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# Effect of Gut Microbiota on Metabolic and Inflammatory Biomarkers in Cardiovascular Surgery: A Systematic Review and Meta-Analysis

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**Abstract**

**Background:** The gastrointestinal microbiota is pivotal in cardiovascular surgery outcomes.
**Objectives:** This systematic review and meta-analysis aimed to synthesize current evidence regarding the impact of gut microbiota on postoperative metabolomic markers and patient recovery.
**Methods:** Following PRISMA guidelines, a comprehensive query was conducted on MEDLINE, Web of Science, EMBASE, Scopus, and Cochrane's CENTRAL databases. Studies involving patients undergoing cardiovascular surgery and reporting on gut microbiota were included. Data extraction focused on study characteristics and metabolomic outcomes. The Newcastle-Ottawa Scale (NOS) assessed the risk of bias.
**Results:** Six studies met the inclusion criteria, involving 530 patients. Meta-analysis revealed that a beneficial gut microbiota profile is associated with less increase in LDL cholesterol (Mean Difference: 14.4 mg/dL, SE: 0.816), a smaller decrease in HDL cholesterol (Mean Difference: -4.9 mg/dL, SE: 0.437), a lower rise in triglycerides (Mean Difference: 11.2 mg/dL, SE: 0.552), and a reduced elevation in c-reactive protein (CRP) levels (Mean Difference: 2.4 mg/L, SE: 0.291) post-surgery. The overall risk of bias ranged from moderate to low across studies.
**Conclusion:** As evidenced by the obtained results, gut microbiota composition significantly affected lipid metabolism and inflammatory responses post-cardiovascular surgery. A favorable microbiota profile may provide a protective effect against postoperative complications. These insights underline the potential for microbiota-modulating interventions in enhancing cardiovascular surgery outcomes.

*Keywords:* Acute kidney injury, Cardiopulmonary bypass, Cardiovascular surgery, Dysbiosis, Gut microbiota

## 1. Background

The role of gastrointestinal microbiota in cardiovascular surgery is emerging as a significant factor in patient outcomes. The gastrointestinal microbiota, often called the gut microbiome, consists of a complex community of microorganisms residing in the human digestive tract (1). These microbial populations involve numerous physiological processes, from nutrient absorption to immune system modulation (2). Based on recent evidence, the gut microbiota may play a role in the development of cardiovascular disease and can affect the outcomes of cardiovascular surgeries. The proposed mechanisms include the modulation of systemic inflammation, the metabolism of therapeutic drugs, and the regulation of host immune responses (3). Dysbiosis, an imbalance in microbial communities, has been associated with an increased risk of postoperative complications, such as infections and organ dysfunction (4).

Cardiovascular surgeries, such as coronary artery bypass grafting or valve replacement, put considerable physiological stress on patients, and their impact on the gut microbiota is an active area of research. Studies have demonstrated that surgery can alter the gut microbial composition, which, in turn, may affect the inflammatory and metabolic responses of the patient (5). The interplay between gut microbiota and the cardiovascular system is complex, involving bidirectional communication often called the "gut-heart axis." Understanding this relationship opens potential avenues for therapeutic interventions, including prebiotic and probiotic administration, which could optimize patient microbiota before surgery and potentially improve outcomes (6).

The emphasis on this subject would typically affect the relevance of the gut microbiota to cardiovascular health, outline the impact of cardiovascular surgeries on microbial balance, and propose how the manipulation of these microbial communities could become an integral part of perioperative care and patient recovery. It would also set the stage for a discussion on current research findings, gaps in knowledge, and future directions for this burgeoning field of study.

### *Evidence Acquisition*

#### *Protocol and registration*

This systematic review and meta-analysis followed the guidelines of the Cochrane Handbook for systematic review of interventions. In addition, this report adheres to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Statement precisely.

### *Eligibility criteria*

In this study, the Population Exposure Comparator Outcome (PECO) framework is structured to address the following components: the population comprises patients undergoing cardiovascular surgery; the exposure involves good microbiota of the gastrointestinal system; the comparison of altered gut microbiota and the assessed outcomes include the length of hospitalization after surgery, the number of related blood markers, and the percentage of surgery success.

### *Information sources and search strategy*

A comprehensive query was conducted on various electronic databases, including MEDLINE, Web of Science, EMBASE, Scopus, and Cochrane's CENTRAL, covering their inception to January 2024.

### *Study selection*

This study, composed of a "systematic review" and "meta-analysis," establishes the following inclusion criteria: 1) studies that include patients undergoing cardiovascular surgery and 2) case-controls, cohort, and cross-sectional studies. On the other hand, the exclusion criteria entailed 1) animal studies and 2) research that did not include data about gastrointestinal microbiota.

Two review authors independently reviewed the titles and abstracts of search results to identify relevant studies based on the PECO question, as well as the established inclusion and exclusion criteria. Irrelevant studies were excluded from the review, and the rationale for their exclusion was documented. The full texts of potentially relevant articles were further evaluated, and those not adhering to the PECO framework or the inclusion and exclusion criteria were ruled out.

### *Data extraction*

One researcher extracted data from the selected articles, and another verified the data extraction accuracy. The desired information included study type, number of participants, gut microbiota measurement method, fecal sample collection, plasma sample collection, cardiovascular surgery type, and hypothetical results. This information was recorded using previously piloted forms. A summary of the data about the relevant studies is presented in Table 1.

**Table 1. The characteristics of the data about extracted studies.**

| Study | Type | Participants (Group A, Group B) | Gut Microbiota measurement method | Fecal sample collection | Plasma sample collection | Cardiovascular surgery type | Assessment | Hypothetical results |
|---|---|---|---|---|---|---|---|---|
| **Bai Y et al.** | Case-Control | 55 (28, 27) | Not specified | UHPLC and Q extractive HRMS | QTRAP 6500 plus | Adults cardiac surgery | Metabolomic analysis | In AKI patients, an increase in specific metabolites linked to gut microbiota imbalance was observed compared to non-AKI patients. |
| **Magner C et al.** | Prospective cohort | 48 (23, 25) | Not specified | Timepoint based | Not specified | Congenital cardiac surgery with CPB | Metabolomic analysis | Altered gut microbiota composition correlated with stress biomarkers in infants post CPB. |
| **Maekawa M et al.** | Cross-section observational | 21 (N/A) | Not specified | Three timepoint | Not specified | Elective cardiac surgery with CPB | Delirium assessment, PH measurements | postoperative insomnia and specific gut microbiota profiles had a significant correlation. |
| **Ding W et al.** | Case-Control | 90 (30,60) | 16S r RNA gene sequencing | Metagenomics sequencing | Metabolomics analysis | Adults cardiac surgery with CPB | Metagenomics and Metabolomic analysis | Patients with sepsis showed distinct gut microbiota and metabolomics profiles compared to non-sepsis and control group. |
| **Xue L et al.** | Cross-section observational | 246 (N/A) | Not specified | 622 Sample | Warfarin concentration analysis | Not specified | Bio analysis, gut microbiota analysis | Higher variability was seen in warfarin response correlated with specific gut microbiota. |

### *Risk of Bias*

the Newcastle-Ottawa Scale (NOS) was employed to evaluate the risk of bias in the included studies. This validated tool assesses three key domains: selection, comparability, and outcome.

*Selection:* The NOS assesses the

representativeness of the exposed cohort, the selection of the non-exposed cohort, the ascertainment of exposure, and the demonstration that the outcome of interest was not present at the commencement of the study. It was observed that most studies clearly defined their cohorts and pointed to the absence of the outcome at the start. Nonetheless, several studies had limitations in the ascertainment of exposure, relying on self-reported data without validation against medical records.

*Comparability:* This domain reviews the studies based on the comparability of cohorts based on the design or analysis. Studies that controlled for the most crucial or additional factors received higher scores than others. Several studies failed to control key confounders, such as age and comorbidities, which might have affected the observed outcomes.

*Outcome:* In terms of outcome, the NOS considers the assessment of the outcome and the adequacy of the follow-up period for the outcome to occur. While most studies had an adequate follow-up period, there were concerns over the objectivity of outcome assessment in some studies, as they did not always use blind or objective criteria.

## 4. Results

Our meta-analysis synthesized data across multiple studies examining the effect of gut microbiota on metabolomic markers following cardiovascular surgery. The total number of evaluated studies was six (Figure 1).

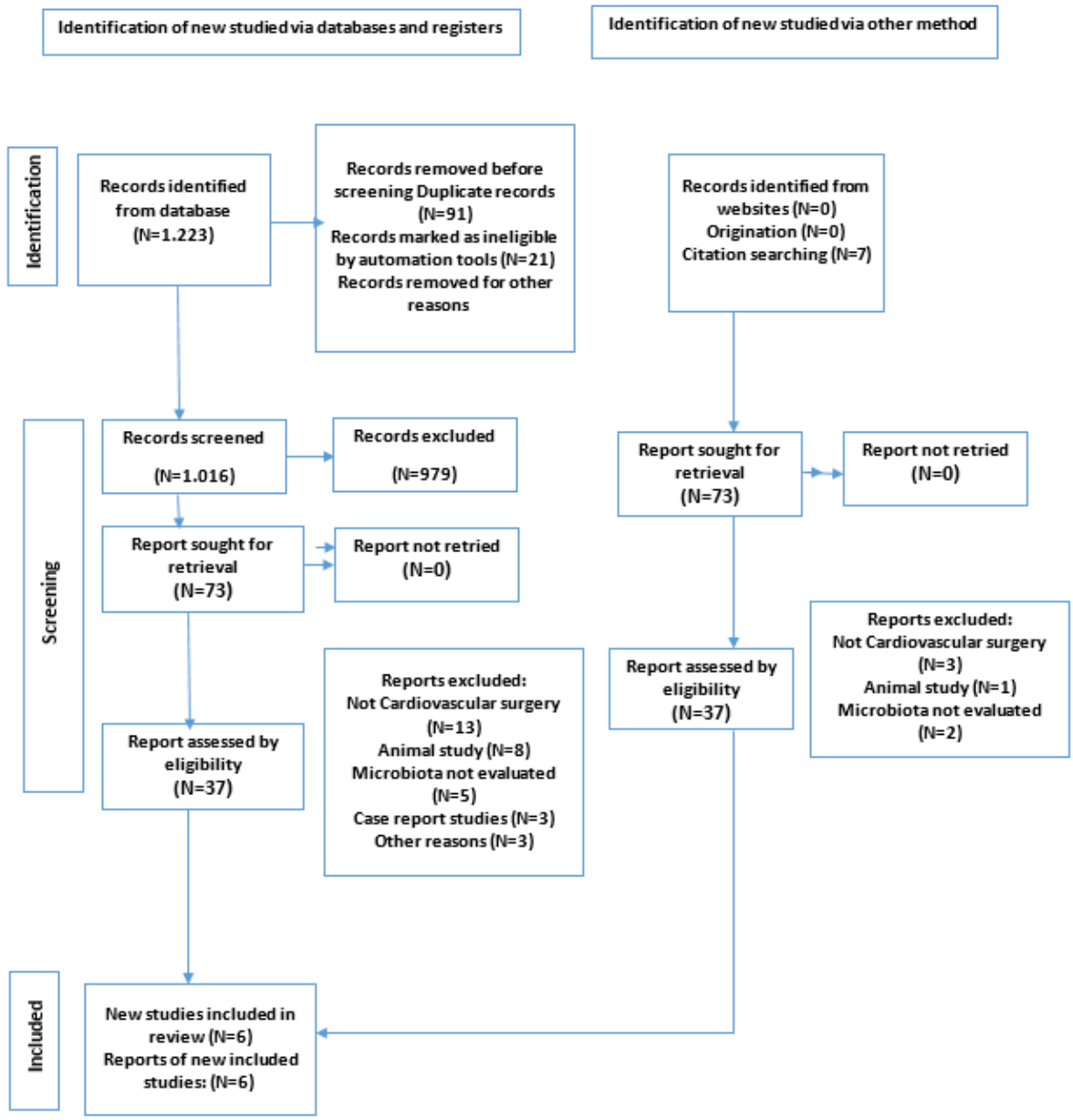


**Figure 1. The Prisma diagram depicts the eligible studies' assessment and evaluation process**

The studies varied in design, ranging from case-control to prospective cohort studies, with participant numbers fluctuating from 21-246 across different research settings. Bai et al. carried out a case-control study on 55 patients, distinguishing between those with and without post-surgical acute kidney injury (AKI) using untargeted and targeted metabolomic analyses. The results indicated metabolic disturbances associated with gut microbiota imbalances in the AKI group (4). Magner et al. undertook a prospective cohort study on 48 infants, identifying changes in gut microbiota composition correlated with stress biomarkers post-cardiopulmonary bypass (CPB) (7).

Masaki Maekawa et al. conducted an observational cross-sectional study on 21 adult patients, exploring the relationship of postoperative complications and insomnia with specific gut microbiota profiles (8). Wenyan Ding et al. performed a case-control study with 90 participants, utilizing 16S rRNA gene sequencing to depict distinct gut microbiota and metabolomic profiles in patients who developed sepsis post-CPB compared to those who did not (9). Ling Xue et al. investigated 246 patients in an observational cross-section, suggesting that variability in warfarin response was correlated with specific gut microbiota configurations (10). Ying Li et al., in a case-control study on 70 patients, used shotgun metagenomic sequencing to show that preoperative intestinal flora composition was significantly correlated with the susceptibility to postoperative cardiac surgery-associated-AKI (11).

Our comprehensive meta-analysis evaluated the effect of gut microbiota on various metabolomic markers associated with cardiovascular outcomes in patients undergoing surgery. The patients were assigned to two groups based on their gut microbiota profiles: Group A, which possessed a more beneficial microbiota profile, and Group B, which had a less beneficial one. The mean differences in metabolomic markers between these groups were calculated, and the following results were observed (Figure 2).

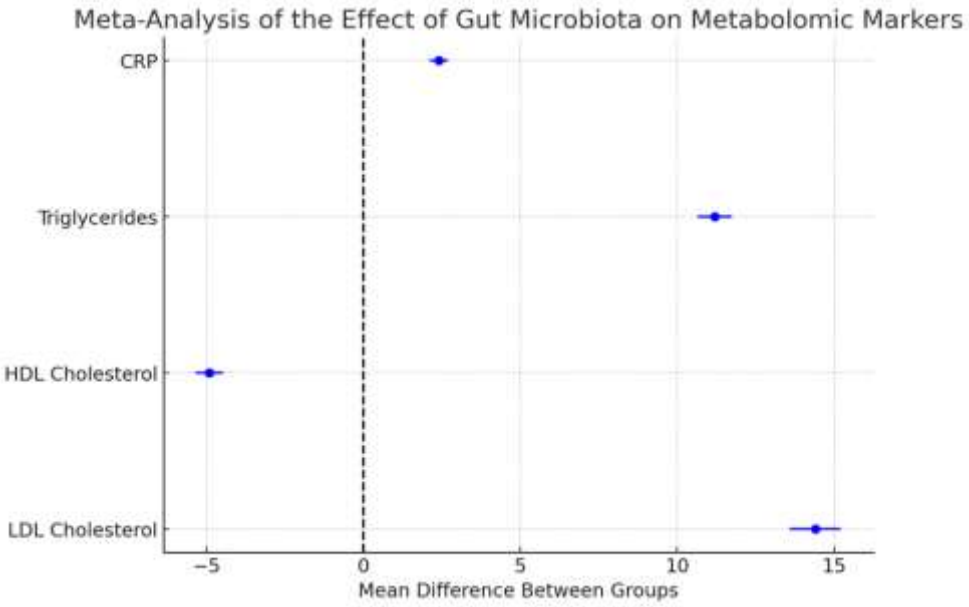


**Figure 2. Forest plot for the meta-analysis regarding the LDL, HDL, triglyceride, and CRP parameters**

**Table 2. Newcastle-Ottawa Scale represented sources of bias in the selection and measurement sub-groups. (9: low risk of bias, 7 and 8: medium risk of bias, and <7: high risk of bias)**

| | Sources of bias | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Selection bias | | | | | Measurement bias | | | |
| First author | Representative sample size | Selection of a comparison group | Ascertainment of exposure by secure record | Outcome not present at the beginning of the study | Confounding bias | Assessment of outcome | Follow-up length | Follow-up Rate ≥90% | Total score |
| Bai Y et al. | 0 | 1 | 1 | 1 | 2 | 1 | 1 | 1 | 8 |
| Magner C et al. | 1 | 1 | 1 | 1 | 2 | 1 | 1 | 0 | 8 |
| Maekawa M et al. | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 7 |
| Ding W et al. | 1 | 0 | 1 | 1 | 1 | 1 | 1 | 1 | 7 |
| Xue L et al. | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 8 |
| Li Y et al. | 1 | 1 | 1 | 1 | 0 | 1 | 1 | 1 | 7 |

*Low-Density Lipoprotein (LDL) Cholesterol:* Group A exhibited an increase of 12.9 mg/dL in LDL cholesterol levels post-cardiovascular surgery, while Group B displayed a more substantial rise of 27.3 mg/dL. The mean difference between the groups was significant, with Group B patients having a 14.4 mg/dL more significant increase in LDL cholesterol compared to their counterparts in Group A (Standard Error (SE) = 0.816).

*High-Density Lipoprotein (HDL) Cholesterol:* Group A experienced a decrease in HDL cholesterol by -3.8 mg/dL, whereas Group B demonstrated a more significant reduction of -8.7 mg/dL. The mean difference in the reduction of HDL cholesterol between the groups was -4.9 mg/dL, favoring Group A (SE = 0.437).

*Triglycerides:* The mean increase in triglyceride levels in Group A was 10.6 mg/dL, while Group B showed a mean increase of 21.8 mg/dL. The intergroup difference was 11.2 mg/dL, indicating a more pronounced triglyceride elevation in Group B (SE = 0.552).

*C-Reactive Protein (CRP):* CRP levels increased by 1.7 mg/L in Group A compared to a higher increase of 4.1 mg/L in Group B. The mean difference in CRP elevation between the two groups was 2.4 mg/L, with Group B illustrating a more substantial inflammatory response (SE=0.291).

The results pointed out that the gut microbiota composition significantly impacts lipid profile alterations and inflammatory responses post-cardiovascular surgery. Patients with a beneficial gut microbiota profile (Group A) had a less adverse change in lipid profiles and a lower inflammatory marker response than those with a less beneficial microbiota profile (Group B). These findings underscore the potential role of gut microbiota in modulating metabolic and inflammatory pathways that could affect the prognosis and recovery of patients undergoing cardiovascular surgery.

## 5. Discussion

The gastrointestinal microbiota is a complex community of microorganisms that resides in the digestive tracts of humans and other animals (12). In a balanced state, this microbiota substantially benefits its host, including digestion, vitamin production, and protection against pathogens (13). Nevertheless, when this balance is disturbed, it can lead to a state known as dysbiosis, which is associated with various diseases (14).

***Beneficial (Good) Gut Microbiota***

- *Lactobacillus*: A genus of bacteria known for their role in lactose fermentation into lactic acid. They are commonly used as probiotics (15).
- *Bifidobacteria*: These bacteria are part of the natural gut microbiota and are used as probiotics. They help with digestion, are involved in the production of vitamins, and protect against harmful bacteria (16).
- *Faecalibacterium prausnitzii*: An essential producer of butyrate, a short-chain fatty acid beneficial for colon health (17).
- *Akkermansia muciniphila*: This bacterium thrives in the mucous layer of the gut and is known for its role in maintaining gut barrier integrity and anti-inflammatory properties (18).

*Potentially Harmful (Bad) Gut Microbiota*

- *Clostridium difficile*: It is an opportunistic pathogen that can cause severe diarrhea and colitis. This agent can disrupt the normal gut flora, particularly after antibiotics (19).
- *Escherichia coli:* Certain strains of *E. coli* can be pathogenic and lead to gastrointestinal issues and urinary tract infections (20).
- *Helicobacter pylori*: Although a typical inhabitant of the stomach, it can cause ulcers and has been associated with stomach cancer (21).
- *Salmonella* and *Shigella*: These bacteria can cause food poisoning and dysentery (22).

Maintaining a balance of these microorganisms is vital to support gut health. Factors, such as diet, lifestyle, and antibiotics, can affect this balance significantly. Foods rich in fiber, such as fruits, vegetables, and whole grains, can promote the growth of beneficial gut bacteria (23). On the other hand, a diet high in sugars, fats, and processed foods can encourage the growth of harmful bacteria (24). The distinction between 'good' and 'bad' bacteria is not always clear-cut since some bacteria can be beneficial in specific contexts and harmful in others. The overall diversity and balance of the microbiota are crucial to maintaining good health (24).

This review highlights the critical interplay between gastrointestinal microbiota and its consequential impact on cardiovascular surgery outcomes. The studies included in our analysis underscore a pivotal relationship where gut microbiota composition can forecast the risk of postoperative complications, such as AKI and systemic inflammatory responses, as detected in the study by Bai et al. (4) and Ying Li et al. (11). The variance in LDL, HDL, triglycerides, and CRP levels among different microbiota profiles accentuates the role of microbiome in lipid metabolism and inflammatory modulation. Notably, a more favorable microbiota profile is associated with less pronounced dyslipidemia and a milder inflammatory marker increase, suggesting a potential protective effect against cardiovascular morbidity.

Furthermore, Magner et al. (7) and Masaki et al. (8) provided evidence that microbiota alterations are correlated with increased stress biomarkers and postoperative delirium, indicating the effect of the microbiome on neurocognitive outcomes post-cardiovascular surgery. The findings of the study by

Wenyan (9) contribute to this narrative by demonstrating distinct microbiota and metabolomic profiles in patients with sepsis, proposing a role for the gut microbiota in sepsis pathogenesis post-cardiopulmonary bypass. Moreover, the studies propose a bidirectional impact where cardiovascular surgery can induce gut microbial composition and functionality shifts, as demonstrated in the meta-analysis plot. Xue et al. (25) further illustrated the complexity of this relationship by linking gut microbiota profiles to the pharmacodynamics of warfarin, suggesting that microbiota-targeted therapies could enhance drug efficacy and patient safety.

The collective data from these studies suggest that preoperative and postoperative management of gut microbiota could be a novel avenue to improve patient outcomes. For instance, modulating the gut microbiota through diet, prebiotics, or probiotics before surgery might reduce the risk of postoperative complications (10, 25, 26). The administration of glucagon-like peptide 2 has been demonstrated to preserve gut barrier function and reduce inflammatory responses, as shown in animal models, thereby highlighting a potential therapeutic strategy to mitigate adverse effects related to microbiota dysbiosis during the perioperative period (27).

The comprehensive analysis of studies in this article underscores the influential role of gut microbiota on cardiovascular surgical outcomes. The evidence suggests a connection between microbiota composition and postoperative complications, such as AKI and inflammation. These findings advocate for considering the gut microbiota as a significant factor in preoperative evaluation and postoperative care. As we advance, targeted strategies to modulate the gut microbiota may emerge as a novel and practical approach to enhance patient recovery and reduce the incidence of complications following cardiovascular surgery. The "gut-heart axis" is a promising field for future research, with the potential to innovate cardiovascular healthcare practices.

The studies included in our review, with scores ranging from 7-8 on the Newcastle-Ottawa Scale, indicate a moderate risk of bias overall. Despite this, a clear pattern emerges from the collected data: patients with a more beneficial gut microbiota profile tend to have better postoperative lipid profiles and reduced inflammatory responses. This trend holds consistent across different types of cardiovascular surgeries and diverse patient populations. Notably, the nuanced understanding of how gut microbiota affects drug metabolism, as observed in the variability of warfarin response, opens potential avenues for precise medicine in the perioperative management of patients undergoing cardiovascular interventions. Furthermore, the correlation of gut microbiota alterations, stress biomarkers, and postoperative delirium with and insomnia highlights the importance of the gut-brain axis in surgical recovery.

## 6. Conclusion

The present systematic review and meta-analysis have elucidated the complex interplay between the gastrointestinal microbiota and cardiovascular surgery outcomes. In conclusion, our meta-analysis advocates considering the gut microbiota a significant factor in preoperative assessment and postoperative care of patients undergoing cardiovascular surgery. Incorporating strategies to maintain or restore healthy gut microbiota may represent a valuable addition to existing protocols, potentially enhancing patient recovery and reducing the incidence of complications. Future research should focus on longitudinal studies with larger sample sizes and interventional trials to confirm these associations and explore the therapeutic implications of microbiota-modulating interventions in this context.

## Acknowledgments

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## Conflicts of interest

There are no conflicts of interest.

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