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Review Article

Connecting the Dots between Gut Microbiota Dysbiosis and Atherosclerosis: A Systematic Review

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ABSTRACT

The prevalence of cardiovascular disease (CVD) is rising despite improvements in risk factor management. Numerous causes, including lifestyle modifications, environmental conditions, and gut microbiota dysbiosis, could be blamed for this. The type of bacteria involved and their primary role in atherosclerosis remain unknown even though the association between gut microbiota and atherosclerosis has been explored. Through a systematic review, this study sought to understand how dysbiosis of the gut microbiota contributes to atherosclerosis. PubMed, EBSCOhost, EMBASE, and Cochrane were searched for relevant literature. The Newcastle-Ottawa Scale for nonrandomized studies was used to measure the risk of bias, and study selection was conducted following PRISMA 2020 recommendations. Both subclinical and symptomatic atherosclerosis were taken into account. Seven of the 783 studies that included 566 patients with vascular disease associated with atherosclerosis met the inclusion criteria. The composition of the gut microbiota varied considerably between the healthy control group and the atherosclerotic group. Patients with coronary artery disease (CAD) have lower alpha diversity. Atherosclerosis was linked to an increase in potentially hazardous bacteria such as *Escherichia sp., Shigella sp., Enterococcus sp.,* and *Ruminococcus gnavus* and a decrease in helpful bacteria like *Subdoligranulum, Roseburia, Faecalibacterium, and Eubacterium rectale*. Conclusively, changes in the makeup of the gut microbiota shown in the atherosclerotic group might have caused an imbalance in the synthesis of metabolites, indicating that dysbiosis of the gut microbiota may contribute to cardiovascular disease in several ways.

Keywords: Atherosclerosis, Coronary artery disease, Gut microbiota, Dysbiosis, Metabolite

Introduction

Around 32.7% of the burden of cardiovascular disease and 2.2% of the global disease burden are caused by coronary heart disease.[1] Hypertension, hyperlipidemia, diabetes, obesity, and smoking are well-established traditional risk factors for coronary heart disease. However, the rising incidence despite advancements in risk factor management suggests that these factors alone do not fully explain the disease's etiology. Genetic predisposition, metabolic disturbances, and emerging contributors such as gut microbiota dysbiosis may also play a significant role.[1] Recent studies have shown a relationship between gut microbiota and the occurrence of atherosclerosis, a key pathophysiology of cardiovascular disease.[2] Gut microbiota plays a crucial role in human physiology, immune system development, and nutrient supply.[3] Evidence suggests that gut microbiota can contribute to undesirable phenotypes, such as altered macronutrient digestion and vitamin production.[4] Gut microbiota dysbisosis, a shift or change in the composition of the microbiome in the gut, is associated with various illnesses, including cardiovascular disease.[2, 4]

The beginning and progression of cardiovascular disease are linked to gut microbiota dysbiosis and its active metabolites, albeit the underlying pathophysiological mechanisms are still unclear. The development of cardiovascular disease has been linked to several metabolites formed by microorganisms, including lipopolysaccharides (LPS), short-chain fatty acids (SCFAs), and secondary bile acids. Furthermore, the gut bacteria aid in the synthesis of trimethylamine (TMA) from dietary carnitine and choline, which the liver then transforms into TMAO. These metabolites affect metabolic pathways associated with cardiovascular disease, inflammation, and endothelial dysfunction.[2, 5] A systematic review indicated that a decreased abundance of *Bacteroides sp.* and *Lachnospiracea sp. is* associated with coronary artery disease (CAD); however, this study included both acute and chronic CAD.[6] Acute CAD, which includes acute coronary syndrome (ACS), refers to the sudden reduction of blood flow due to thrombus formation on a ruptured plaque. Chronic CAD, which includes stable angina and, in some cases, myocardial ischemia, refers to the progressive development of atherosclerotic plaques. However, myocardial ischemia can also result from other mechanisms, such as coronary vasospasm or microvascular dysfunction, independent of atheroma formation.[7] Another systematic review has also shown that the pathogenesis of gut microbiota in acute and chronic CAD is quite different.[3] The purpose of this study was to investigate how the gut microbiota dysbiosis contributes to atherosclerosis, specifically chronic CAD. This study's main goal was to determine how the gut microbiota profiles of people with chronic CAD differed from those of healthy controls. The study intends to clarify the possible involvement of gut microbiota in the pathogenesis of CAD by contrasting these two groups.

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Materials and Methods

Study design and setting

Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 standards for systematic reviews and meta-analyses, a systematic review was carried out.[8] this study seeks to determine how variations in gut microbiota composition and diversity may contribute to the mechanisms underlying chronic CAD, thereby providing insights that could inform future therapeutic strategies and interventions.

Eligibility criteria

Inclusion criteria in this systematic review were based on the PICO framework (Population, Intervention, and Control, Outcome, and Study design). Included studies had the following criteria: (1) Population: patients with atherosclerosis and healthy controls; (2) Intervention: none; (3) Comparison: microbiota of atherosclerosis patients vs. healthy controls; and (4) Outcome: microbiota composition and diversity in each group such as alpha diversity (diversity within a single sample, often measured by indices like the Shannon index, which considers both the richness (number of species) and evenness (distribution of species) and beta diversity (diversity between different samples or groups, highlighting differences in microbial composition). The literature search included clinical trials and observational studies, written in English, involving both non-diabetic and diabetic patients, and included symptomatic and subclinical forms of atherosclerosis including CAD, subclinical atherosclerosis, and atherosclerotic cardiovascular disease (ACVD). Patients with CAD should be diagnosed by a cardiologist and confirmed by coronary angiography.[9] Coronary angiography was used to confirm the diagnosis of ACVD, and those with ≥50% stenosis in one or more arteries were included.[10] Subclinical atherosclerosis was identified by measuring intima-media thickness (IMT) with a manual calliper and it was confirmed when the measuring IMT exceeded 1.3 mm or when focal atherosclerotic lesions were larger than 1.3 mm.[11] All animal studies, molecular studies, review articles, and papers without full-text access were excluded.

Search strategy

Systematic literature searches were conducted across four databases as of November 12, 2023: PubMed, EBSCO, EMBASE, and Cochrane. Keywords and medical subject heading (MeSH) used were: (1) gut microbiota OR gut microbiome OR intestinal microbiota AND (2) coronary artery disease OR subclinical atherosclerosis OR atherosclerosis cardiovascular disease. Detailed keywords used in each database are presented in Table 1.

Screening and selection of the records

Relevant studies were imported into and managed using Mendeley (Elsevier, London, United Kingdom) which facilitated the removal of duplicate entries. The eligibility of each study was assessed through a systematic review process that involved screening titles and abstracts, followed by applying the predetermined inclusion and exclusion criteria to identify studies suitable for full-text review.

Data extraction

Two investigators (MS and MF) separately extracted data from the included studies, and disagreements were discussed with the third and fourth investigators (AEP and MSR) to resolve them. Information gathered includes the first author's information, the year of publication, the study design, the sample size, the sample characteristics, and the gut microbiota results. The main goal was to evaluate how gut microbiota dysbiosis, including bacterial strains and subclinical forms of atherosclerosis involvement, affected the incidence of atherosclerotic cardiovascular disease.

Quality assessment

The Newcastle-Ottawa Scale (NOS) was used to evaluate the risk of bias in non-randomized studies, such as case-control, cross-sectional, and cohort designs. The NOS assesses participant selection (maximum 3 points for cross-sectional and 4 points for cohort/case-control), comparability of study groups (up to 2 points), and assessment of exposure and outcomes (up to 3 points). Studies were classified based on their scores, with those meeting predefined thresholds considered to have high (5 points or less) or low (up to 7 points for cross-sectional and up to 8 points for cohort and case-control) risk of bias.

Table 1: Database and keyword of the study

Database	Keywords
EMBASE	("gut microbiome" OR gut microbiota OR intestinal microbiota) AND (Coronary Artery Disease OR "Subclinical Atherosclerosis" OR Atherosclerosis Cardiovascular Disease)
Cochrane	#1 MeSH descriptor: [gut microbiota] explode all trees #2 (gut microbiota):ti,ab,kw OR (intestinal microbiota):ti,ab,kw AND (atherosclerosis):ti,ab,kw OR (cardiovascular disease):ti, ab,kw (Word variations have been searched) #3 MeSH descriptor: [Atherosclerosis] explode all trees
EBSCO	("gut microbiome" OR gut microbiota OR intestinal microbiota) AND (Coronary Artery Disease OR "Subclinical Atherosclerosis" OR "Atherosclerosis Cardiovascular Disease") Limiters - Publication Type: Randomized Control Trial, Cohort, Cross-sectional, Case-control
PubMed	((("gut microbiome" [Title/Abstract]) OR ("gut microbiota" [Title/Abstract])) OR (intestinal microbiota [Title/Abstract])) AND ((coronary artery disease [Title/Abstract])) OR (subclinical atherosclerosis [Title/Abstract])) OR (atherosclerosis cardiovascular disease [Title/Abstract])

Statistical analysis

No additional statistical analysis was conducted in this study. The number of patients with and without cardiovascular disease events in each group was recorded and analysed qualitatively allowing for an in-depth discussion of the underlying factors influencing these occurrences.

Results and Discussion

A total of 783 studies were obtained from all the databases used for this study. 414 records were examined following the removal of 445 duplicates, 200 entries that automated tools determined were ineligible, and 27 records that were eliminated for other reasons. Seventy-two of these were not included. 38 of the 69 reports that were requested for retrieval were not found. Seven papers were finally included in the analysis after the remaining 31 publications were evaluated for eligibility (Figure 1).[9-15] Table 2 provides a summary and presentation of the characteristics of the included research. This research consisted of four observational cross-sectional studies, two case-control studies, and one cohort study. Publications from different researchers were consulted for this study including the country and nationality of researchers [9, 10, 15](Chinese), [12](USA), [13](Hungary), [14](Japan) and [11](Italy).

Data from included studies reported an increase in pathogenic or pro-inflammatory bacteria, such as *Escherichia coli*, *Klebsiella spp.*, *Enterococcus sp.*, and *Ruminococcus gnavus* in CAD or ACVD patients (Table 2). Conversely, beneficial microbes like *Faecalibacterium*

prausnitzii, *Subdoligranulum sp*, *Roseburia intestinalis*, and *Bacteroides sp*. were found to be reduced in CAD patients, suggesting a potential shift toward a more pro-inflammatory microbiome.[9,10] A total of 78 CAD patients (confirmed by angiography) and 90 healthy controls were included, from whom fecal samples were collected and analyzed using a customized process to ensure efficient and unbiased DNA extraction.[9]According to this study, the microbial diversity of the CAD group was dramatically reduced; the CAD group's Shannon index was significantly lower than that of the healthy group.[9] While helpful

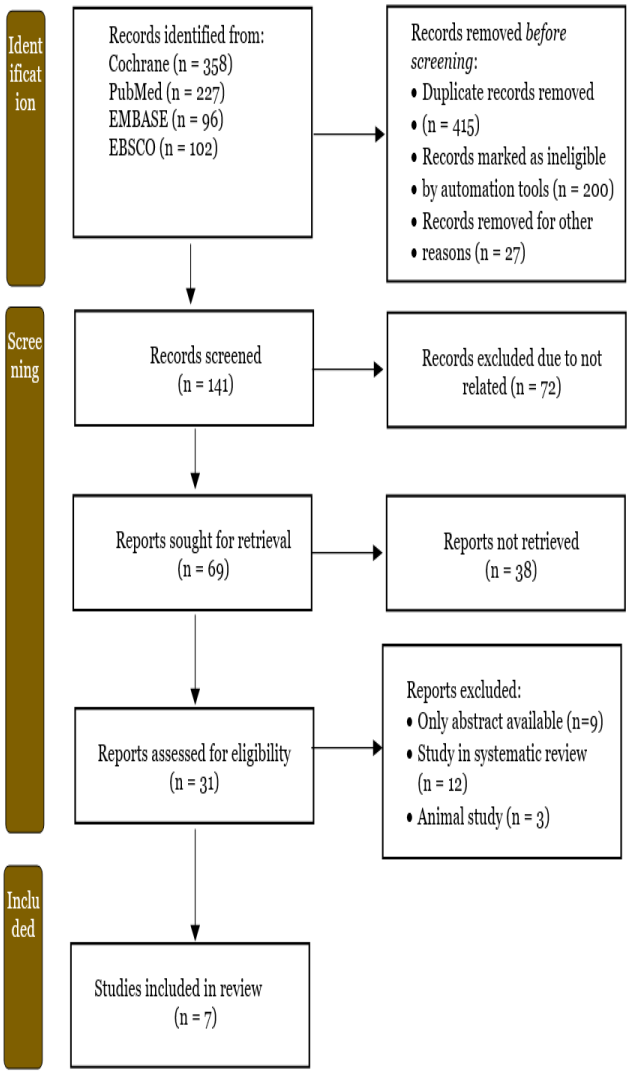

Figure 1: PRISMA flowchart of the included studies.

Bacteria including *Faecalibacterium*, *Subdoligranulum*, *Roseburia*, and *Eubacterium rectale* were decreased in CAD patients, specific bacteria like *Escherichia-Shigella* and *Enterococcus sp.* were elevated (Table 2). In CAD, this points to a change toward a less varied and possibly more pro-inflammatory microbiota. Fecal samples were collected from 53 healthy controls and 53 patients with advanced CAD, with significant CAD diagnosed using non-invasive stress testing, coronary CT, and coronary angiography.[12] the study reported decreased microbiome diversity in CAD patients, with the Shannon index lower in the CAD group (Table 2). Notably, *Ruminococcus gnavus* was elevated in CAD patients, while *Lachnospiraceae* NK4B4 and *Ruminococcus gauvreauii* were reduced. These microbial alterations may indicate the progression of atherosclerosis and suggest potential gut-related mechanisms in CAD pathogenesis.[12]. An analysis of fecal metagenomes from 218 individuals with ACVD and 187 healthy controls revealed no statistically significant difference in gut microbiome diversity, as assessed by the Shannon diversity index (p = 0.974).[10] However, microbial composition differed significantly between the groups. Specifically, pathogenic bacteria such as *Klebsiella spp*., *Enterobacter aerogenes*, and *Escherichia coli* were more abundant in ACVD patients, while beneficial species such as *Prevotella copri*, *Faecalibacterium prausnitzii*, *Alistipes shahii*, and *Bacteroides sp*. were significantly reduced.

In a study that used comprehensive carotid ultrasonography to evaluate atherosclerosis in monozygotic twins, the microbiome diversity did not sigificantly differ between the two groups, as indicated by the Shannon index.[13] However, the study found that an increased Firmicutes/Bacteroidetes ratio was associated with increased IMT, a marker of early atherosclerosis.[13] This suggests that an imbalance between these two bacterial phyla could influence atherosclerotic development, potentially through metabolic or inflammatory pathways.[13] Another study examined 29 CAD patients and 35 healthy volunteers and found increased microbiome diversity in the CAD group (Shannon index, p<0.01).[15] Notably, *Firmicutes* were increased, while *Bacteroidetes* were decreased in CAD patients, highlighting a potential shift in microbial composition associated with atherosclerosis.[15] A study used 16S rRNA gene sequencing of faecal samples to discover species with differential abundance between 30 CAD patients and 30 controls.[14] The Shannon diversity index did not significantly differ between the CAD and control groups in this investigation.[14] However, specific species, such as *Bacteroides vulgatus* and *Bacteroides dorei*, were found to be decreased in CAD patients, indicating potential dysbiosis related to CAD.[14] A study involving 144 individuals with subclinical atherosclerosis and 201 controls identified significant differences in gut microbiota composition between the groups (p = 0.016), despite the absence of changes in richness across all alpha-diversity measurements (p > 0.05).[11] However, *Escherichia coli* was found to be associated with the presence of subclinical atherosclerosis.[11] Overall, several studies report decreased microbial diversity in patients with CAD or ACVD compared to healthy controls, as evaluated by alpha diversity metrics, including the Shannon index. However, the results are not always consistent (Table 2). Further studies are needed to explore the factors contributing to the variability in microbiome diversity results, such as differences in patient populations, geographic location, diet, and comorbidities. Additionally, larger longitudinal studies with more diverse cohorts and advanced microbiome analysis techniques could provide more consistent and comprehensive insights.

The gut microbiota is essential for human physiological functions, immune enhancement, and nutrient supply.[16] Two findings from our comprehensive review are the diversity and composition of the gut microbiota confirmed the importance of the gut microbiota in the pathogenesis of atherosclerosis. The onset and advancement of atherosclerosis have been repeatedly linked to changes in the makeup of the gut microbiota, which are indicated by an imbalance of these microbial groups, particularly a higher proportion of the phylum *Firmicutes* to *Bacteroidetes*. Numerous reviewed research also linked increased levels of *Enterococcus sp.*, *Ruminococcus gnavus*, *Escherichia-Shigella*, *Klebsiella spp*., *Enterobacter aerogenes*, and *Escherichia coli* to the onset and advancement of atherosclerosis.[14] In most studies, α-diversity was either decreased[9, 12] or not significantly different in the CAD group.[10, 11, 13, 14] This suggests that reduced microbial diversity might be linked to a higher risk of CAD.[9, 10, 12, 13]

Through several pathways, dysbiosis, or an imbalance in the gut microbiota, may be a major factor in the development of atherosclerosis. Since dysbiosis increases the production of pro-atherogenic factors such as interleukins, tumour necrosis factor (TNF), and C-reactive protein (CRP), one of the main mechanisms includes the stimulation of systemic inflammation. By increasing the expression of adhesion molecules, these inflammatory mediators can aid in the development of atherosclerotic plaques. Furthermore, gut microbiota dysbiosis disrupts the autonomic nervous system through the gut-brain axis, altering neuroendocrine-immune interactions. This occurs via microbial metabolites such as short-chain fatty acids (SCFAs), lipopolysaccharides (LPS), and trimethylamine N-oxide (TMAO), which modulate vagal tone, promote systemic inflammation, and contribute to endothelial dysfunction, key factors in atherosclerosis progression.[11] Butyrate-producing microbes were found to be relatively

depleted in the ACVD samples.[10] On the other hand, ACVD samples had more *Enterobacteriaceae* than control samples. According to the study, the ACVD group had higher levels of TMA formation and O-antigen of lipopolysaccharide synthesis than the control group, However, their capacity to synthesize butyrate, an anti-inflammatory short-chain fatty acid (SCFA), was similarly reduced (Figure 2).[10] Folate is crucial for cardiovascular health through its role in homocysteine metabolism.[17] In comparison to healthy people, the ACVD microbiome also showed altered capability for homocysteine metabolism and reduced glycan metabolism, namely glycosaminoglycans.[12,18] These metabolic changes were linked to alterations in the microbial population, which further links gut microbiota dysbiosis to the development of atherosclerosis.[12]. A decrease in butyrate producing bacteria including *Faecalibacterium, Roseburia, Lachnospiraceae,* and *Ruminococcaceae* has been observed in CAD patients, suggesting reduced SCFA levels that may impair intestinal cell energy metabolism and compromise gut barrier integrity (Figure 2).[9] The decrease in *Lachnospiraceae* correlated with higher TMAO levels and increased blood clot risk, marking it as a significant prognostic marker for CAD.[9,19] Through toll-like receptor 4, an inflammatory polysaccharide produced by *Ruminococcus gnavus* causes dendritic cells to release tumour necrosis factor-alpha (TNF-α).

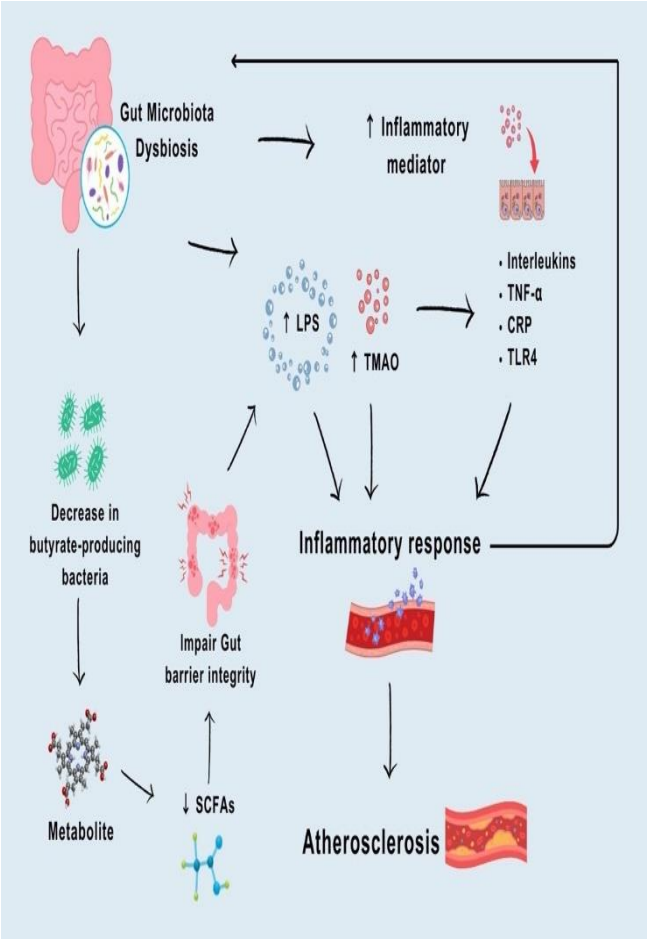

Figure 2: Illustration of key bacterial changes and metabolite production in gut microbiota dysbiosis associated with atherosclerosis.

One strong pleiotropic cytokine that contributes to the development of atherosclerosis is TNF-α.[12] The *Lachnospiraceae* family is capable of generating butyrate by fermenting dietary fibre. Recent research indicates that the gut microbiota, enriched with butyrate-producing microbes, may play a key role in the heart-protective benefits associated with dietary fibre intake.[12] *Bacteroides vulgatus* and *Bacteroides dorei* are the predominant species of the *Bacteroides sp.* group in the microbiota of the human gut. Interestingly, these species' LPS molecules, which include penta- and tetra-acylated lipid A, are structurally different from *Escherichia coli*'s hexa-acylated LPS and elicit weakened TLR4 responses. Based on this, it was initially hypothesized that the anti-inflammatory properties of *Bacteroides vulgatus* and *Bacteroides dorei* LPS would suppress immune activation and provide protection against atherosclerosis.[14]

Compared to healthy individuals, CAD patients exhibited a decrease in *Proteobacteria* and *Bacteroidetes,* along with an increase in *Firmicutes* and *Fusobacteria*.[15] The phylum *Bacteroidetes* primarily consists of the genera *Bacteroides sp.* and *Prevotella sp.* within this group, *Bacteroides fragilis* is crucial for maintaining mucosal T-cell balance by regulating T-cell functions.[15] Other species of *Bacteroides sp* form mutualistic relationships with the host by producing essential biological by-products while thriving in the plant polysaccharide-rich environment of the gut. Moreover, *Bacteroides distasonis* is predominantly found in the gut of healthy individuals, contributing to improved bowel health.[15] *Firmicutes* are highly effective at extracting and absorbing energy from food, which can lead to the development of obesity and metabolic syndrome both of which are significant risk factors for atherosclerosis.[20]. Firmicutes have been identified as carriers of *bbu* genes, which facilitate the conversion of the intermediate γ-butyrobetaine into TMA under anaerobic gut conditions.[13] Additionally, the *caiTABCDE* operon genes of *E. coli,* responsible for membrane transport and the metabolism of L-carnitine to γ-butyrobetaine and TMA, have been found to be overrepresented in individuals with increased intima-media thickness and subclinical atherosclerosis.[11] (TMAO) which is the end product of L-Carnitine metabolism is correlated with the process of atherosclerosis. After TMAO activation, SR-A1 and CD36 in macrophages can also activate heat shock protein 60 (HSP60), which has been demonstrated to be the first step in atherosclerosis and to participate in the production of foam cells through Toll-like receptors. Furthermore, TMAO may activate NLRP3, which stimulates the production of IL-18 and IL-1β to cause inflammation and endothelial damage that leads to atherosclerosis (Figure 2).[22]

Previous studies have identified key metabolites contributing to cardiovascular diseases such as trimethylamine N-oxide (TMAO), secondary bile acids, lipopolysaccharides (LPS), and short-chain fatty acids (SCFAs).[2] Because gut bacteria synthesize choline and trimethylamine (TMA), they contribute to the creation of TMAO, which is strongly linked to higher risks of mortality, nonfatal heart attacks, and strokes.[2,23,24] Our study also showed a decrease in butyrate-producing bacteria, which correlates with an increased risk of atherosclerosis.[9,12] It was previously discovered that butyrate served as IECs' primary energy source and could keep the gut barrier stable.[22] In general, our studies have reported a reduction in microbial diversity in the CAD group. This decrease in diversity has also been associated with other conditions, such as metabolic syndrome and diabetes.[6,25] A meta-analysis similarly identified reduced alpha diversity in the CAD group.[6] That study also observed an increase in *Enterobacteriaceae, Lactobacillus,* and *Streptococcus* taxa, along with a decrease in *Bacteroidetes* and *Lachnospiraceae*.[6] However, their study included acute coronary syndrome (ACS) patients within the CAD group, which may have introduced a confounding factor between acute and chronic CAD processes. In contrast, our study exclusively included patients with chronic coronary disease.[9,10,12,13] Although bacteria have been detected in atherosclerotic plaques, their direct role in the pathogenesis of atherosclerosis remains unclear.[26] identified several bacterial species in atherosclerotic plaques, with *Curvibacter,* unclassified *Burkholderiales, Propionibacterium,* and *Ralstonia* being the most prevalent taxa.[26] Bacteria within biofilm matrices exhibit heightened resistance to antibiotics and immune defences compared to free-floating bacteria, potentially exacerbating medical biofilm-related issues, including those associated with atherosclerosis.[26] While these bacterial biofilms may contribute to chronic inflammation in atherosclerosis, they are not considered direct causes of the disease.[26] Bacteria, as single cells or biofilm fragments, can enter the bloodstream through both normal and inflammatory pathways.[26,27]

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Table 2: Characteristics of the included studies

First author, year, country	Study design	Number of participants	Assessment of atherosclerosis	Comparison	Diversity α	$ß$	Diversity result	Shannon index	Result
Zhu *et al*, 2018, China[9]	Cross-sectional	78 patients with CAD and 90 controls	Coronary angiography	Healthy control	Decreased	Decreased	Decreased diversity in CAD group	P = 0.0348	*Escherichia-shigella* and *Enterococcus sp.* increased in CAD group *Faecalibacterium, Subdoligranulum, Roseburia* and *Eubacterium rectale* decreased in CAD group
Jie *et al*, 2017, China [10]	Cohort	405 fecal samples (218 with ACVD and 187 healthy control	Coronary angiography	Healthy control	No difference	No data	No significant difference between two groups	P = 0.974	*Klebsiella spp., Enterobacter aerogenes, and Escherichia coli* increased in ACVD group. *Prevotella copri, Roseburia intestinalis, Faecalibacterium prausnitzii, Alistipes shahii,* and *Bacteroides spp.*, decreased in ACVD group
Baragetti *et al*, 2021, Italy[11]	Case-control	144 subjects with subclinical atherosclerosis by carotid ultrasound examination and 201 gender-matched subjects without subclinical atherosclerosis	Coronary angiography	Healthy control	No difference	No difference	No significant difference between two groups	$P > 0.05$	*Escherichia coli* in the presence of subclinical atherosclerosis *Faecalibacterium prausnitzii* in the absence of subclinical atherosclerosis
Toya *et al*, 2020, USA[12]	Case-control	53 advanced CAD patients and 53 controls	Noninvasive stress testing, and coronary imaging studies including coronary computed tomography and/or coronary angiography	Healthy control	Decreased	No data	Decreased diversity in CAD group	P = 0.014	*Ruminococcus gnavus* increased in CAD. *Lachnospiraceae NK4B4* group and *Ruminococcus gauvreauii* decreased in CAD.
Szabo *et al*, 2021, Hungary[13]	Cross-sectional	14 discordant monozygotic pairs (n=28)	Carotid ultrasound	Normal IMT (intima-media thickness)	No difference	No data	No significant difference between two groups	P = 0.153	*Increased Firmicutes/Bacteroidetes* ratio was associated with increased IMT
Yoshida *et al*, 2018, Japan[14]	Cross-sectional	30 patients with CAD and 30 controls without CAD with coronary risk factors	Coronary angiography	CAD with risk coronary risk factors	No difference	No data	No significant difference between two groups	$P > 0.05$	*Bacteroides vulgatus* and *Bacteroides dorei* decreased in patients with CAD
Cui *et al*, 2017, China[15]	Cross-sectional	29 CAD in-hospital patients and 35 healthy volunteers	Coronary angiography	Healthy control	Increased	No data	Increased diversity in CAD group	$P < 0.01$	*Firmicutes* increased in CAD group *Bacteroidetes* decreased in CAD group

Microbiota imbalances contribute to coronary heart disease both directly, by influencing cholesterol metabolism through microbial metabolites, and indirectly, by modulating immune responses that promote inflammation and atherosclerosis.[5] Targeting gut microbiota imbalances, either through dietary interventions, probiotics, or other microbiome-modulating therapies, may offer novel strategies for preventing or mitigating the development of atherosclerosis. Additionally, the correlation between a higher Firmicutes-to-Bacteroidetes ratio and increased intima-media thickness (IMT) provides a potential biomarker for early detection of subclinical atherosclerosis.[4]

However, this present study has some limitations. The sample size is limited, reducing the generalizability of the findings, and the geographic scope of the study might not represent global microbiota diversity. Additionally, the use of specific detection techniques, such as 16S rRNA sequencing, may overlook broader microbial diversity and functional dynamics. The short-term nature of the study might fail to capture long-term trends, and focusing on single variables, such as diet or antibiotics, could neglect multifactorial influences. Moreover, the observational design limits the ability to establish causal relationships.

Future research should consider conducting longitudinal studies to explore long-term microbiota changes, including diverse populations from various regions and cultures to improve generalizability. Research on gut microbiota dysbiosis and its relationship to atherosclerosis in Indonesia is also limited, indicating a need for further exploration in this country. Employing advanced techniques like metagenomics and metabolomics can provide a more comprehensive understanding of microbial functions and interactions. Intervention studies on probiotics, prebiotics, and dietary changes should also be explored, along with multi-omics approaches that integrate genomics, proteomics, and transcriptomics to investigate microbiota-host interactions.

The Newcastle-Ottawa Scale (NOS), which uses a star system to evaluate three important aspects of study group selection, group comparability, and result determination was used to measure the risk of bias rated the average risk of bias for five of the included studies as low risk of bias (7 points or more for cross-sectional, 8 points or more for case-control/cohort).[10] Several authors,[11-15], and two studies reported a medium risk of bias (6 points for crossectional and 7 or 6 points for case-control/ cohort).[9] The results are presented in Table 3.

Table 3: Quality assessment of the included studies

Study	Selection (Max 4 stars)	Comparability (Max 2 stars)	Exposure (Max 3 stars)	Total Stars (Max 9 stars)
Zhu *et al.*, 2018[9]	***	*	**	***6***
Jie *et al.*, 2017[10]	****	**	***	***9***
Baragetti *et al.*, 2021[11]	****	**	*	***7***
Toya *et al.*, 2021[12]	***	**	***	***8***
Szabo *et al.*, 2021[13]	***	**	**	***7***
Yoshida *et al.*, 2018[14]	***	**	***	***8***
Cui *et al.*, 2016[15]	***	**	***	***8***

Conclusion

This study shows a strong correlation between gut microbiota dysbiosis and the onset of atherosclerosis. In particular, people with atherosclerosis have been found to have higher levels of pro-inflammatory and possibly harmful bacteria, including *Enterococcus sp*., *Ruminococcus gnavus*, *Escherichia-Shigella*, *Klebsiella spp*., *Enterobacter aerogenes*, and *Escherichia coli*. Increased synthesis of pro-atherogenic metabolites, such as lipopolysaccharides (LPS) and trimethylamine N-oxide (TMAO), is associated with these alterations. These metabolites lead to endothelial dysfunction, plaque development, and systemic inflammation. Furthermore, the loss of butyrate-producing bacteria like *Ruminococcaceae*, *Lachnospiraceae*, *Roseburia*, and *Faecalibacterium* may worsen inflammation and compromise the integrity of the gut barrier. The necessity for more consistent methods in subsequent research is shown by the variation in microbial diversity results between studies. By addressing abnormalities in the gut microbiota, microbiome-modulating treatments including probiotics, prebiotics, and dietary changes may offer new ways to prevent or lessen atherosclerosis.

Conflict of Interest

The authors declare no conflicts of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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