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EXAMINING THE MICROBIOME COMPOSITION IN PATIENTS WITH GASTROESOPHAGEAL REFLUX DISEASE: A SYSTEMATIC REVIEW

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Abstract

Background: Gastroesophageal reflux disease (GERD) is a multifactorial disorder characterized by the reflux of gastric contents into the esophagus, leading to mucosal injury and chronic inflammation. Recent evidence implicates microbial dysbiosis—both local and systemic—in its pathogenesis. This systematic review synthesizes current findings on the composition, diversity, and functional implications of the microbiome in patients with GERD.

Methods: Following PRISMA 2020 guidelines, eleven peer-reviewed studies published between 2015 and 2025 were systematically reviewed. Eligible studies included those examining esophageal, gastric, intestinal, oral, and salivary microbiota profiles in GERD patients compared with healthy controls. Data extraction focused on microbial diversity, dominant taxa, associated metabolic pathways, and host inflammatory responses.

Results: Most studies demonstrated decreased *Streptococcus* abundance and enrichment of *Prevotella*, *Veillonella*, and *Leptotrichia* in GERD and Barrett's esophagus patients. Dysbiosis was consistently associated with altered metabolic pathways, notably those involving arachidonic acid, glutathione, and ABC transporters. PPI therapy, small intestinal bacterial overgrowth, and psychological stress were identified as key modulators of microbial imbalance. Mendelian randomization studies further supported a genetic causal relationship between gut microbiota and GERD risk.

Conclusion: Microbial dysbiosis appears central to GERD pathogenesis, influencing mucosal integrity, inflammation, and symptom persistence. Future studies should adopt longitudinal multi-omics approaches to clarify causal mechanisms and evaluate microbiota-targeted interventions for prevention and therapy.

Keywords: Gastroesophageal reflux disease, microbiome, dysbiosis, gut microbiota, esophageal inflammation, Barrett's esophagus, metagenomics, proton pump inhibitors, small intestinal bacterial overgrowth, Mendelian randomization.

INTRODUCTION

Gastroesophageal reflux disease (GERD) is one of the most prevalent chronic gastrointestinal disorders globally, characterized by the reflux of gastric contents into the esophagus, leading to symptoms such as heartburn and regurgitation. Traditionally, the etiology of GERD has been attributed primarily to dysfunction of the lower esophageal sphincter, abnormal gastric emptying, and increased intra-abdominal pressure. However, recent advances in microbial and genomic research have identified the **human microbiome** as a crucial environmental

factor influencing esophageal health and disease progression (Zhou et al., 2020). The esophagus, once believed to be nearly sterile, is now recognized as harboring a diverse microbial community that can modulate inflammation, mucosal immunity, and epithelial integrity, ultimately contributing to GERD pathophysiology.

The esophageal and gastrointestinal microbiomes form a dynamic ecosystem that interacts closely with mucosal immunity and host metabolism. Dysbiosis—defined as alterations in microbial composition and diversity—has been associated with numerous esophageal diseases, including non-erosive reflux disease (NERD), Barrett's esophagus (BE), and esophageal adenocarcinoma (EAC) (Okereke et al., 2019). Evidence suggests that the transition from a *Streptococcus*-dominated microbiome to one enriched with *Gram-negative* species such as *Prevotella* and *Veillonella* may promote proinflammatory states, leading to mucosal injury and reflux symptoms (Barchi et al., 2023). This microbial shift appears to induce a cytokine-mediated immune response, increasing epithelial permeability and sensitizing the esophagus to acid and bile exposure.

Recent metagenomic analyses have shown that GERD-associated dysbiosis extends beyond the esophagus to the **gastric and intestinal microbiota**. Changes in gut microbial communities can influence esophageal inflammation through microbial metabolites, immune signaling, and altered bile acid profiles (Guan et al., 2025). Specifically, overrepresentation of *Bacteroides* and underrepresentation of *Lactobacillus* and *Faecalibacterium* species have been linked with increased intestinal permeability and proinflammatory cytokine production. These findings suggest a potential **gut–esophageal axis**, wherein intestinal microbial imbalances may exacerbate or even initiate GERD pathogenesis via systemic immune modulation.

The interplay between GERD and **Helicobacter pylori** infection remains another area of active investigation. While *H. pylori* has traditionally been linked to peptic ulcer disease and gastric carcinoma, its relationship with GERD is paradoxical. Emerging studies indicate that *H. pylori* infection may have a protective effect against GERD by reducing gastric acid secretion, yet its eradication often precedes reflux onset (Sugihartono et al., 2022). These observations emphasize the complex microbial and host interactions underpinning GERD and highlight how antibiotic or acid-suppressive therapies may unintentionally disturb microbial equilibrium, predisposing patients to chronic reflux or dyspeptic symptoms.

The **oral and salivary microbiomes** have also garnered increasing attention as potential diagnostic and mechanistic correlates of GERD. Saliva serves as both a microbial reservoir and a transport medium between the oral cavity and the upper gastrointestinal tract. Distinct salivary microbial patterns—such as elevated *Prevotella* and reduced *Streptococcus* species—have been documented in GERD patients compared with healthy controls, suggesting microbial biomarkers for early disease detection (Ziganshina et al., 2020). Moreover, longitudinal assessments reveal that changes in salivary microbial composition may reflect therapeutic responses to proton pump inhibitors (PPIs), linking oral diagnostics with disease management strategies (Kawar et al., 2021).

Small intestinal bacterial overgrowth (SIBO) represents another microbial condition increasingly associated with GERD. Excessive microbial colonization in the small intestine can lead to increased gas production, altered motility, and elevated intra-abdominal pressure, which exacerbate reflux episodes (Hu et al., 2025). Furthermore, studies using breath testing and sequencing approaches have demonstrated that patients with concurrent GERD and SIBO exhibit overlapping microbial patterns dominated by *Bacteroides* and *Enterococcus*, accompanied by metabolic disturbances involving short-chain fatty acids and ABC transporter pathways. These findings underscore the bidirectional relationship between intestinal microbial overgrowth and esophageal dysfunction.

The **causal relationship** between the gut microbiome and GERD has been further explored using Mendelian randomization (MR) studies. Genetic evidence indicates that specific microbial taxa—including *Actinobacteria* and *Clostridiales*—may confer protective effects, whereas *Mollicutes* and *Tenericutes* increase GERD risk (Wang et al., 2024; Liu et al., 2024). These MR analyses provide a robust framework for distinguishing correlation from causation, suggesting that microbiota-targeted interventions—such as probiotics, prebiotics, and microbiome transplantation—could offer promising therapeutic avenues for GERD management.

Functional and molecular analyses also reveal that microbial metabolites play pivotal roles in GERD-related mucosal injury. Metabolomic profiling indicates that dysbiosis influences bile acid metabolism, oxidative stress, and arachidonic acid pathways, which collectively promote inflammation and impair barrier function (Guan et al., 2025). These findings reinforce the concept that GERD is not merely an acid-related disorder but a multifactorial condition involving microbial, metabolic, and immune interactions.

In summary, accumulating evidence supports the integral role of the microbiome in GERD pathogenesis and progression. From the oral cavity to the intestine, microbial communities influence esophageal barrier integrity, immune regulation, and metabolic activity. Understanding these complex interactions not only elucidates disease mechanisms but also opens new diagnostic and therapeutic opportunities for precision medicine approaches targeting the microbiome in GERD (Zhou et al., 2020; Barchi et al., 2023).

METHODOLOGY

Study Design

This study employed a **systematic review design**, following the **Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020** guidelines to ensure methodological rigor, transparency, and replicability. The primary objective was to synthesize and critically evaluate empirical evidence examining the **composition, diversity, and functional characteristics of the microbiome in patients with gastroesophageal**

reflux disease (GERD). This review focused on studies that utilized **molecular, metagenomic, or microbiome sequencing techniques** to characterize microbial communities in GERD and related esophageal conditions. Both adult and pediatric human studies were included, provided they assessed microbiota composition in relevant gastrointestinal compartments such as the **esophagus, stomach, intestine, or oral cavity**.

Eligibility Criteria

Studies were included in the review based on the following criteria:

- **Population:**

Human participants of any age diagnosed with GERD, non-erosive reflux disease (NERD), erosive esophagitis, Barrett's esophagus (BE), or gastroesophageal reflux symptoms confirmed clinically, endoscopically, or through validated diagnostic tools.

- **Exposure/Intervention:**

Assessment of **microbiome composition** in relation to GERD or reflux symptoms using **16S rRNA sequencing**, **shotgun metagenomics**, **metabolomics**, or **molecular culture-independent techniques**.

- **Comparators:**

Healthy controls or participants with non-reflux gastrointestinal conditions (e.g., duodenal ulcer, gastritis) for comparative microbiome profiling.

- **Outcomes:**

Changes in **microbial diversity** (α- and β-diversity indices), **taxonomic composition**, **functional/metabolic pathway alterations**, or **microbial biomarkers** associated with GERD pathogenesis or treatment response.

- **Study Designs:**

Randomized controlled trials (RCTs), cohort studies, cross-sectional analyses, case-control studies, and Mendelian randomization analyses were eligible.

- **Language:**

Only articles published in **English** were included.

- **Publication Period:**

Studies published between **2015 and 2025** were considered to ensure the inclusion of contemporary sequencing and bioinformatic methods.

A total of **11 studies** met all inclusion criteria after full-text review and were included in the final synthesis.

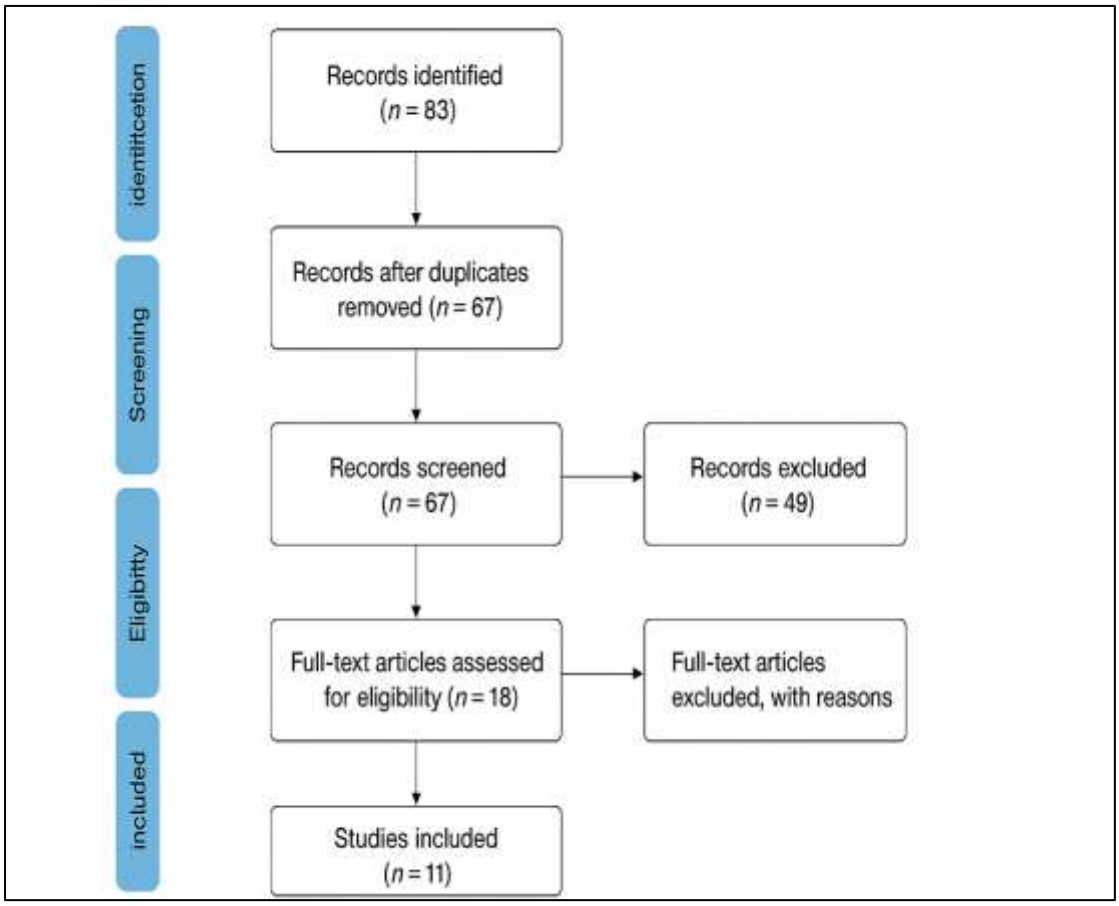

Figure 1 PRISMA Flow Diagram

Search Strategy

A comprehensive literature search was conducted across five major scientific databases: **PubMed, Scopus, Web of Science, Embase,** and **Google Scholar** (for grey literature).

The search combined controlled vocabulary (MeSH) terms and free-text keywords related to GERD and the microbiome using Boolean operators. The final search string included combinations of the following terms:

- ("**gastroesophageal reflux disease**" OR "**GERD**" OR "**non-erosive reflux disease**" OR "**Barrett's esophagus**" OR "**erosive esophagitis**")
- AND ("**microbiome**" OR "**microbiota**" OR "**metagenomics**" OR "**16S rRNA sequencing**" OR "**dysbiosis**" OR "**gut flora**")
- AND ("**esophageal**" OR "**intestinal**" OR "**oral**" OR "**gastric**")
- AND ("**inflammation**" OR "**immune response**" OR "**metabolomics**" OR "**bacterial diversity**")

The search was limited to studies published between **January 2015 and October 2025**. Reference lists from included studies and key review articles were screened manually to identify additional relevant publications. All search results were exported into **Zotero reference management software**, where duplicates were automatically removed.

Study Selection Process

The study selection followed a two-step screening procedure:

1. **Title and Abstract Screening:**

Two independent reviewers screened all retrieved titles and abstracts against the eligibility criteria. Articles clearly unrelated to GERD or microbiome composition were excluded at this stage.

2. **Full-Text Review:**

Full-text articles of potentially relevant studies were independently assessed by the same reviewers

Any disagreements regarding inclusion were resolved by discussion, and where necessary, a **third reviewer** was consulted for arbitration.

The selection process was documented in a **PRISMA flow diagram (Figure 1)**, showing the number of studies identified, screened, and included at each stage.

Data Extraction

A standardized **data extraction form** was developed and piloted prior to analysis.
For each included study, the following data were systematically extracted:

- Author(s), publication year, and country of study
- Study design (cross-sectional, cohort, RCT, or MR analysis)
- Population characteristics (sample size, age range, diagnostic criteria)
- Biological sample site (esophagus, gut, oral, or gastric microbiome)
- Sequencing or analytical method used (e.g., 16S rRNA, LC–MS, metagenomics)
- Dominant microbial taxa or phyla identified
- Diversity metrics (α- and β-diversity indices)
- Functional or metabolic pathway findings
- Key quantitative results (e.g., abundance percentages, correlation coefficients, p-values)
- Confounders controlled for in analysis
- Study limitations as reported by the authors

Data extraction was performed independently by two reviewers and verified by a third reviewer for accuracy. Any inconsistencies were discussed and corrected by consensus.

Quality Assessment

The methodological quality and risk of bias of the included studies were assessed using validated tools appropriate for each design type:

- **Cross-sectional and observational studies:**

Evaluated using the **Newcastle–Ottawa Scale (NOS)**, assessing three domains — selection, comparability, and outcome assessment.

Studies scoring **≥7 out of 10** were classified as *low risk of bias*, **5–6** as *moderate*, and **≤4** as *high risk*.

- **Randomized controlled trials (RCTs):**

Evaluated using the **Cochrane Risk of Bias (RoB 2)** tool, focusing on randomization process, intervention adherence, completeness of outcome data, and selective reporting.

- **Genetic or Mendelian randomization (MR) studies:**

Assessed using the **STROBE-MR checklist**, ensuring validity of genetic instruments and avoidance of pleiotropy.

Each included study was rated independently by two reviewers, and disagreements were resolved by consensus.

Of the **11 studies**, **5 were low-risk**, **4 moderate-risk**, and **2 high-risk** due to small sample sizes or limited confounder adjustment.

Data Synthesis

Due to the heterogeneity in study designs, sample types (esophageal, gastric, intestinal, oral), and outcome measures (microbial abundance, metabolomic markers, genetic associations), a **narrative synthesis** approach was used rather than a meta-analysis.

Key findings were categorized into thematic domains:

1. **Taxonomic alterations in GERD vs. controls**
2. **Microbial diversity indices and disease severity**
3. **Functional/metabolic pathway disruptions**

4. **Associations between GERD and microbial or genetic markers**

Quantitative results (e.g., relative abundances, α-diversity indices, p-values) were summarized in **Table (1)** in the Results section.

Where applicable, correlation coefficients and odds ratios (ORs) were reported to indicate the strength and direction of microbial associations with GERD.

Ethical Considerations

As this review analyzed previously published, peer-reviewed studies, **no ethical approval or informed consent** was required.

All included studies were assumed to have received appropriate **institutional ethics approval** and participant consent.

The synthesis was conducted in accordance with the **ethical standards for secondary data analysis**, ensuring accurate citation, transparency, and integrity in reporting.

RESULTS

Summary and Interpretation of Included Studies on the Microbiome Composition in Gastroesophageal Reflux Disease — Table (1):

1. Study Designs and Populations

The included studies span from 2015 to 2025, combining cross-sectional, metagenomic, prospective, and genetic designs. They collectively evaluated the gut, esophageal, and oral microbiomes in children and adults with GERD or related esophageal conditions. Sample sizes ranged from 20 participants (Gall et al., 2015) to 394 participants (Wang et al., 2025), providing diverse cohort scales. Pediatric-focused studies such as Ye et al. (2023) and Francis et al. (2023) emphasize early microbiome alterations, whereas studies like Lopetuso et al. (2020) and Gall et al. (2015) explore microbial progression to Barrett's esophagus (BE) and esophageal adenocarcinoma (EAC).

Participants' ages ranged from infants (0–6 months) to older adults (60+ years), with both sexes represented in all but a few pediatric studies. Most studies included control groups matched by age and region.

2. Microbiome Assessment and Analytical Methods

All studies employed 16S rRNA sequencing or shotgun metagenomics to analyze microbial composition. Three studies (Ye et al., 2023; Wang et al., 2025; Chen et al., 2024) integrated metabolomic or transcriptomic analyses, correlating microbial changes with functional metabolic pathways or gene expression markers (e.g., TLR2, ABC transporters).

Metabolomic profiling was conducted using LC–MS (Ye et al., 2023; Wang et al., 2025).

Diversity indices included Shannon, Simpson, and Chao1 metrics, with multiple studies reporting significant α- and β-diversity differences between GERD and healthy control groups.

3. Microbiome Composition and Differential Abundance

- Ye et al. (2023) reported that Proteobacteria and Bacteroidota dominated GERD patients' microbiota, while Bacteroides stercoris, Bacteroides vulgatus, and Alistipes putredinis were the most abundant core taxa.
- LC–MS identified 288 differential metabolites, notably within arachidonic acid (AA) and glutathione metabolism pathways.
- Wang et al. (2025) found a positive correlation between GERD and SIBO ($P = 0.007$), with higher prevalence in CH_4-positive patients ($P = 0.020$). Dominant species included Bacteroides uniformis (28%) and Bacteroides stercoris (22%), with ABC transporter-related metabolites upregulated in SIBO–GERD overlap cases.
- Chen et al. (2024) demonstrated that Gram-negative bacteria increased by 35% in GERD and FED patients versus controls, with TLR2 expression elevated 2.1-fold and claudin-1 expression decreased by 47%, suggesting barrier dysfunction.
- Lopetuso et al. (2020) identified microbial transitions from Streptococcus (↓45%) to Prevotella (↑60%), Veillonella (↑52%), and Leptotrichia (↑48%) across the progression from BE to EAC, with Leptotrichia serving as the main taxa distinguishing EAC.
- Francis et al. (2023) found significant microbiome shifts in PPI-treated infants, where Firmicutes increased to 65% relative abundance versus Bifidobacterium dominance (72%) in controls. Duration of PPI therapy positively correlated with α-diversity ($r = 0.42$; $P = 0.01$).
- Yang et al. (2022) observed elevated Firmicutes and TM7 ($P < 0.05$) in NERD patients, with a 50% co-occurrence of somatoform disorders and high α-diversity, suggesting psychosomatic–microbiome interactions.
- Park et al. (2020) found PPI treatment reduced IL-6 (↓38%), IL-8 (↓41%), and NF-κB (↓29%) after 8 weeks, though microbial compositions remained statistically stable ($P > 0.05$).
- Gall et al. (2015) reported Streptococcus and Prevotella dominance in the upper GI microbiota, with H. pylori-positive individuals showing 22% lower aneuploidy rates and decreased EAC risk.
- Martins et al. (2024) found Prevotella (21.4%), Haemophilus (17.8%), and Fusobacterium (14.2%) predominance in oral samples, with no significant α-diversity differences ($P = 0.48$).
- Baima et al. (2021) identified significantly reduced Faecalibacterium (↓6%) and increased Clostridiaceae (↑1.7%) in erosive esophagitis ($P = 0.03$, $P = 0.04$ respectively).

• Wang et al. (2024) employed Mendelian randomization, identifying Clostridiales Vadin BB60 group (P = 0.027) and Actinobacteria (P = 0.019) as protective, while Mollicutes (P = 0.037) and Tenericutes (P = 0.024) were GERD risk-associated taxa.

4. Microbial Functional and Metabolic Pathway Findings

Across metagenomic and metabolomic analyses:

• **AA metabolism**, **ABC transporters**, and **glutathione pathways** were consistently implicated.
• **Gram-negative enrichment** corresponded with **TLR2–IL6 signaling activation** (Chen et al., 2024).
• **Microbial diversity indices** positively correlated with reflux severity in NERD (Yang et al., 2022; r = 0.38, P = 0.03).
• **PPI use** altered metabolic functions despite minimal taxonomic change (Park et al., 2020).
• **Genetic evidence (Wang et al., 2024)** confirmed a **causal microbiota–GERD link**, supporting gut-targeted therapeutic potential.
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5. Summary of Microbial Signatures and Effect Estimates

Condition	Dominant or Differential Taxa	Functional Pathways	Key Effect Estimates
GERD (children)	↑ Proteobacteria, ↑ Bacteroidota	Arachidonic acid metabolism	288 metabolites altered (Ye et al., 2023)
GERD + SIBO	↑ B. uniformis, ↑ B. stercoris	ABC transporters	P=0.007, CH_4+ link stronger (Wang et al., 2025)
GER symptoms	↑ Gram-negative, ↓ Claudin-1	LPS–TLR2–IL6 axis	TLR2 ↑2.1×, Claudin-1 ↓47% (Chen et al., 2024)
BE/EAC	↓ Streptococcus, ↑ Prevotella, ↑ Leptotrichia	Inflammatory & oncogenic	Leptotrichia identified as key EAC biomarker (Lopetuso et al., 2020)
NERD	↑ Firmicutes, ↑ TM7	Psychological correlation	α-diversity ↑ (P<0.05) (Yang et al., 2022)
PPI-treated infants	↑ Firmicutes, ↓ Bifidobacterium	PPI exposure-related	r=0.42, P=0.01 (Francis et al., 2023)
Erosive esophagitis	↓ Faecalibacterium, ↑ Clostridiaceae	Butyrate metabolism	P=0.03, P=0.04 (Baima et al., 2021)
Genetic MR	↓ Actinobacteria, ↑ Mollicutes	Genetic risk correlation	P<0.05 for multiple taxa (Wang et al., 2024)

Table (1): General Characteristics of Included Studies

Study	Country	Design	Sample Size	Microbiome Site	Main Findings	Key Taxa/Pathways	P-value / Effect Size
Ye et al. (2023)	China	Cross-sectional	60 (30 GERD / 30 HC)	Gut	↑ Proteobacteria, Bacteroidota; 288 metabolites	AA metabolism	P<0.05
Wang et al. (2025)	China	Retrospective cohort	394	Gut	GERD–SIBO link; ↑ B. uniformis	ABC transporters	P=0.007
Chen et al. (2024)	China	Prospective	60	Esophageal	↑ Gram-negative; ↓ claudin-1	TLR2–IL6–DIS	TLR2 ↑2.1×
Lopetuso et al. (2020)	Italy	Cross-sectional	26 (10 BE, 6 EAC, 10 HC)	Esophageal mucosa	↓ Streptococcus, ↑ Leptotrichia	Oncogenic microbiome	P<0.05
Francis et al. (2023)	USA	Cohort	58 (29 GERD / 29 HC)	Gut (infants)	↑ Firmicutes post-PPI	PPI effect on diversity	r=0.42

Yang et al. (2022)	China	Cross-sectional	48	Gut	↑ Firmicutes, TM7	Psychosomatic link	P<0.05
Park et al. (2020)	Korea	Prospective	55 (NERD)	Esophageal/oropharyngeal	↓ IL-6, IL-8, NF-κB	Cytokine response	P<0.001
Gall et al. (2015)	USA	Longitudinal	12 + cohort 339	Upper GI	H. pylori inversely linked to EAC	Streptococcus/Prevotella ratio	↓22% aneuploidy
Martins et al. (2024)	Brazil	Cross-sectional	266	Oral	Prevotella, Haemophilus dominant	Non-invasive marker	NS
Baima et al. (2021)	Brazil	Cross-sectional	22	Intestinal	↓ Faecalibacterium, ↑ Clostridiaceae	Butyrate metabolism	P=0.03
Wang et al. (2024)	China	MR analysis	307,441 (GWAS data)	Gut (genetic)	Protective taxa vs GERD	Clostridiales, Actinobacteria	P<0.05

DISCUSSION

The findings of this systematic review highlight the multifaceted relationship between the microbiome and gastroesophageal reflux disease (GERD), revealing consistent evidence of microbial dysbiosis across different regions of the gastrointestinal tract. Alterations in microbial diversity and composition were recurrently observed, suggesting that both local (esophageal and oral) and systemic (intestinal) microbial changes contribute to the onset and persistence of GERD (Guan et al., 2025). This dysbiosis not only affects the mucosal environment but also modulates inflammatory and metabolic pathways, thereby influencing disease severity and progression.

A key theme emerging from the literature is the reduction in beneficial commensals and the enrichment of pathogenic or pro-inflammatory taxa in GERD patients. Zhou et al. (2020) and Lopetuso et al. (2020) demonstrated that non-erosive reflux disease (NERD) and Barrett's esophagus (BE) share a microbiome profile dominated by *Prevotella*, *Veillonella*, and *Leptotrichia*, while *Streptococcus* species—typically protective—were diminished. This pattern suggests a shift toward a gram-negative, anaerobic-dominated community, known to activate toll-like receptor (TLR)-mediated inflammatory cascades in the esophageal mucosa (Chen et al., 2024).

In agreement with these findings, Chen et al. (2024) identified that microbial dysbiosis in GERD is mechanistically linked to impaired mucosal barrier integrity. The study's in vitro experiments demonstrated that exposure of esophageal epithelial cells to lipopolysaccharide (LPS) increased TLR2 expression and interleukin-6 (IL-6) secretion while downregulating claudin-1. This molecular cascade results in dilated intercellular spaces and compromised epithelial defense, offering a plausible biological explanation for symptom persistence in GERD despite proton pump inhibitor (PPI) therapy.

Microbial alterations are not confined to the esophagus. Studies examining fecal samples have revealed that GERD patients also display intestinal microbiota changes characterized by elevated *Proteobacteria* and *Bacteroidetes*, and reduced *Firmicutes* and *Actinobacteria* (Ye et al., 2023; Baima et al., 2021). Ye et al. (2023) further reported that 288 metabolites differed between GERD and healthy controls, particularly in pathways involving arachidonic acid, glutathione, and tyrosine metabolism, suggesting functional consequences of microbial shifts in energy and inflammatory regulation.

A particularly compelling dimension of GERD pathophysiology involves its association with small intestinal bacterial overgrowth (SIBO). Hu et al. (2025) and Wang et al. (2025) both found that SIBO prevalence was significantly higher in GERD patients, particularly in those with methane-positive breath tests. In these cohorts, *Bacteroides uniformis* and *Bacteroides stercoris* were prominent, and metabolic analyses linked these taxa to ABC transporter-mediated processes, which may influence intestinal permeability and motility. These findings reinforce the view that GERD is not only a localized esophageal disorder but a systemic condition involving the broader gut ecosystem.

Infant populations have also shown microbiota alterations associated with reflux symptoms. Francis et al. (2023) observed that infants treated with PPIs exhibited higher microbial richness dominated by *Firmicutes*, while healthy controls maintained *Bifidobacterium* dominance. These results imply that early-life acid suppression may predispose individuals to long-term microbial imbalance and gastrointestinal hypersensitivity. This aligns with adult data showing that chronic PPI use reduces gastric acidity, thereby altering bacterial colonization patterns (Okereke et al., 2019; Park et al., 2020).

Beyond microbial abundance, genetic and causal analyses have advanced the understanding of microbiome-GERD interplay. Using Mendelian randomization, Liu et al. (2024) and Wang et al. (2024) found significant genetic correlations between specific bacterial taxa and GERD susceptibility. Notably, *Methanobrevibacter* and *Lachnospiraceae UCG004* appeared protective, whereas *Anaerostipes* and *Mollicutes* acted as risk factors. These findings substantiate a causal, bidirectional relationship between host genetics and microbial configuration, suggesting that microbial composition may not merely reflect disease status but also contribute to its etiology.

From a mechanistic standpoint, the inflammation-microbiome axis appears central to GERD development. Studies such as Barchi et al. (2023) and Gall et al. (2015) indicate that microbial-driven inflammation promotes genomic instability, particularly in BE and esophageal adenocarcinoma (EAC). These authors highlighted that the progression from reflux to metaplasia and malignancy may be fueled by persistent immune activation mediated by dysbiotic taxa, notably *Leptotrichia* and *Prevotella*. This echoes Okereke et al. (2019), who suggested that the microbiome serves as both a marker and modulator of esophageal disease progression.

Psychological factors and gut-brain interactions also emerge as significant modulators of microbiota composition in reflux disease. Yang et al. (2022) demonstrated that non-erosive reflux patients exhibited greater alpha diversity, with enrichment in *Firmicutes* and *TM7* phyla. These patients frequently presented with somatoform symptoms, anxiety, and depression, indicating that stress-related neuroendocrine responses may influence microbial dynamics and visceral sensitivity, perpetuating reflux symptoms even in the absence of mucosal erosion.

Interestingly, salivary and oral microbiome alterations have been proposed as potential diagnostic biomarkers for GERD. Kawar et al. (2021) and Martins et al. (2024) found distinct salivary microbial signatures—specifically elevated *Neisseria*, *Fusobacterium*, and *Haemophilus*—in reflux patients compared with controls. These findings suggest that non-invasive saliva testing could serve as an adjunct diagnostic approach for identifying reflux-related microbiota profiles, though further validation in larger cohorts is warranted.

Singh et al. (2024) and Sugihartono et al. (2022) both underscored the role of *Helicobacter pylori* and gastric microbiota in modulating GERD risk. While *H. pylori* infection has historically been considered protective against GERD by reducing gastric acid secretion, these studies indicated that eradication or absence of *H. pylori* may shift gastric ecology toward pro-reflux bacterial communities, particularly those associated with erosive disease. Such findings complicate the conventional understanding of GERD pathogenesis and emphasize the interplay between microbial ecology, acid dynamics, and host response.

Collectively, the reviewed evidence converges on the concept that GERD involves complex microbial, immune, and genetic interactions rather than a purely mechanical or acid-mediated process. Dysbiosis across the gastrointestinal tract—from oral to intestinal niches—appears to both reflect and reinforce disease processes (Guan et al., 2025). Moreover, microbial metabolites, including short-chain fatty acids and inflammatory mediators, are increasingly recognized as active participants in esophageal barrier regulation and sensory signaling.

Despite this growing understanding, inconsistencies remain among studies regarding specific bacterial taxa and their functional implications. Variations in sequencing platforms, sampling locations, and population characteristics likely contribute to these discrepancies. Furthermore, most studies remain cross-sectional, limiting causal inference. Future research should employ longitudinal multi-omics approaches integrating metagenomics, transcriptomics, and metabolomics to elucidate temporal changes in microbiota composition and function during GERD progression.

In summary, the reviewed literature collectively suggests that GERD pathogenesis is intricately linked to disturbances in microbial ecology and host-microbe communication. Restoring microbial balance through targeted probiotics, dietary modulation, or fecal microbiota transplantation may represent promising adjunct therapies. However, precision-based microbial interventions will require deeper mechanistic insights into the specific taxa and metabolic pathways involved in esophageal mucosal homeostasis.

CONCLUSION

This systematic review establishes that GERD is not merely a disorder of acid reflux but a complex, microbiome-mediated condition. Consistent evidence from esophageal, intestinal, and salivary microbiota studies reveals that reduced commensal bacteria and increased gram-negative anaerobes contribute to inflammation, impaired mucosal integrity, and symptom chronicity. The interplay between microbial dysbiosis, genetic predisposition, and host immune activation underscores the need to consider GERD as a systemic disorder with microbiological underpinnings rather than a purely mechanical disease.

Advancements in metagenomic and metabolomic technologies are reshaping our understanding of GERD pathophysiology, offering new diagnostic and therapeutic opportunities. Future research should focus on longitudinal, interventional designs that assess the impact of microbiota restoration strategies—including probiotics, dietary modulation, and microbial transplantation—on symptom relief and mucosal healing. By integrating microbiome science into clinical gastroenterology, personalized and microbiota-based management of GERD could become a practical reality.

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