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Meta-analysis of the effect of probiotics or synbiotics on the risk factors in patients with coronary artery disease

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Objective: The objective of this study was to study the effect of probiotics or synbiotics on the risk factors for coronary artery disease (CAD) in the context of conventional drug therapy for CAD.

Methods: The literature on probiotics or synbiotics for the treatment of CAD was collected from PubMed, Scopus, Web of Science, Embase, and Cochrane Library. The search period was conducted on November 5, 2022, and the search covered all literature before November 5, 2022. The included literature consisted of randomized controlled trials of probiotics or synbiotics for CAD, and a meta-analysis was performed using Stata 14 software and RevMan 5.4 software.

Results: The meta-analysis explored the effect of probiotics or synbiotics on the risk factors for coronary artery lesions in a treatment setting with conventional medications for CAD. After a rigorous literature screening process, 10 studies were finally included for data consolidation to objectively evaluate the effect of probiotics or synbiotics on coronary lesions. The results of this study showed that the addition of probiotics or synbiotics to conventional medications for CAD reduced the levels of low-density lipoprotein cholesterol [weighted mean difference (WMD) -9.13 (-13.17 , -5.09)], fasting glucose (FPG) [WMD -13.60 (-23.57 , -3.62)], and hypersensitive C-reactive protein (hs-CRP) [standardized mean difference (SMD) -0.60 (-0.83 , -0.37)] and increased the levels of high-density lipoprotein cholesterol (HDL-C) [WMD 1.94 (0.32 , 3.57)], nitric oxide (NO) [WMD 5.38 (3.23 , 7.54)] but did not affect the triglyceride (TG) level [WMD -13.41 (-28.03 , 1.21)], systolic blood pressure (SBP) [WMD -0.88 (-3.72 , 1.96)], or diastolic blood pressure (DBP) [WMD -0.21 (-2.19 , 1.76)].

Conclusion: Adding probiotics or synbiotics to conventional medications for CAD may improve patient prognosis.

Systematic Review Registration: <https://www.crd.york.ac.uk/PROSPERO/>, identifier CRD42022362711.

KEYWORDS

coronary artery disease, probiotics, synbiotics, meta-analysis, coronary atherosclerosis

1. Introduction

Coronary artery disease (CAD) is a cardiovascular disease characterized by a chronic inflammatory response and plaque accumulation, eventually leading to myocardial ischemia, hypoxia, or necrosis. It is one of the leading causes of death in patients. Hypertension, diabetes mellitus, hyperlipidemia, and long-term chronic inflammatory response are the important risk factors for CAD (1). Although conventional drugs for CAD have achieved good results in delaying coronary artery

lesions, the morbidity and mortality of patients with CAD are still increasing (2). Therefore, further controlling the risk factors of coronary artery lesions is of great importance in improving the prognosis of patients.

Probiotics or synbiotics are living microorganisms and are used as non-invasive therapeutic tools. They have been found to delay the progression of coronary artery lesions through the “entero-cardiac axis,” providing new insights to improve the prognosis of patients with CAD (3, 4). The use of probiotics or synbiotics to modulate the gut microbiota in patients with CAD may reduce the risk factors for CAD, such as hypersensitive C-reactive protein (hs-CRP), nitric oxide (NO), low-density lipoprotein cholesterol (LDL-C), and total cholesterol (TC) (5, 6). However, some studies have yielded different results (7, 8), and there is a lack of evidence-based medical proof. Therefore, the present meta-analysis included a population of patients with CAD and integrated all relevant studies on using probiotics or synbiotics to reduce the risk factors for coronary artery lesions, beginning in November 2022. The aim is to provide a theoretical basis for probiotics or synbiotics to further improve the prognosis of patients with CAD.

2. Materials and methods

2.1. Protocols

This systematic review and meta-analysis was conducted strictly in accordance with the protocol registered in the PROSPERO (CRD42022362711) and PRISMA guidelines.

2.2. Search criteria

2.2.1. Inclusion criteria

The inclusion criteria include the design using the PICOS principles: (1) study subjects (P): patients with CAD using probiotics or synbiotics; (2) intervention (I): probiotics or synbiotics; (3) control measures (C): patients with CAD not using probiotics or synbiotics; (4) outcome indicators (O): TC, triglycerides (TGs), LDL-C, high-density lipoprotein cholesterol (HDL-C), very low-density lipoprotein (VLDL), TC-to-high-density lipoprotein cholesterol ratio (TOTAL-/HDL-C%), fasting glucose (FPG), insulin, insulin sensitivity index (QUICKI), insulin resistance index (HOMA-IR), systolic blood pressure (SBP), diastolic blood pressure (DBP), trimethylamine oxide (TMAO), lipopolysaccharide (LPS), ultrasensitive C-reactive protein (hs-CRP), glutathione (GSH), NO, and total antioxidant capacity (TAC); and (5) study type (S): randomized controlled trials (RCTs).

2.2.2. Exclusion criteria

The exclusion criteria are as follows: (1) animal experiments; (2) reviews and case reports; (3) inaccessible valid data; (4) duplicate published papers; and (5) patients with severe hepatic and renal insufficiency.

2.3. Search databases

PubMed, Scopus, Web of Science, Embase, and Cochrane library were searched from their respective establishment dates on November 5, 2022, and the scope of the search was all the literature before November 5, 2022. The search strategy is shown in **Supplementary Table S1**.

2.4. Search strategy, data extraction, and quality assessment

Two researchers independently screened the literature and extracted the data based on the established inclusion and exclusion criteria. The literature was initially screened by reading the titles and abstracts, and those not meeting the inclusion criteria were excluded. The remaining articles were then read to determine their final inclusion. Any disagreements were resolved through discussion among all researchers. Regarding the quality assessment of the literature, the final included RCTs were evaluated by two investigators using a bias assessment tool. This tool assessed randomization, allocation concealment, blinding, incomplete results, selective reporting, and other potential risks. Any disagreements were resolved through discussion among all investigators. Finally, the evidence contained within the article was rated using “grade grading” (**Supplementary Table S3**).

2.5. Statistical analysis

The meta-analysis was performed using Stata 14.0 software and RevMan 5.4 software. The sample size, mean, and variance before and after the intervention were extracted. The means and standard deviations of changes in outcome variables before and after the intervention were calculated according to the method provided in the Cochrane Handbook 5.0.2 (16.1.3.2) using the following formula: $\text{Mean}_{E, \text{change}} = \text{Mean}_{E, \text{final}} - \text{Mean}_{E, \text{baseline}}$ $\text{SD}_{E, \text{change}} =$

$$\sqrt{\text{SD}_{E, \text{baseline}}^2 + \text{SD}_{E, \text{final}}^2 - (2 * \text{Corr} * \text{SD}_{E, \text{baseline}} * \text{SD}_{E, \text{final}})}, \text{Corr} = 0.50$$

The statistical heterogeneity of the included studies was analyzed using the Q test and I^2 test. $I^2 < 50\%$ was considered low heterogeneity, and $I^2 > 50\%$ was considered high heterogeneity. A fixed-effects model was used if there was no statistical heterogeneity among the findings. In case of significant clinical heterogeneity, methods such as subgroup analysis or sensitivity analysis were used to address it (**Supplementary Figure S1**). A funnel plot was used to evaluate the publication bias of the literature (**Supplementary Figure S2**).

3. Results

3.1. Literature search results

A total of 34 relevant studies were obtained in the preliminary examination, and 10 records were finally included after screening.

Nine records were eliminated because they did not have specific values, two records were excluded because they were not RCT experiments, and 13 records were excluded because they did not comply with the inclusion and exclusion criteria of this systematic review. The literature screening processes and results are shown in **Figure 1**.

3.2. Description of included trials

All articles were RCTs and included values for TC, TG, LDL-C, HDL-C, VLDL, TOTAL-/HDL-C%, FPG, insulin, QUICKI, HOMA-IR, SBP, DBP, TMAO, hs-CRP, GSH, NO, TAC, and beneficial bacteria species including *Lactobacillus acidophilus*, *Bifidobacterium bifidum*, *Lactobacillus reuteri*, *Lactobacillus fermentum*, and *Lactobacillus rhamnosus*. The details of the study characteristics are presented in **Supplementary Table S2**.

3.3. Risk of bias assessment

All articles were randomly assigned using computer software, and the records of the assignments were kept confidential by a third physician. The assignments were made using a double-masked method, and the data were considered reliable if the patient follow-up process and the number of missed visits were recorded in detail in the article. There must be drug company or institution funds in order to select results (**Figure 2**).

3.4. Lipid metabolism

Seven RCTs reported LDL-C data that could be included in the meta-analysis (5–7, 9–12). The result of the heterogeneity analysis was $I^2 = 28.0\%$ and $P = 0.21$, indicating low heterogeneity among the seven studies. Therefore, the fixed-effects model was used. The final result indicates that probiotics may decrease LDL-C [WMD -9.13 (-13.17 , -5.09), $P < 0.01$].

Six RCTs reported HDL-C, TC, and TG data that could be included in the meta-analysis (5–7, 9–11). The result of the heterogeneity analysis was $I^2 = 10.0\%$ and $P = 0.35$ for HDL-C, the result of the heterogeneity analysis was $I^2 = 31.0\%$ and $P = 0.20$ for TC, the result of the heterogeneity analysis was $I^2 = 0.0\%$ and $P = 0.72$ for TG, indicating low heterogeneity among the six studies. Therefore, the fixed-effects model was used. The final result showed that probiotics may increase HDL-C [WMD 1.94 (0.32 , 3.57), $P = 0.02$]. However, there was no statistically significant difference between the experimental group and the control group for TC [WMD -7.74 (-15.40 , -0.07), $P = 0.05$] and TG [WMD -13.41 (-28.03 , 1.21), $P = 0.07$], indicating low heterogeneity among the four studies. Therefore, the fixed-effects model was used. The results of the meta-analysis showed no statistically significant difference between the experimental group and the control group [WMD -2.83 (-6.34 , 0.68), $P = 0.11$].

All four RCTs reported VLDL data that could be included in the meta-analysis (9, 13–15). The result of the heterogeneity

analysis was $I^2 = 0.0\%$ and $P = 0.74$, indicating low heterogeneity among the four studies. Therefore, the fixed-effects model was used. The results of the meta-analysis showed no statistically significant difference between the experimental group and the control group [WMD -2.83 (-6.34 , 0.68), $P = 0.11$].

Two RCTs reported total-/HDL-cholesterol ratio (TOTAL-/HDL-C %) data that could be included in the meta-analysis (5, 9). The heterogeneity among the two studies was low, so the fixed-effects model was used. The final result showed that probiotics may decrease TOTAL-/HDL-C % [WMD -0.26 (-0.49 , -0.03), $P = 0.03$] (**Figure 3**).

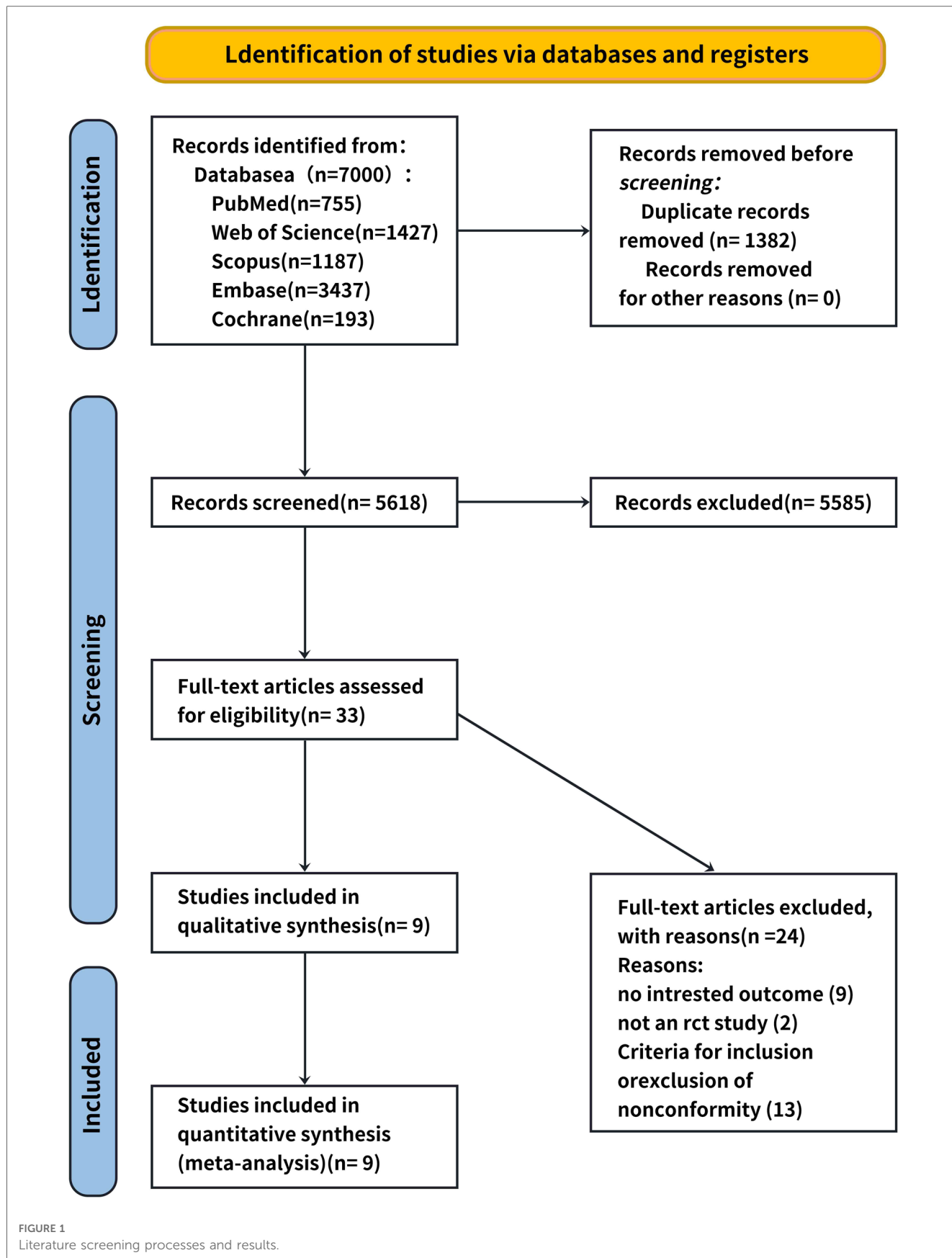
3.5. Glycometabolism

Six RCTs reported FPG data that could be included in the meta-analysis (5–7, 9–11). The result of the heterogeneity analysis was $I^2 = 1.1\%$ and $P = 0.41$, indicating low heterogeneity among the six studies. Therefore, the fixed-effects model was used. The final result showed that probiotics may decrease FPG [WMD -13.60 (-23.57 , -3.62), $P < 0.01$].

Four RCTs reported insulin, HOMA-IR, and QUICKI data that could be included in the meta-analysis (5–7, 9). The result of the heterogeneity analysis was $I^2 = 0.0\%$ and $P = 0.86$ for insulin, indicating low heterogeneity among the four studies. Therefore, the fixed-effects model was used. The results of the meta-analysis showed a statistically significant difference between the experimental group and the control group ($P < 0.01$), indicating that probiotics may decrease insulin [WMD -3.39 (-4.92 , -1.86)]. The result of the heterogeneity analysis was $I^2 = 0.0\%$ and $P = 0.89$ for HOMA-IR, indicating low heterogeneity among the four studies. Therefore, the fixed-effects model was used. The final result showed that probiotics may decrease HOMA-IR [WMD -0.98 (-1.63 , -0.32), $P < 0.01$]. The result of the heterogeneity analysis was $I^2 = 72.0\%$ and $P = 0.01$ for QUICKI, indicating high heterogeneity among the four studies. Therefore, the random-effects model was used. The results of the meta-analysis showed a statistically significant difference between the experimental group and the control group [WMD 0.02 (0.01 , 0.03), $P < 0.01$] (**Figure 4**).

3.6. Blood pressure

Five RCTs reported SBP and DBP data (5–7, 10, 11). The result of the heterogeneity analysis was $I^2 = 0.0\%$ and $P = 0.88$ for SBP. The result of the heterogeneity analysis was $I^2 = 0.0\%$ and $P = 0.82$ for DBP. These results indicate low heterogeneity among the five studies, so the fixed-effects model was used. The results of the meta-analysis showed that there was no statistically significant difference between the experimental group and the control group in terms of SBP [WMD -0.88 (-3.72 , 1.96), $P = 0.54$] and DBP [WMD -0.21 (-2.19 , 1.76), $P = 0.83$] (**Figure 5**).



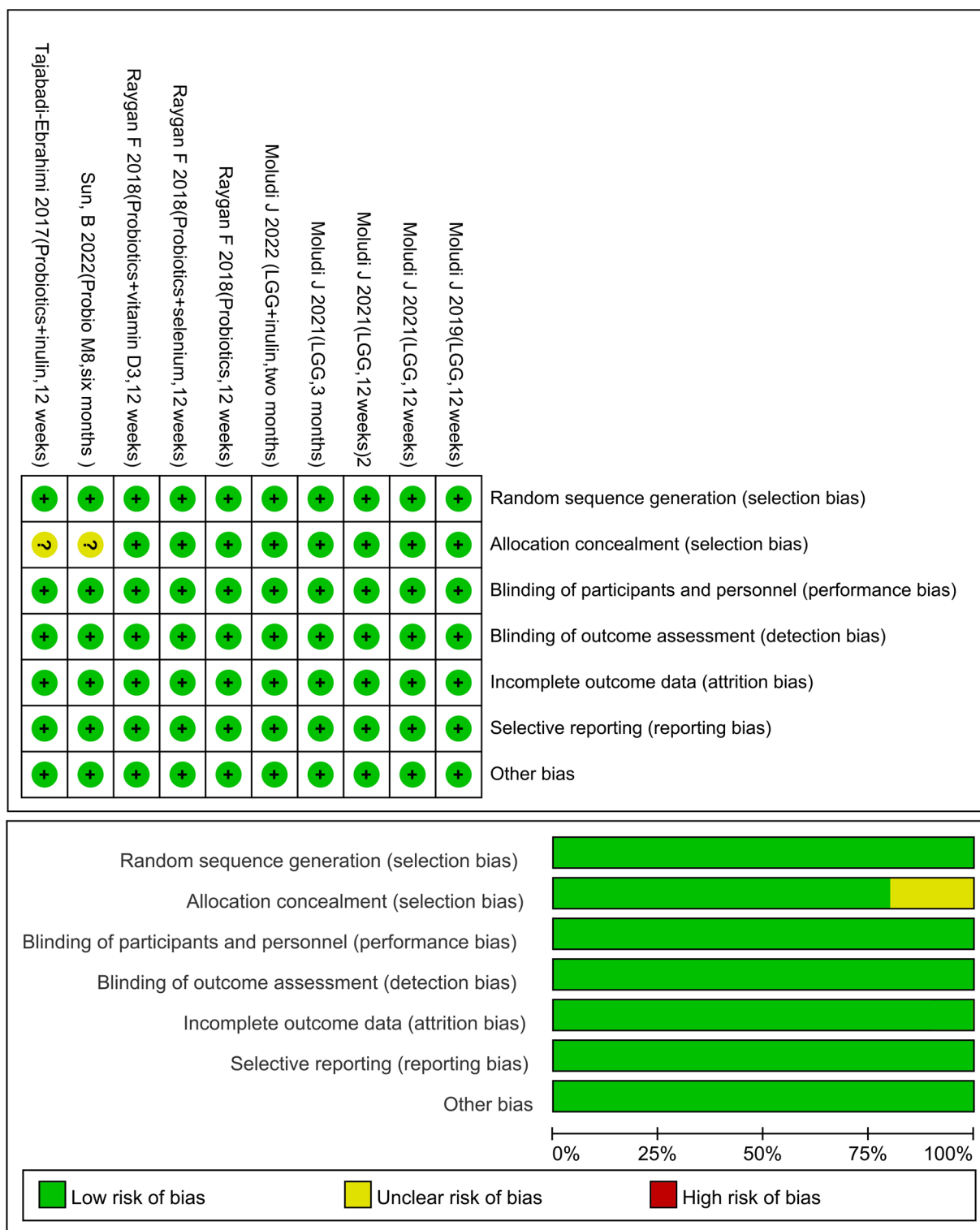


FIGURE 2 Risk of bias graph.

3.7. Other risk factors

The analysis of the included literature revealed LPS, hs-CRP, GSH, TAC, and NO data that could be meta-analyzed. There were two articles for LPS (10, 11, 16). The result of the heterogeneity

analysis was $I^2 = 57.0\%$ and $P = 0.13$, indicating high heterogeneity between the two studies. Therefore, the random-effects model was used, which indicated that probiotics did not reach statistical significance in relation to LPS [SMD $-0.55 (-1.19, 0.09)$, $P = 0.09$]. In addition, three RCTs reported GSH, TAC, and NO data

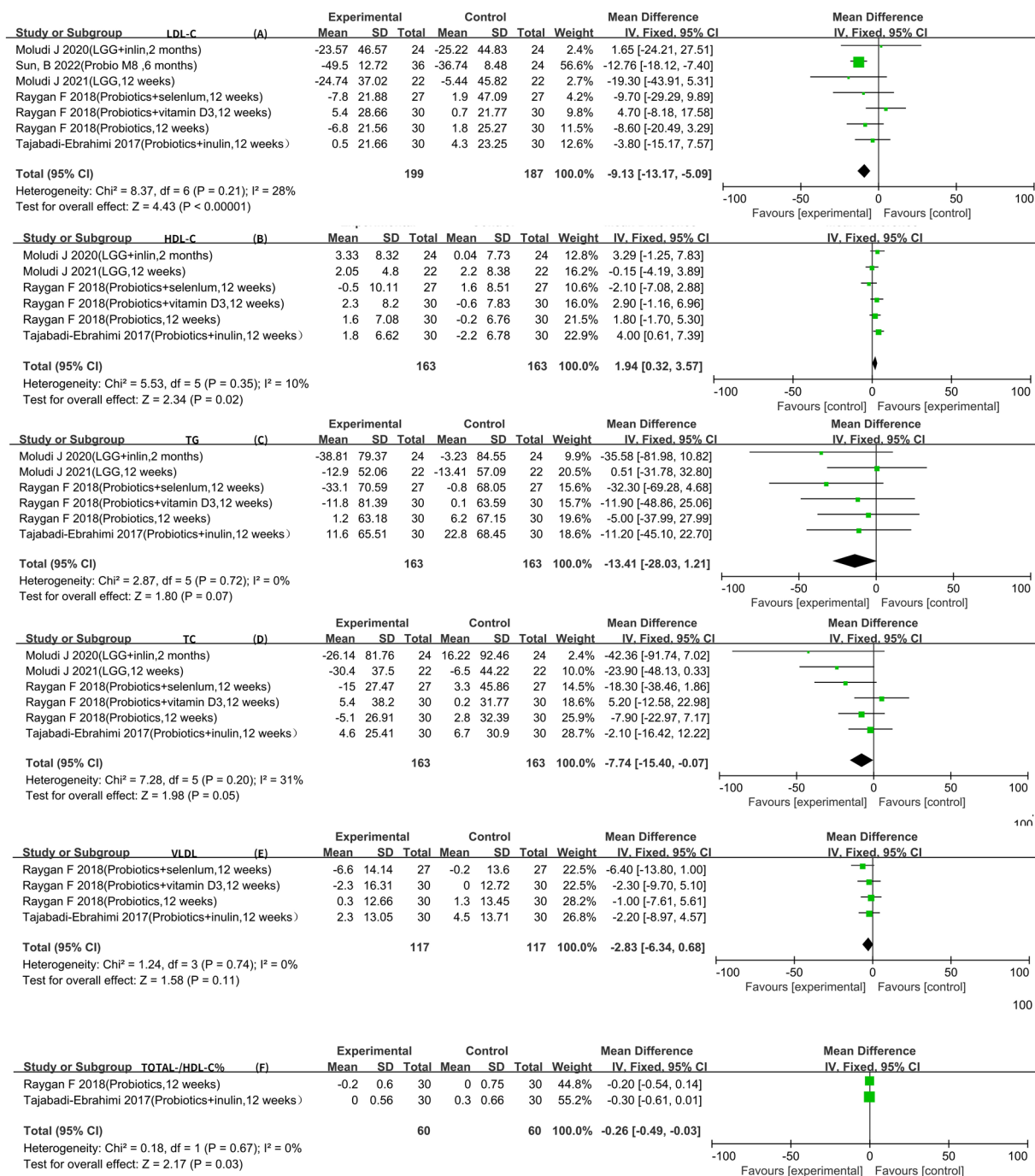


FIGURE 3 Result of lipid metabolism.

(5–7), and six RCTs reported hs-CRP data that could be meta-analyzed (5–7, 11, 17, 18). In conclusion, using the fixed-effects model, it was observed that probiotics could further increase the levels of GSH [SMD 0.51 (0.03, 0.99), $P=0.04$] and TAC [WMD 104.74 (42.67, 166.81), $P<0.01$]. In the meantime, using a fixed-effects model, it was confirmed that probiotics could further increase the levels of NO [WMD 5.38 (3.23, 7.54), $P<0.01$]. Six RCTs reported the hs-CPR data that can be meta-analyzed. The result of heterogeneity analysis was $I^2=0.0\%$ and $P=0.60$, which

showed that the heterogeneity among the six studies was low, so the fixed-effects model was used. The results of the meta-analysis showed that there was a statistical difference between the experimental group and the control group ($P<0.01$), which indicates that probiotics may decrease hs-CPR [SMD -0.60 ($-0.83, -0.37$)]. Furthermore, a meta-analysis of TMAO was conducted using a fixed-effects model, and it was observed that probiotics could further decrease the levels of TMAO [SMD -0.58 ($-0.98, -0.18$), $P<0.01$] (Figure 6).

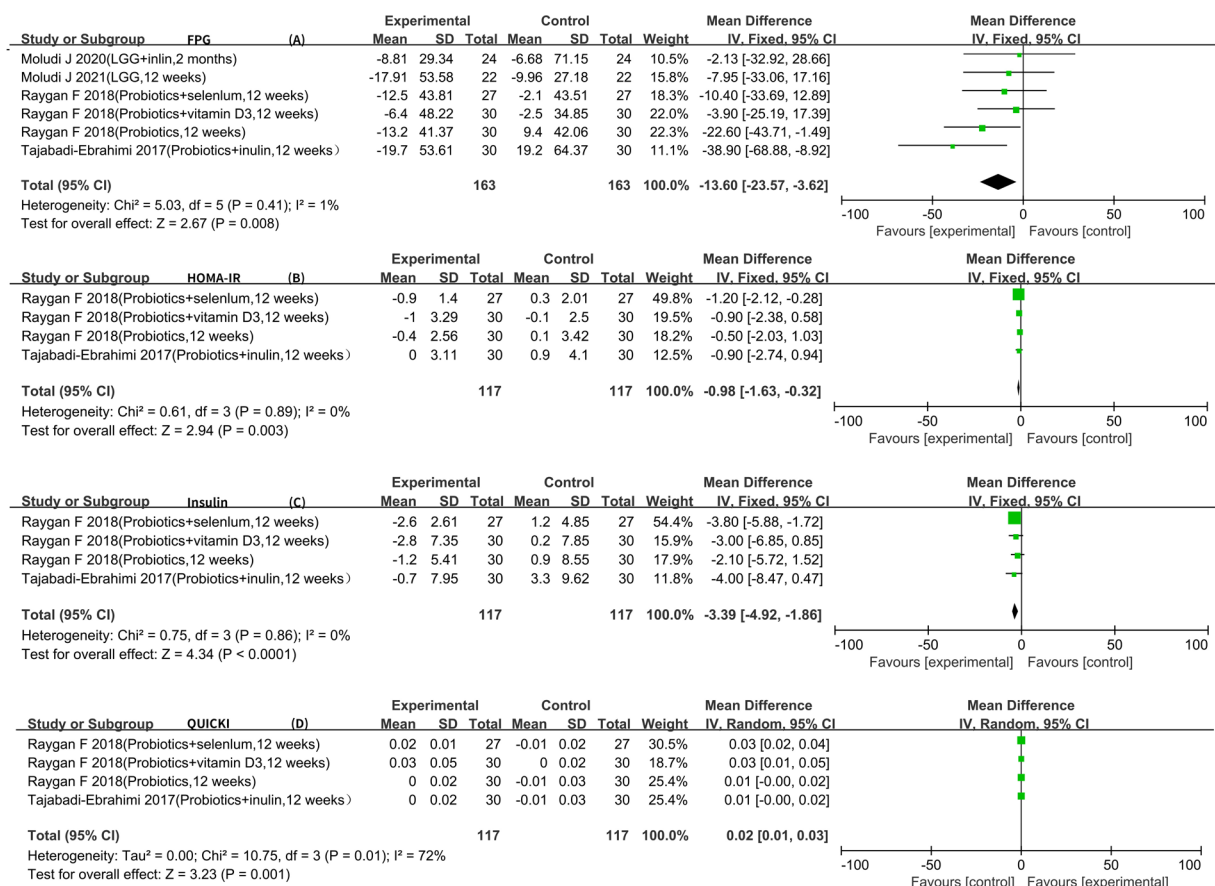


FIGURE 4 Result of glycometabolism.

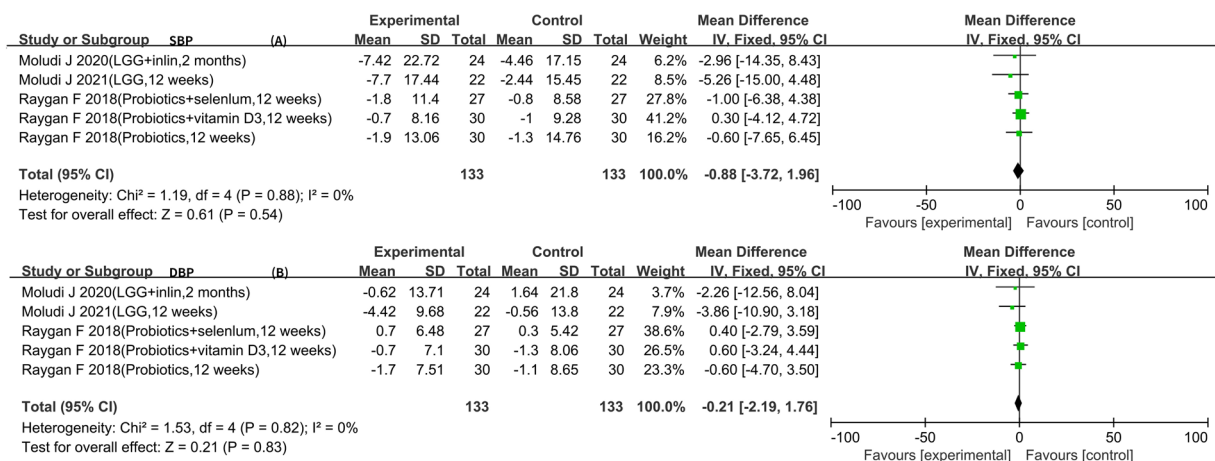


FIGURE 5 Result of blood pressure.

3.8. Adverse events

Moludi et al. found that 4.5% of the placebo group and 9% of the probiotic group reported symptoms, including gastrointestinal problems and gastric upset, after 12 weeks of intervention using

Lactobacillus rhamnosus (18). However, Sun et al. did not find evidence that probiotics could increase the probability of adverse events (12). Other literature either did not report any associated adverse events or did not provide documentation regarding them.

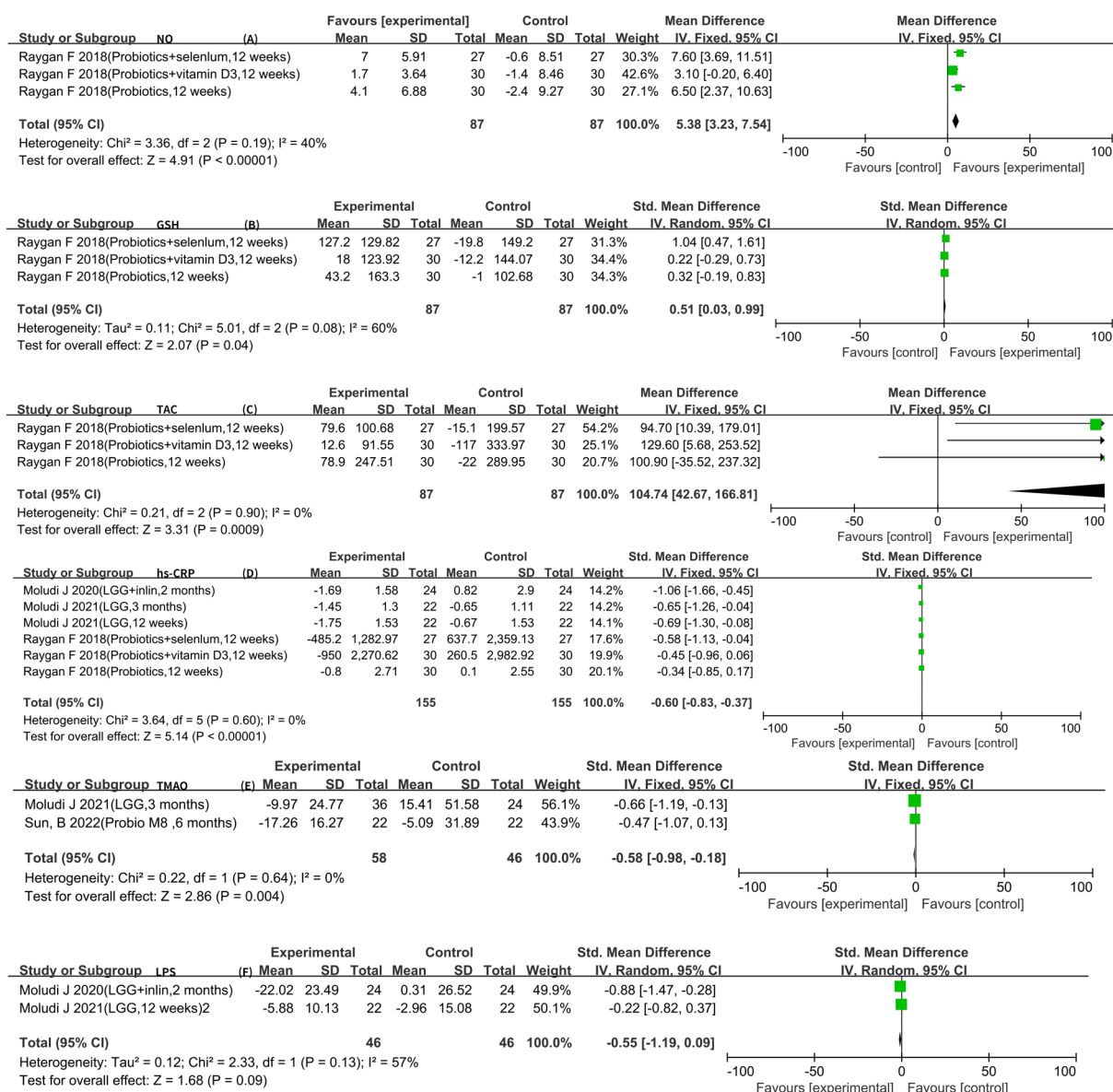


FIGURE 6 Result of other risk factors.

4. Discussion

CAD, a cardiovascular disease characterized by a chronic inflammatory response and plaque accumulation, has become a major cause of cardiovascular death. While CAD drugs have shown promising effects in delaying coronary artery lesions, the mortality rate associated with CAD remains high. Therefore, it is crucial to further reduce the risk factors of coronary artery lesions (2). In recent years, intestinal microorganisms have gained attention in research on coronary artery lesions. The imbalance of intestinal microorganisms is closely linked to the progression of the disease. The advancements in microbial research have led to the proposal of the “gut–heart axis” theory, highlighting the close relationship between the intestine and coronary artery lesions. Intestinal disorders can contribute to the

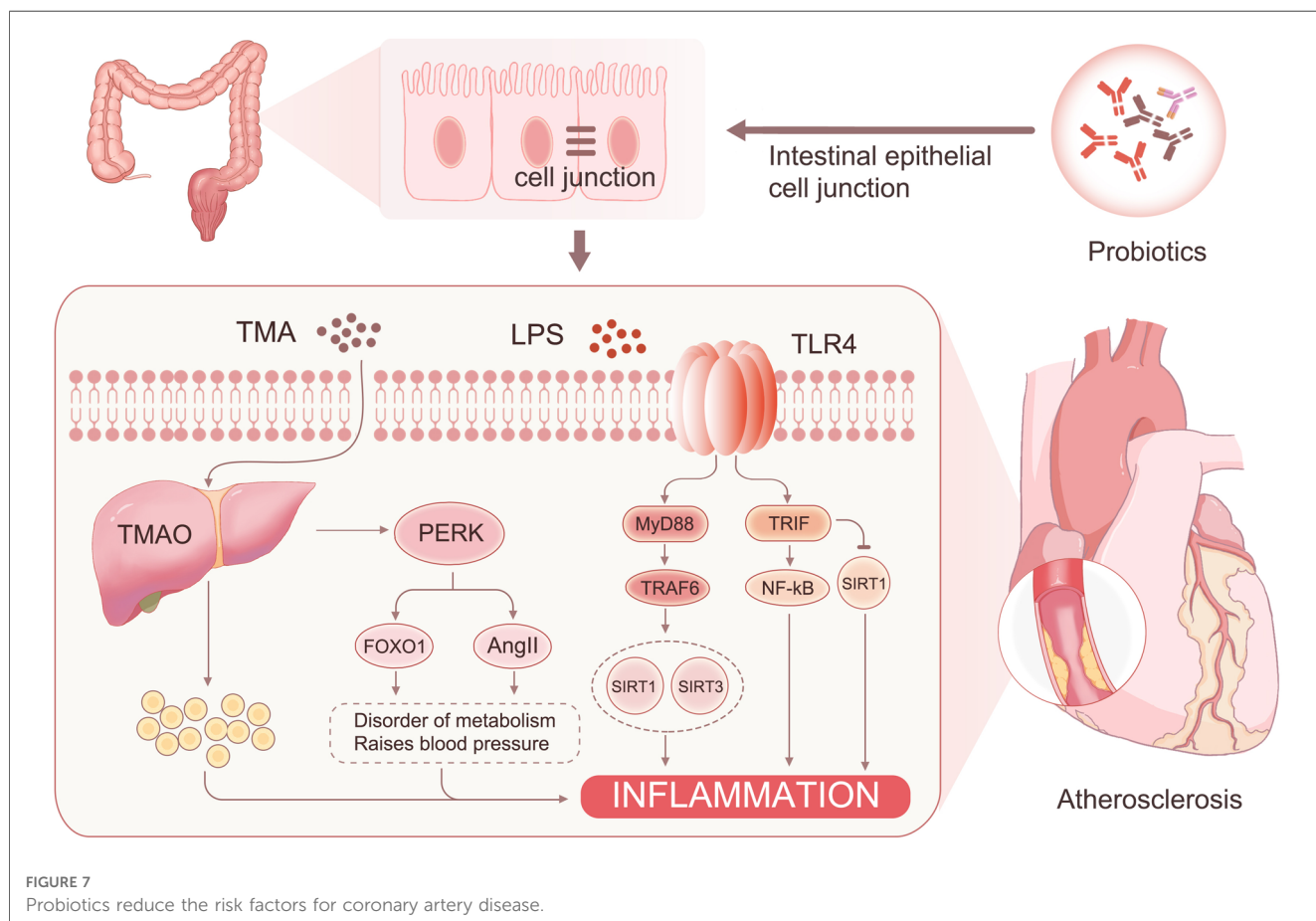
progression of coronary artery lesions (19). Gut microbes have the ability to positively modulate the host immune system, play an immunomodulatory role, defend against pathogenic microbes, and maintain normal physiological functions (20). Studies have indicated that treatment targeting gut microbes can delay the progression of coronary lesions (21). Although there have been meta-analyses on the effects of probiotics on lipid metabolism, glucose metabolism, blood pressure, and inflammatory factors (22, 23), they do not consider the effects of conventional drugs on the intestinal flora (24–26). Therefore, the objective of this meta-analysis was to examine the effect of probiotics on the risk factors for coronary artery lesions in conjunction with conventional drug therapy for CAD.

Regarding the effect of probiotics on lipid metabolism, although some studies have shown that probiotics can reduce TG

and TC concentrations (24); this phenomenon was not observed in this meta-analysis. This discrepancy may be attributed to the specific population and conditions included in the analysis. Most of the existing meta-analyses do not restrict the disease population. In contrast, certain coronary drugs, such as aspirin (27) and atorvastatin (28), have been found to modulate the intestinal flora, which might diminish the impact of probiotics on the intestinal flora. Furthermore, the absence of a standardized dietary structure among patients is a crucial factor influencing the outcomes of intestinal flora changes. The included literature did not provide means to achieve dietary uniformity, which could be an important factor influencing the intervention outcomes. Therefore, considering that diabetic patients typically adhere to a diabetic diet, we conducted a subgroup analysis of patients with coronary heart disease combined with diabetes and different types of interventions and discovered a significant hypoglycemic effect of probiotics/synbiotics in this subgroup (Supplementary Tables S4, S6). However, such an effect was not observed in patients with CAD alone. In terms of intervention duration, time is another factor that affects the results. Significant reduction of LDL may require probiotic intervention for more than 12 weeks to have a notable effect, while hs-CRP shows a statistically significant difference with intervention lasting ≤12 weeks (Supplementary Table S5). This discrepancy may be related to the cycle of changes in the intestinal flora structure. In addition, probiotics can potentially

increase the concentrations of TAC, GSH, and NO, which contribute to cardiovascular dilation and antioxidant capacity (29). Moreover, they can further decrease the levels of LPS, TMAO, and inflammatory response, all of which are beneficial in delaying the progression of coronary artery lesions and improving the prognosis of patients (30).

The mechanism behind this phenomenon may originate from the following sources: (1) The intestinal flora reduces the permeability of intestinal epithelial cells through LRP6 and Wnt/ β -catenin pathway activation (31). This reversal of intestinal barrier damage further decreases the entry of harmful substances such as LPS and TMAO into the bloodstream (32). (2) LPS can activate NF- κ B through MyD88 and TRIF pathways, leading to the production of inflammatory factors and an increase in reactive oxygen species (33). This process ultimately sustains a chronic inflammatory response. TMAO binds to PERK (34), leading to increased FOXO1 activity and activation of the AKT signaling pathway, resulting in insulin resistance and diabetes. FOXO1 can also affect the farnesol X receptor and small heterodimeric chaperone receptor activation, which downregulates the expression of the *Cyp7a1* gene and upregulates the expression of bile acid transporter genes *Abcb11* and *Slc10a1* (35). These changes contribute to metabolic syndrome in patients. In addition, PERK can activate AngII, which leads to hypertension (36). However, probiotics reduce the entry of TMAO and LPS into the blood, thereby mitigating the effects of



these risk factors. (3) GSH and NO play essential roles in the cardiovascular system. Studies have shown that GSH is negatively correlated with fasting blood glucose (37), and individuals with reduced plasma GSH levels have a significantly increased risk of cardiovascular disease (38). The increase in GSH and NO may be associated with a reduction in the metabolic syndrome of the patient (39). The elevated GSH levels can react with various free radicals, such as hydroxyl, hypochlorous, superoxide, and peroxynitrite (40, 41), and reduce hydrogen peroxide production, thereby mitigating cellular damage and oxidative stress (42). In addition, NO inhibits leukocyte adhesion to blood vessels and platelet aggregation and adhesion, contributing to the delay of coronary lesion progression (43) (Figure 7).

Therefore, this meta-analysis confirmed the effect of probiotics or synbiotics on the risk factors for coronary artery lesions in the treatment setting with conventional medications. After a rigorous literature screening process, 10 papers with 10 studies were finally included for data consolidation to objectively evaluate the effect of probiotics on coronary artery lesions. The results of this study showed that the addition of probiotics or synbiotics to conventional medications for CAD reduced the levels of LDL-C [WMD -9.13 (-13.17, -5.09)], FPG [WMD -13.60 (-23.57, -3.62)], insulin [WMD -3.39 (-4.92, -1.86)], LPS [SMD -0.55 (-1.19, -0.09)], hs-CRP [SMD -0.60 (-0.83, -0.37)], and TMAO [SMD -0.58 (-0.98, -0.18)] and increased the levels of HDL-C [WMD 1.94 (0.32, 3.57)] and NO [WMD 5.38 (3.23, 7.54)] but did not affect TG [WMD -13.41 (-28.03, 1.21)], SBP [WMD -0.88 (-3.72, 1.96)], and DBP [WMD -0.21 (-2.19, 1.76)].

This study has some limitations and strengths. The limitations include the following: (1) Since no specific drugs for coronary heart disease were given in the included literature, this may introduce bias to the intervention results. (2) The literature included in this study mainly consists of small-sample RCTs, with a maximum sample size of 36 cases in the trial group and 36 cases in the control group. The small sample size of some outcome indicators reduces the precision of the results. (3) Due to the limited number of included literature, the direct analysis of patient survival could not be conducted in the article. Instead, the risk factors for the prognosis of coronary heart disease were selected for analysis. Future studies should focus on direct analysis of major cardiovascular adverse events. (4) Most of the articles come from Iran, and the difference in ethnicity may have varying effects on the intervention effect. Future studies should consider a more diverse population. (5) The dietary structure and calorie intake of the subjects in different studies were not entirely consistent, which may influence the composition of the intestinal flora and interfere with the intervention results. (6) The number and lack of uniformity of probiotic species in the article hindered further subgroup analysis based on specific probiotic species.

Despite these limitations, the study also has strengths. This article demonstrated, through an evidence-based medical approach, that the use of probiotics/synbiotics in addition to conventional medications for coronary heart disease can further reduce the risk factors in patients, potentially improving their

prognosis. Different diseases are closely related to the structure of intestinal flora, and most current articles do not separately analyze specific diseases. This study specifically conducted a meta-analysis of probiotic interventions to minimize the influence of disease on intervention factors. In this study, the control group consisted of patients receiving conventional drugs for coronary heart disease, while the experimental group received conventional drugs for coronary heart disease in combination with probiotic treatment. The study highlights the additional benefits provided by the addition of probiotics and suggests that future treatment regimens incorporating probiotics may further enhance the prognosis of patients with coronary heart disease.

In summary, the current evidence suggests that probiotics can significantly reduce the risk of coronary artery lesions, and the addition of probiotics to conventional medications for CAD may improve the prognosis of patients with CAD. However, the aforementioned findings still require further confirmation through large-sample and high-quality RCTs due to the potential impact of probiotic species type, intervention duration, CAD subtype, and sample size.

Conclusion

Using probiotics or synbiotics, along with conventional medications for CAD, can further reduce the risk factors for coronary artery lesions and improve the prognosis of patients.

Data availability statement

The data sets presented in this study can be found in online repositories. The names of the repository/repositories and accession number(s) can be found in the article/**Supplementary Material**.

Author contributions

All experiments were conducted at the Scientific Research Center, the Third Affiliated Hospital of Zunyi Medical University (The First People's Hospital of Zunyi). YL and NH conceived and designed the research. ZY and MX reviewed the controversial points of the retrieved documents. ZY guided the design of the article and pointed to the discussion section of the article. All authors approved the final version of the manuscript and agreed to be accountable for all aspects of the work in ensuring that questions associated with the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed. All authors contributed to the article and approved the submitted version.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: <https://www.frontiersin.org/articles/10.3389/fcvm.2023.1154888/full#supplementary-material>

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