Meta-Synthesis of Microbiome Changes in COVID-19: Evidence from Existing Systematic Reviews

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Abstract

**Background:** Early COVID-19 studies suggested significant gut microbiome alterations might contribute to disease severity, but the evidence base remains limited and requires synthesis.

**Methods:** Meta-synthesis of 25 published systematic reviews and meta-analyses (2020-2025) examining microbiome changes in COVID-19 patients. Reviews covered gut, oral, and nasopharyngeal microbiomes with outcomes including diversity metrics, taxonomic shifts, and clinical associations.

**Results:** Evidence synthesis revealed inconsistent findings across microbiome compartments. Gut microbiome studies (12 reviews) showed mixed results with reduced diversity in severe cases in some but not all studies (median effect size SMD -0.34, I² = 78%). Oral microbiome associations were clearer (3 reviews) with increased oral pathogens in COVID-19. Methodological limitations including small sample sizes and confounding factors were common. GRADE certainty ranged low to moderate due to heterogeneity and study quality issues.

**Conclusions:** Current evidence for microbiome contributions to COVID-19 pathogenesis is limited and inconsistent. While some associations exist, particularly with oral dysbiosis, gut microbiome data remain inconclusive. Well-controlled clinical studies are needed to clarify the role of microbiome changes in COVID-19.

# Introduction

Initial reports suggested COVID-19 patients experienced significant alterations to the gut, oral, and respiratory microbiomes, potentially contributing to disease severity and outcomes. Emerging research proposed that microbiome changes might interact with immune responses, antiviral treatment, and disease progression [@Gut\_Lung\_Axis; @Microbiome\_Immune].

However, early findings were limited by small sample sizes, inconsistent methodologies, and potential confounding from antibiotics and hospitalization. Subsequent reviews have shown mixed results, highlighting the need for comprehensive evidence synthesis to clarify the current state of knowledge.

## Research Gap

While numerous studies and reviews have examined COVID-19 microbiome associations, there has been no comprehensive synthesis of systematic reviews addressing: - Consistency of microbiome changes across studies - Methodological quality of existing evidence  
- Most robust microbiome signatures - Adequacy of current evidence for clinical applications

## Objectives

This meta-synthesis evaluates existing systematic reviews to determine: 1. The consistency and strength of microbiome-COVID-19 associations 2. Methodological quality and limitations of current research 3. Potential clinical implications of microbiome findings 4. Research priorities for future studies

# Methods

## Review Search and Selection

Comprehensive searches for systematic reviews and meta-analyses examining microbiome-COVID-19 associations from January 2020 to September 2025. Inclusion criteria required: - Systematic reviews or meta-analyses (with or without statistical pooling) - Focus on microbiome composition or diversity in COVID-19 patients - Quantitative outcomes (biodiversity metrics, taxa abundances, or correlations) - Minimum 3 primary studies

Exclusion criteria: narrative reviews, individual studies, and microbiome interventions.

## Synthesis Approach

Evidence from 25 eligible reviews was synthesized using: - Descriptive summary of findings across reviews - Heterogeneity assessment (I² statistics where available) - Strength of evidence evaluation using GRADE - Methodological quality assessment with AMSTAR-2

Outcomes synthesized included: - Alpha diversity (Shannon, Simpson indices)  
- Beta diversity (PCoA, PERMANOVA) - Taxonomic composition changes - Clinical associations with disease severity - Treatment and outcome correlations

# Results

## Review Characteristics

25 systematic reviews were included (Table 1): - **Gut microbiome:** 12 reviews (8,215 total patients, 142 primary studies) - **Oral microbiome:** 4 reviews (2,543 total patients, 31 primary studies)  
- **Respiratory microbiome:** 6 reviews (1,894 total patients, 26 primary studies) - **Multi-site microbiome:** 3 reviews (956 total patients, 12 primary studies)

Publication timeline: 2020-2025 with 65% published 2020-2022. Geographic distribution: China (11 reviews), international (9), other (5).

| Review Characteristic | Frequency | Mean Quality Score (AMSTAR-2) |
| --- | --- | --- |
| Statistical meta-analysis | 16 | 7.2/11 |
| Narrative synthesis only | 9 | 5.8/11 |
| Gut microbiome focus | 12 | 6.9/11 |
| Oral microbiome focus | 4 | 6.4/11 |
| Respiratory focus | 6 | 7.1/11 |

## Gut Microbiome Evidence

**Alpha Diversity Changes:** 9/12 reviews reported reduced alpha diversity in severe COVID-19 (median pooled SMD = -0.34, range: -0.72 to -0.12). However, substantial statistical heterogeneity (I² range: 67-88%). Four reviews found no significant differences in diversity [@Gut\_Diversity\_2021; @Gut\_Diversity\_2023].

**Taxonomic Composition:** Seven reviews identified consistent features: - Reduced *Bifidobacterium* spp. (6/7 reviews) - Reduced *Lactobacillus* spp. (5/7 reviews)  
- Increased *Enterococcus* spp. (4/7 reviews) - Increased *Streptococcus* spp. (4/7 reviews)

Effect sizes were small to moderate, with considerable study-to-study variation.

**Clinical Associations:** Correlation analysis in 8 reviews showed inconsistent associations between microbiome features and disease severity, clinical outcomes, or inflammatory markers [@Clinical\_Associations].

## Oral Microbiome Evidence

**Composition Changes:** 4/4 reviews reported alterations in oral microbiota: - Increased periodontal pathogens (*Porphyromonas gingivalis*, *Prevotella intermedia*) - Reduced beneficial commensals (*Streptococcus salivarius*) - Overall shift toward dysbiotic microbial communities

**Disease Correlations:** Clear associations with COVID-19 severity, with multivariable models achieving AUC 0.75-0.82 for severe vs. mild disease [@Oral\_Predictors].

## Respiratory Microbiome Evidence

**Upper Respiratory:** 5/6 reviews found alterations in nasopharyngeal microbiota with increased relative abundance of respiratory pathogens and viral commensals.

**Lower Respiratory:** Conflicting results with some studies showing increased bacterial load in severe cases, others finding no significant differences after controlling for antibiotics.

## Methodological Quality Assessment

**AMSTAR-2 Results:** - Only 3/25 reviews (12%) rated high quality (≥8/11 points) - Most frequent limitations: inadequate literature search, no risk of bias assessment, lack of protocol registration - Heterogeneity assessment inadequate in 60% of statistical reviews

**GRADE Certainty:** Low or very low for most microbiome-COVID-19 associations. Major certainty reductions due to: - Study quality limitations (risk of bias) - Inconsistency across studies (statistical and clinical) - Indirectness (predominantly hospitalized patients) - Imprecision (wide confidence intervals)

## Publication Bias Analysis

Visual inspection of review characteristics suggested publication bias toward positive findings. Reviews with larger COVID-19 cohorts (≥500 patients) reported weaker associations than smaller studies, suggesting small study effects.

# Discussion

## Principal Findings

This comprehensive meta-synthesis reveals inconsistent and limited evidence for microbiome changes in COVID-19: - Gut microbiome associations are weak and variable across studies - Oral microbiome changes are more consistent but specific to periodontal pathogens  
- Methodologic limitations significantly affect interpretation - Current evidence inadequate for clinical decision-making

## Interpretation

While some consistent patterns emerge (reduced beneficial taxa, increased opportunistic pathogens), these associations are not robust. Potential confounders including diet, antibiotic use, hospitalization, and host factors complicate interpretation [@Confounding\_Factors].

The stronger oral microbiome findings may reflect local effects of COVID-19 symptoms (xerostomia, gingivitis) rather than systemic pathophysiological mechanisms.

## Limitations

**Evidence Synthesis:** - No individual participant data meta-analysis possible - Review heterogeneity in outcome definitions and methods - Publication bias toward novel findings

**Primary Studies:** - Small sample sizes in most original research - Limited adjustment for confounders - Lack of prospective, controlled designs

## Implications for Research

1. **Well-designed cohort studies** with pre-COVID-19 microbiome baseline
2. **Standardized collection protocols** and bioinformatic pipelines
3. **Multi-omics integration** to understand microbiome-immune interactions
4. **Intervention studies** examining microbiome modulation effects

## Implications for Practice

Current microbiome-COVID-19 associations remain research questions, not clinical facts. Healthcare providers should avoid microbiome-targeted interventions without evidence from rigorous clinical trials.

# Conclusions

Evidence synthesis reveals weak and inconsistent microbiome changes in COVID-19, with oral dysbiosis being the most consistent finding. Current research base suffers from methodological limitations preventing clinical applications. Future studies with improved design and confounding adjustment are needed before microbiome changes can be integrated into COVID-19 understanding or treatment.

# References

[References from included systematic reviews]

# Supplementary Materials

**Appendix A:** Characteristics of Included Reviews **Appendix B:** Methodological Quality Assessment Results  
**Appendix C:** GRADE Evidence Profile Tables **Appendix D:** Forest Plots of Gut Microbiome Meta-Analyses