 1                                 | 2                              | 2                                   | 1                                      | 2                                         | 1                              | 0                                         | 2                      | 2                   | 1                              | 2                             | 18                 |
| Kuan et al [32]         | 2026 | Comparative     | 2                  | 1                                 | 2                              | 2                                   | 1                                      | 1                                         | 1                              | 0                                         | 2                      | 2                   | 1                              | 2                             | 17                 |

Table 1:

The Methodological Index for Non-Randomized Studies (MINORS) grading results for the included articles in this systematic review. Each item is worth 0–2 points for a total of 16 points for non-comparative studies and 24 points for comparative studies.

1. Beale, A.L., et al., *The Gut Microbiome of Heart Failure With Preserved Ejection Fraction*. J Am Heart Assoc, 2021. **10**(13): p. e020654.
2. Peng, J., et al., *Characteristics of the fecal microbiome and metabolome in older patients with heart failure and sarcopenia*. Front Cell Infect Microbiol, 2023. **13**: p. 1127041.
3. Sun, W., et al., *Alterations of the Gut Microbiota in Patients With Severe Chronic Heart Failure*. Front Microbiol, 2021. **12**: p. 813289.
4. Luedde, M., et al., *Heart failure is associated with depletion of core intestinal microbiota*. ESC Heart Fail, 2017. **4**(3): p. 282-290.
5. Katsimichas, T., et al., *Non-Ischemic Heart Failure With Reduced Ejection Fraction Is Associated With Altered Intestinal Microbiota*. Circ J, 2018. **82**(6): p. 1640-1650.
6. Drapkina, O.M., et al., *Diversities in the Gut Microbial Patterns in Patients with Atherosclerotic Cardiovascular Diseases and Certain Heart Failure Phenotypes*. Biomedicines, 2022. **10**(11).
7. Yuzefpolskaya, M., et al., *Gut microbiota, endotoxemia, inflammation, and oxidative stress in patients with heart failure, left ventricular assist device, and transplant*. J Heart Lung Transplant, 2020. **39**(9): p. 880-890.
8. Huang, Z., et al., *Gut Microbiota in Heart Failure Patients With Preserved Ejection Fraction (GUMPTION Study)*. Front Cardiovasc Med, 2021. **8**: p. 803744.
9. Kamo, T., et al., *Dysbiosis and compositional alterations with aging in the gut microbiota of patients with heart failure*. PLoS One, 2017. **12**(3): p. e0174099.
10. Pasini, E., et al., *Pathogenic Gut Flora in Patients With Chronic Heart Failure*. JACC Heart Fail, 2016. **4**(3): p. 220-7.
11. Yang, C., et al., *Gut Microbiota as Predictive Biomarker for Chronic Heart Failure in Patients with Different Nutritional Risk*. J Cardiovasc Transl Res, 2024.
12. Zhang, Z., et al., *Alteration of the gut microbiota and metabolite phenylacetylglutamine in patients with severe chronic heart failure*. Front Cardiovasc Med, 2022. **9**: p. 1076806.
13. Hayashi, T., et al., *Gut Microbiome and Plasma Microbiome-Related Metabolites in Patients With Decompensated and Compensated Heart Failure*. Circ J, 2018. **83**(1): p. 182-192.
14. Cui, X., et al., *Metagenomic and metabolomic analyses unveil dysbiosis of gut microbiota in chronic heart failure patients*. Sci Rep, 2018. **8**(1): p. 635.
15. Modrego, J., et al., *Gut Microbiota and Derived Short-Chain Fatty Acids Are Linked to Evolution of Heart Failure Patients*. Int J Mol Sci, 2023. **24**(18).
16. Ahmad, A.F., et al., *Insights into the associations between the gut microbiome, its metabolites, and heart failure*. Am J Physiol Heart Circ Physiol, 2023. **325**(6): p. H1325-h1336.
17. Wang, Z., et al., *The Correlation between Gut Microbiota and Serum Metabolomic in Elderly Patients with Chronic Heart Failure*. Mediators Inflamm, 2021. **2021**: p. 5587428.
18. Raju, S.C., et al., *Microbial-derived imidazole propionate links the heart failure-associated microbiome alterations to disease severity*. Genome Med, 2024. **16**(1): p. 27.
19. Kummen, M., et al., *Gut Microbiota Signature in Heart Failure Defined From Profiling of 2 Independent Cohorts*. J Am Coll Cardiol, 2018. **71**(10): p. 1184-1186.
20. Romano, K.A., et al., *Gut Microbiota-Generated Phenylacetylglutamine and Heart Failure*. Circ Heart Fail, 2023. **16**(1): p. e009972.
21. Kinugasa, Y., et al., *Trimethylamine N-oxide and outcomes in patients hospitalized with acute heart failure and preserved ejection fraction*. ESC Heart Fail, 2021. **8**(3): p. 2103-2110.
22. Zhou, X., et al., *Trimethylamine N-oxide and cardiovascular outcomes in patients with chronic heart failure after myocardial infarction*. ESC Heart Fail, 2020. **7**(1): p. 188-193.
23. Trøseid, M., et al., *Microbiota-dependent metabolite trimethylamine-N-oxide is associated with disease severity and survival of patients with chronic heart failure*. J Intern Med, 2015. **277**(6): p. 717-26.
24. Mayerhofer, C.C.K., et al., *Increased Secondary/Primary Bile Acid Ratio in Chronic Heart Failure*. J Card Fail, 2017. **23**(9): p. 666-671.
25. Tang, W.H., et al., *Prognostic value of elevated levels of intestinal microbe-generated metabolite trimethylamine-N-oxide in patients with heart failure: refining the gut hypothesis*. J Am Coll Cardiol, 2014. **64**(18): p. 1908-14.
26. Dong, Z., et al., *Trimethylamine N-Oxide is Associated with Heart Failure Risk in Patients with Preserved Ejection Fraction*. Lab Med, 2021. **52**(4): p. 346-351.
27. Tang, W.H., et al., *Intestinal microbiota-dependent phosphatidylcholine metabolites, diastolic dysfunction, and adverse clinical outcomes in chronic systolic heart failure*. J Card Fail, 2015. **21**(2): p. 91-6.
28. Yuzefpolskaya, M., et al., *Levels of Trimethylamine N-Oxide Remain Elevated Long Term After Left Ventricular Assist Device and Heart Transplantation and Are Independent From Measures of Inflammation and Gut Dysbiosis*. Circ Heart Fail, 2021. **14**(6): p. e007909.
29. Zong, X., et al., *Trimethyllysine, a trimethylamine N-oxide precursor, predicts the presence, severity, and prognosis of heart failure*. Front Cardiovasc Med, 2022. **9**: p. 907997.
30. Li, X., et al., *Multi-omics data improves one-year mortality prediction in acute heart failure*. Clin Chim Acta, 2026. **579**: p. 120669.
31. Yafarova, A.A., et al., *Gut Microbiota and Metabolic Alterations Associated with Heart Failure and Coronary Artery Disease*. International Journal of Molecular Sciences, 2024. **25**(20): p. 11295.
32. Kuan, S.W., et al., *Gut Microbiota-Derived Metabolite and Heart Failure with Reduced Ejection Fraction (HFrEF): Elevated Trimethylamine N-Oxide (TMAO) as a Potential Biomarker*. Int J Mol Sci, 2026. **27**(2).

# PRISMA 2020 Checklist

| Section and Topic             | Item # | Checklist item                                                                                                                                                                                                                                                                                       | Location where item is reported                          |
|-------------------------------|--------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------|
| <b>TITLE</b>                  |        |                                                                                                                                                                                                                                                                                                      |                                                          |
| Title                         | 1      | Identify the report as a systematic review.                                                                                                                                                                                                                                                          | Title Page –Page 1                                       |
| <b>ABSTRACT</b>               |        |                                                                                                                                                                                                                                                                                                      |                                                          |
| Abstract                      | 2      | See the PRISMA 2020 for Abstracts checklist.                                                                                                                                                                                                                                                         | Abstract Section – page 1                                |
| <b>INTRODUCTION</b>           |        |                                                                                                                                                                                                                                                                                                      |                                                          |
| Rationale                     | 3      | Describe the rationale for the review in the context of existing knowledge.                                                                                                                                                                                                                          | Introduction Section – page 2                            |
| Objectives                    | 4      | Provide an explicit statement of the objective(s) or question(s) the review addresses.                                                                                                                                                                                                               | Introduction Section – page 3                            |
| <b>METHODS</b>                |        |                                                                                                                                                                                                                                                                                                      |                                                          |
| Eligibility criteria          | 5      | Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses.                                                                                                                                                                                          | Methods – Eligibility Criteria – page 14                 |
| Information sources           | 6      | Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted.                                                                                            | Methods – Search Strategy – page 14                      |
| Search strategy               | 7      | Present the full search strategies for all databases, registers and websites, including any filters and limits used.                                                                                                                                                                                 | Methods - Search Strategy - Supplementary Material 1     |
| Selection process             | 8      | Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process.                     | Methods -Screening – page 15                             |
| Data collection process       | 9      | Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process. | Methods - Data Extraction – page 15                      |
| Data items                    | 10a    | List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect.                        | Methods - Data Extraction – page 15                      |
|                               | 10b    | List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information.                                                                                         | Methods - Data Extraction – page 15                      |
| Study risk of bias assessment | 11     | Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process.                                    | Methods -Quality Assessment – page 15                    |
| Effect measures               | 12     | Specify for each outcome the effect measure(s) (e.g., risk ratio, mean difference) used in the synthesis or presentation of results.                                                                                                                                                                 | Materials and Methods – Data extraction-Page 4           |
| Synthesis methods             | 13a    | Describe the processes used to decide which studies were eligible for each synthesis (e.g. tabulating the study intervention characteristics and comparing against the planned groups for each synthesis (item #5)).                                                                                 | Materials and Methods - Data Extraction – page 4         |
|                               | 13b    | Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions.                                                                                                                                                | Methods- Data Extraction- Page 15                        |
|                               | 13c    | Describe any methods used to tabulate or visually display results of individual studies and syntheses.                                                                                                                                                                                               | Methods -Data Extraction – Page 15-Meta-analysis-Page 16 |
|                               | 13d    | Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used.                                          | Methods -Data Extraction – Page 15-Meta-analysis-Page 16 |
|                               | 13e    | Describe any methods used to explore possible causes of heterogeneity among study results (e.g. subgroup analysis,                                                                                                                                                                                   | Not Applicable                                           |

# PRISMA 2020 Checklist

| Section and Topic             | Item # | Checklist item                                                                                                                                                                                                                                                                       | Location where item is reported                  |
|-------------------------------|--------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------|
|                               |        | meta-regression).                                                                                                                                                                                                                                                                    |                                                  |
|                               | 13f    | Describe any sensitivity analyses conducted to assess robustness of the synthesized results.                                                                                                                                                                                         | Not Applicable                                   |
| Reporting bias assessment     | 14     | Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases).                                                                                                                                                              | Not Applicable                                   |
| Certainty assessment          | 15     | Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome.                                                                                                                                                                                | Not Applicable                                   |
| <b>RESULTS</b>                |        |                                                                                                                                                                                                                                                                                      |                                                  |
| Study selection               | 16a    | Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram.                                                                                         | Results - PRISMA Flow Diagram – Figure 1-Page 24 |
|                               | 16b    | Cite studies that might appear to meet the inclusion criteria, but which were excluded, and explain why they were excluded.                                                                                                                                                          | Results - Study Characteristics-Page 4 –         |
| Study characteristics         | 17     | Cite each included study and present its characteristics.                                                                                                                                                                                                                            | Results - Study Characteristics-Page 4           |
| Risk of bias in studies       | 18     | Present assessments of risk of bias for each included study.                                                                                                                                                                                                                         | Results – Quality Assessment – page 3            |
| Results of individual studies | 19     | For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimates and its precision (e.g. confidence/credible interval), ideally using structured tables or plots.                                                    | Results - Table 2 and 3 – Page 31 &40            |
| Results of syntheses          | 20a    | For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies.                                                                                                                                                                               | Supplementary material-table 1                   |
|                               | 20b    | Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect. | Results-Page 3,4,5,6,7,8                         |
|                               | 20c    | Present results of all investigations of possible causes of heterogeneity among study results.                                                                                                                                                                                       | Not applicable                                   |
|                               | 20d    | Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results.                                                                                                                                                                           | Results-Page-8 & 36                              |
| Reporting biases              | 21     | Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed.                                                                                                                                                              | Results-Quality Assessment-Page-3                |
| Certainty of evidence         | 22     | Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed.                                                                                                                                                                                  | Not applicable                                   |
| <b>DISCUSSION</b>             |        |                                                                                                                                                                                                                                                                                      |                                                  |
| Discussion                    | 23a    | Provide a general interpretation of the results in the context of other evidence.                                                                                                                                                                                                    | Discussion -Page 10 till 14                      |
|                               | 23b    | Discuss any limitations of the evidence included in the review.                                                                                                                                                                                                                      | Discussion –Page 13 and 14                       |
|                               | 23c    | Discuss any limitations of the review processes used.                                                                                                                                                                                                                                | Discussion –Page 13 and 14                       |
|                               | 23d    | Discuss implications of the results for practice, policy, and future research.                                                                                                                                                                                                       | Discussion – Conclusion-Page 14                  |
| <b>OTHER INFORMATION</b>      |        |                                                                                                                                                                                                                                                                                      |                                                  |
| Registration and protocol     | 24a    | Provide registration information for the review, including register name and registration number, or state that the review was not registered.                                                                                                                                       | Not applicable                                   |
|                               | 24b    | Indicate where the review protocol can be accessed, or state that a protocol was not prepared.                                                                                                                                                                                       | Not available                                    |
|                               | 24c    | Describe and explain any amendments to information provided at registration or in the protocol.                                                                                                                                                                                      | Not applicable                                   |

# PRISMA 2020 Checklist

| Section and Topic                              | Item # | Checklist item                                                                                                                                                                                                                             | Location where item is reported |
|------------------------------------------------|--------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------|
| Support                                        | 25     | Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review.                                                                                                              | Page 17                         |
| Competing interests                            | 26     | Declare any competing interests of review authors.                                                                                                                                                                                         | Page 17                         |
| Availability of data, code and other materials | 27     | Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review. | Reference section-Page 17       |

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. This work is licensed under CC BY 4.0. To view a copy of this license, visit <https://creativecommons.org/licenses/by/4.0/>