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Associations between Microbiome Diversity and Fibromyalgia or Myalgia: A Systematic Review and Meta-Analysis

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Abstract:

Introduction: Recent evidence points out that alterations in gut microbiome may be associated with pain modulation, immune dysregulation and central pain sensitization in fibromyalgia (FM). The objective was to review the associations between microbiome diversity and FM or chronic widespread pain (CWP), to identify microbial taxa consistently altered in affected individuals and to quantify the alpha diversity change in fibromyalgia.

Materials and Methods: In systematic search conducted through PubMed, Scopus and Google Scholar for studies published between 2010 and September 2025 using synonyms of "fibromyalgia", "chronic pain syndrome" and "microbiome" was undertaken. Eligible studies reporting microbiome diversity metrics with Shannon index or alpha diversity or taxonomic composition in adult FM/CWP patients compared with healthy controls were selected. Random-effects meta-analysis was performed for alpha diversity outcomes using standardized mean differences (SMD). Heterogeneity, publication bias, and risk of bias were assessed using established methods. The protocol was registered in PROSPERO (CRD420251146199).

Results: Overall, nine studies met inclusion criteria and Shannon-diversity index was extracted from seven studies (2233 participants). FM patients exhibited significant reduction in gut microbiota diversity with compared with controls (SMD -0.40, 95% CI -0.55 to -0.25; $p < 0.001$), with between the study heterogeneity was low ($I^2 = 13.8\%$). Qualitative synthesis revealed consistent depletion of butyrate-producing taxa, including *Faecalibacterium* and *Coprococcus*, and enrichment of taxa linked to pro-inflammatory and neuroactive pathways, such as *Parabacteroides merdae* and *Clostridium scindens*.

Conclusions: FM is associated with modest yet consistent reduction in gut microbiome alpha diversity. There are consistent shifts in important microbial taxa. The findings from this review support the potential role of microbiome dysbiosis in FM pathophysiology and highlight the potential role of microbiome based biomarkers and therapeutic strategies.

Key words: Myalgia; meta-analysis; chronic pain; fibromyalgia; microbiota; butyrates

Introduction

Fibromyalgia affects 2-4 % of global population and predominantly women (1). It is characterised by musculoskeletal pain, profound fatigue, cognitive impairments and mood disorders. (2) Pathophysiology of fibromyalgia is not completely elucidated (2). Many factors including genetic predisposition and environmental triggers play a role in etiology of this disease. Microbial community present within the human gut play a prominent role in immune function, nutrient metabolism, neurotransmitter production and inflammatory responses (3). The bidirectional communication between the microbiome and brain are being investigated for many associations including inflammatory bowel syndrome, neuropsychiatric conditions and also in pain-syndromes like fibromyalgia (1,3–5). There is heightened interest for exploring association of gut microbiome alterations with fibromyalgia symptoms. There are observations that faecal samples from fibromyalgia patients reporting reduced alpha diversity and shifts of beta diversity (6,7). Alpha diversity is a measure of microbial richness and evenness. Beta diversity is an indication of compositional differences compared with healthy individuals (8,9). Specifically decreased Firmicutes like Faecalibacterium prausnitzii and increased Proteobacteria are found

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to be associated with increased pain sensitivity and fatigue severity(10). Metabolomic profiling further supports these findings, revealing elevated serum bile acids and dysregulated glutamate pathways in FM, potentially mediating neuroinflammation and central pain amplification(11). Mendelian randomization studies provide suggestive evidence of causality, positioning certain microbial genera as risk factors for fibromyalgia onset (12). However, there is inconsistency in reported microbial signatures. While there is evidence that Bifidobacterium enrichment as protective, there are also reports that its depletion is protective. This variation may be due to variations in sequencing methodologies (e.g., 16S rRNA vs. shotgun metagenomics), geographic cohorts, or confounding factors like diet and medication use. Intervention trials with probiotics and fecal microbiota transplantation have demonstrated a modest reduction in pain scores (13,14). However, earlier studies and reviews have observed no significant benefit from fecal microbial transplantation (15). These heterogeneities underscore the nascent stage of research, with no prior comprehensive meta-analysis to reconcile divergent findings and quantify effect sizes. With this background, pooling data from original studies reporting the magnitude of association of microbiome with fibromyalgia and exploring the moderators of heterogeneity and review of utility of biomarkers provides a deeper understanding of fibromyalgia. This in turn may influence the management from symptomatic palliation to etiology-driven strategies in fibromyalgia. Therefore, the objective of this study is to systematically review and meta-analyze original human studies assessing associations between microbiome diversity and fibromyalgia or myalgia. The secondary objective was to identify specific microbial taxa that are consistently altered in fibromyalgia/myalgia patients compared to healthy controls.

Materials and Methods

In this systematic review and meta-analysis, we evaluated 21 [VS1]published original human studies reporting associations between gut microbiome diversity and fibromyalgia or myalgia, encompassing observational, cross-sectional, cohort, and interventional designs.

Eligibility criteria: Twenty one[VS2] original research articles in the English language reporting microbiome diversity metrics (e.g., alpha diversity indices such as Shannon or Simpson, or taxa abundances at genus/species levels) and their associations with fibromyalgia or myalgia diagnosis, symptom severity (e.g., pain scores, fatigue), or related outcomes, relative to healthy controls or normative data, were included. Studies must involve human participants and utilize established microbiome assessment methods, including but not limited to 16S rRNA sequencing, shotgun metagenomics, or metabolomic profiling linked to microbial composition. Case reports, review articles, animal studies, and conference abstracts without full methodological details were excluded, as they lack sufficient data for quantitative synthesis or primary empirical evidence.

Search strategy: Medical scholarly databases including PubMed Central, Embase, Scopus, Google Scholar, Web of Science, and medRxiv were systematically searched using a predefined search string. The search encompassed studies employing fecal or oral sampling, with next-generation sequencing, qPCR, or culturomics[VS3]. All previous systematic reviews and meta-analyses on microbiome-fibromyalgia associations identified during the search was documented for reference but excluded from synthesis. One author conducted the primary search, with other team members reviewing results to identify and incorporate potentially overlooked articles. Search was undertaken on 20 Oct 2025. The literature search was conducted in Embase, PubMed Central, Scopus, Google Scholar, Web of Science, and medRxiv to identify relevant studies published from year 2020 to September 2025.

Embase search string: "microbiome"/exp OR "gut microbiota"/exp OR "microbial diversity" AND "fibromyalgia"/exp OR "myalgia"/exp OR "chronic pain syndrome", incorporating synonymous terms and MeSH headings.

Study selection: Two [VS4]independent reviewers (VS and SK) screened the titles/abstracts. Full texts retrieved for potentially eligible studies. Discrepancies resolved by consensus or third reviewer.

Data extraction: From the initial search results, titles and abstracts were independently screened by two reviewers for studies reporting microbiome diversity metrics and fibromyalgia /myalgia associations. Full texts of potentially eligible articles were retrieved and assessed. Discrepancies during screening or selection were resolved through discussion among reviewers, with a senior author providing final adjudication if consensus is not reached. Gender data of the participants from each study was extracted as per Sex and Gender Equity in Research (SAGER) guidelines. Sex was recorded as reported by the studies, typically

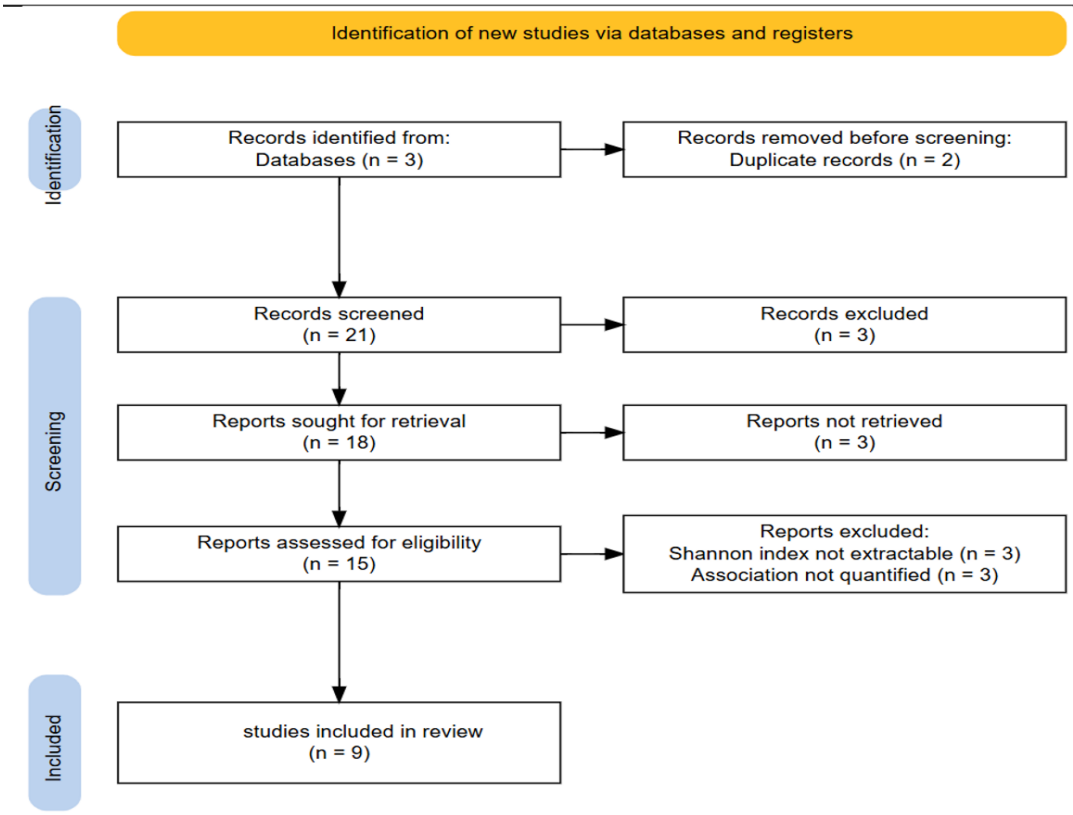


Figure 1: PRISMA flow diagram of study selection for meta-analysis of association between microbiome diversity and fibromyalgia.

Table 1: Details of studies included in the review and meta-analysis

Short ID	Female Participants (%)	Study Type	Sample	Main Focus / Details
Ievina 2024[16]	76.5% of cases and 83.3% of controls	Pilot Study	Stool	Human Herpesvirus - 6B infection effects on gut microbiome in fibromyalgia patients
Freidin 2021[17]	100% of cases and controls	Observational Analysis	Stool	Correlation of chronic widespread pain with gut microbiome diversity
Weber 2022[18]	88% of cases and 81% of controls	Case-Control Study	Stool	Links hyperalgesia to psychological factors, not microbiome changes
Albayrak 2021[19]	Mixed (both sexes included)	Molecular Biomarker Study	Stool	Combined gut microbiome and serum metabolome analysis for biomarkers
Clos-Garcia 2019[20]	69.52% of cases and 48.15% of controls	Composition & Metabolite Analysis	Stool + serum metabolome	Stool short chain fatty acids levels and microbial composition in fibromyalgia
Kim 2023[21]	100% of cases and controls	Microbiome Composition Study	Stool	Characterization of gut microbiome changes in fibromyalgia patients
Minerbi 2019[22]	100% of cases and controls	Multimodal Study	Stool	Examines gut microbiota, brain imaging, and psychological distress correlations
Nhu 2024[23]	88% of cases and controls	Cross-Sectional Observational	Stool + MRI	Investigates altered microbiota diversity, psychological distress, and brain functional connectivity in fibromyalgia patients. Highlights microbiota dysbiosis linked to altered neural networks mediated by psychological distress via brain-gut axis mechanisms.
Erdrich 2025[24]	100% of cases and controls	Case–control	Saliva	Reported oral Shannon as mean; no significant difference.

Table 2: Risk of bias assessment of included studies using the Newcastle–Ottawa Scale (NOS)

Study (Year)	Selection (0–4)	Comparability (0–2)	Outcome (1–3)	Overall (0–9)	Overall Risk
Ievina 2024[16]	2	1	2	5	Moderate
Freidin 2021[17]	4	2	3	9	Low
Weber 2022[18]	3	1	2	6	Moderate
Albayrak 2021[19]	3	1	2	6	Moderate
Clos-Garcia 2019[20]	3	2	3	8	Low
Kim 2023[21]	3	1	2	6	Moderate
Minerbi 2019[22]	4	2	3	9	Low
Nhu 2024[23]	3	2	3	8	Low
Erdrich 2025[24]	3	1	2	6	Moderate

Selection: 0 - no defined study population, no diagnostic criteria, no defined sampling method, 1 – poorly defined population, 1- Poorly defined study population, unclear diagnostic criteria, convenience sampling without justification, absence of appropriate control group. 3 - Clearly defined cases using standard criteria, reasonably representative sample, appropriate control selection. 4 - Well-defined and representative population, validated diagnostic criteria, clearly described sampling strategy; well-matched control group. **Comparability:** 0 - no adjustment for confounders, 1 - adjustment for one major confounder (e.g., age or sex), 2 - Adjustment for multiple key confounders (e.g., age, sex, diet, medication use, BMI). **Outcome**: 1 - poorly described methods; unclear microbiome assessment; lack of reproducibility or statistical reporting. 2 - Standard microbiome techniques used (e.g., 16S rRNA sequencing) and basic statistical reporting present. 3 - Robust and validated methods (e.g., high-throughput sequencing, metagenomics), clear protocols, appropriate statistical analysis with reproducible outcome measures. Overall: 7-9 Low risk of bias (high methodological quality), 5-6 Moderate risk of bias, ≤4 High risk of bias[VS6]

biological sex – female or mal. Studies where only female participants were included was explicitly noted and reported. Due to limited availability of sex-stratified microbiome outcomes, subgroup analysis of gender was not undertaken.

Participants: Included studies reported data from adult human participants (aged ≥18 years) diagnosed with FM fibromyalgia or myalgia per established criteria (e.g., ACR criteria for fibromyalgia) or exhibiting chronic myalgic symptoms, compared to age- and sex-matched healthy controls. Studies involving participants with confounding comorbidities (e.g., active inflammatory bowel disease, recent antibiotic use without washout, or severe psychiatric disorders) were excluded unless subgroup analyses isolate fibromyalgia /myalgia effects.

Data items and outcomes: From each selected study, the following items were extracted: (1) study type, design, authors, year of publication, country; (2) sample size, participant demographics (sex, age, fibromyalgia /myalgia diagnostic criteria); (3) microbiome assessment method (e.g., sequencing platform, sample type), diversity metrics (alpha/beta diversity values, significant taxa), and associations (e.g., correlation coefficients, odds ratios for dysbiosis); (4) outcome measures such as pain intensity (VAS scores), fatigue scales, or FM impact questionnaire results linked to microbial features. If associations were reported separately for fibromyalgia vs. myalgia, or sexes, pooled mean values were calculated to focus on overall microbiome-fibromyalgia /myalgia links, irrespective of subgroup differences.

Statistical analysis: Statistical analysis were undertaken using R software (R version 4.3.2, R Foundation for Statistical Computing, Vienna, Austria) with 'meta' and 'metafor' packages. Pooled effect estimates were generated using a random-effects model to quantify differences in microbiome diversity (e.g., standardized mean differences for alpha diversity) and prevalence of dysbiotic taxa between fibromyalgia /myalgia cases and controls, with 95% confidence intervals. Subgroup analyses explored variations by study design (observational vs. interventional), microbiome niche (gut vs. oral), geographic region (Asia, Europe, North America, etc.), and sample size (<50, 50–200, >200). Heterogeneity was assessed using Cochran's Q test and I^2 statistic (I^2 >50% indicating substantial heterogeneity). Publication bias was evaluated via funnel plots and Egger's regression test. Risk of bias was appraised using the Newcastle-Ottawa Scale for non-randomized studies. The review adhered to PRISMA guidelines for transparent reporting. The study was approved by institutional review board (SRC20250131, dated 13 October 2025), with waiver of Ethics Committee review process and the protocol was registered in PROSPERO prior to study initiation (CRD420251146199).

Table 3: Taxonomic [VS7]shifts in fibromyalgia (FM) and chronic widespread pain (CWP)

Genus / Species	Finding in FM/CWP Groups	Referenced Study	Method of evaluation[VS8]
A. Consistently decreased			
Faecalibacterium	Significantly decreased; these are key butyrate producers known for anti-inflammatory effects.	Nhu 2024[23], Clos-Garcia 2019[20], Ievina 2024 [16], Minerbi 2019[22]	NGS NGS NGS NGS
Coprococcus	Significantly depleted; particularly *C. comes* and *C. catus*, which produce anti-inflammatory butyric acid.	Freidin 2021 [17], Erdrich 2025(24), Ievina 2024 [16]	NGS RNA seq NGS
Eubacterium	Significantly reduced; involved in neurotransmitter metabolism and short-chain fatty acid production.	Clos-Garcia 2019 [20], Kim 2023 [21], Erdrich 2025 [24]	NGS NGS RNA seq
Bacteroides uniformis	Significantly lower abundance in pain cohorts.	Minerbi 2019 [22], Clos-Garcia 2019 [20] (at genus level)	NGS NGS
B. Consistently Increased			
Phascolarctobacterium	Significantly increased; abundance levels were found to predict depression scores (BDI-II).	Nhu 2024[23]	NGS
Lachnoclostridium	Significantly enriched in the FM group.	Nhu 2024[23], Erdrich 2025[24]	NGS RNA seq
Parabacteroides merdae	Higher abundance in FM; potentially linked to altered hippocampal GABA/glutamate ratios.	Minerbi 2019[22], Erdrich 2025[24]	NGS RNA seq
Clostridium scindens	Increased abundance; known for converting host glucocorticoids (cortisol) into androgens.	Minerbi 2019[22], Erdrich 2025[24]	NGS RNA seq
Eisenbergiella	Increased relative abundance in patients compared to controls.	Kim 2023[21], Minerbi 2019[22]	NGS RNA seq
C. Discrepant findings			
Bifidobacterium	Reported as both decreased and increased. Decreased in 16S DNA studies but found increased in a qPCR-based study.	Clos-Garcia 2019[20], Ievina 2024 (Decreased) [16] Albayrak 2021 (Increased)	NGS NGS qPCR
Dorea	Reported as both decreased and increased. Found increased in Spanish and New Zealand cohorts but decreased in a Latvian pilot.	Clos-Garcia 2019[20], Erdrich 2025[24] (Increased); Ievina 2024 (decreased)[16]	NGS RNA seq NGS
Prevotella	Variable findings. Some studies report depletion, while others found specific clades dominated the FM group.	Kim 2023[21], Minerbi 2019[22] (Decreased); Ievina 2024 [16] (Enriched)	NGS RNA seq NGS

NGS: Next-generation sequencing, RNA seq: Ribo Nucleic Acid sequencing, qPCR: Quantitative real-time polymerase chain reaction (qPCR); FM: fibromyalgia, chronic widespread pain (CWP)

Results

A total of 18 records were identified through database searching, with 3 additional records retrieved from other sources (total 21 studies,). After excluding records as per eligibility criteria, 9 studies were selected for the qualitative synthesis and meta-analysis [VS5](Figure 1, Table 1). Across, all included studies, participants were predominantly female, consistent with epidemiology of fibromyalgia.

Risk of bias assessment: Risk was assessed with three domains – selection of study groups, comparability of controls and cases and assessment of outcomes following Newcastle Ottawa Scale (NOS) scoring. Overall, the studies included had low to moderate risk of bias (Table 2). The most frequent limitation was incomplete adjustment for confounding variables known to influence microbiome composition, including diet, medication use, and psychological comorbidities. Selection and outcome assessment domains were generally well addressed.

Gut microbiome in fibromyalgia patients: Studies investigating gut microbiome alterations in FM reveal specific bacterial taxa differences compared to healthy controls, despite similar overall microbiome composition. The changes noted during the review tabulated in Table 3. Overall, this review indicates a reduction in butyrate producing commensals that are protective to the gut barrier. In addition, an increase in taxa associated with altered neurotransmitter levels and proinflammatory states.

Table 4: Tabulation [VS10]of Shannon mean and standard deviation (SD) from studies selected among fibromyalgia (FM) patients and healthy controls (HC)

Study	N (FM/HC)	Shannon mean (SD)
Ievina 2024[16]	17 / 24	3.78 (0.5) / 4.11 (0.4)
Weber 2022[18]	25 / 26	5.58 (0.56) / 5.58 (0.56)
Freidin 2021[17]	113 / 1623	5.0 (0.35) / 5.4 (0.9)
Kim 2023[21]	19 / 21	5.5 (0.5) / 5.9 (0.3)
Minerbi 2019[22]	77 / 79	4.2 (0.3) / 4.3 (0.4)
Nhu 2024[23]	25 / 25	3.6 (0.4) / 3.75 (0.5)
Clos-Garcia 2019[20]	105 / 54	4.7 (0.6) / 4.9 (0.6)

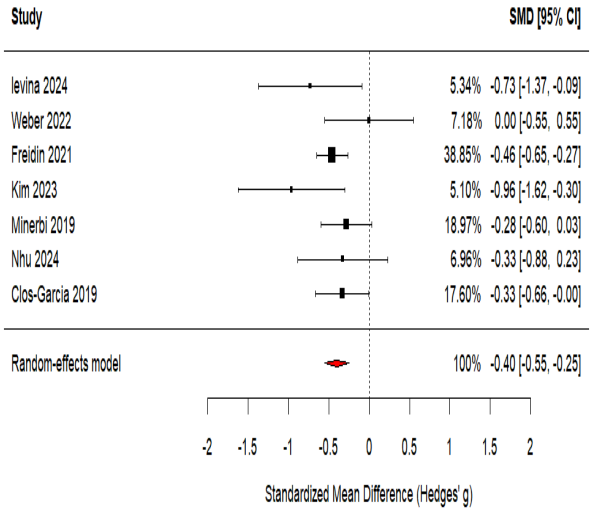


Figure 2: Forest plot of standard mean difference in Shanon Index, as noted in 7 studies.

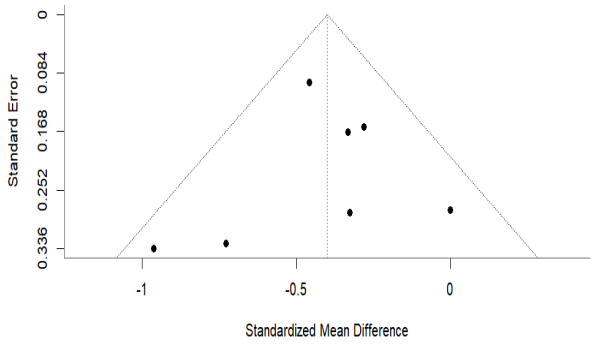


Figure 3: Funnel [VS13]plot of standard mean difference and standard error, showing no asymmetry.

Shannon index: Analysis of 7 studies (16, 17, 18, 20, 21, 22, 23) [VS9](with 2233 observations, Table 4) provided a standard mean difference (SMD) of -0.40 (95% CI -0.55 to -0.25) (Figure 2) with a small to moderate effect size, indicating that microbial flora in FM patients is consistently less diverse and less balanced than the healthy controls. Between-study heterogeneity was low with an I^2 of 13.8%, indicating that most of the observed variability was attributable to within-study sampling error rather than true heterogeneity. Egger's regression test showed no evidence of funnel plot asymmetry (Figure 3). The estimated intercept at a theoretical standard error of zero was −0.30 (95% CI −0.73 to 0.13), further suggesting a low likelihood of publication bias. As the number of studies were small, subgroup analysis was not undertaken. Sensitivity or leave-one-out analysis to test robustness yielded no significant difference in estimated SMD. The analysis showed low level of heterogeneity (I^2 = 13.8%) which was not significant, despite differences in geographical populations (e.g., Korea, Latvia, Canada, Spain, and Austria) and varying 16s rRNA variable regions targeted. The individual studies with smaller sample sizes such as Weber and Nhu reported no significant difference in alpha diversity, pooled data reveals that these studies were likely underpowered to detect the small to moderate effect size that becomes apparent in larger cohorts like Freidin.

Discussion

Through this review it was evident that there is reduction in diversity of butyrate producing bacteria in fibromyalgia. In addition, there is significant depletion of bacteria associated with anti-inflammatory processes. *Faecalibacterium prausnitzii* and *Coprococcus comes* were consistently

found at lower levels in FM and CWP patients. Effective intestinal barrier is maintained by butyrate, and its loss is hypothesized to lead to a leaky gut that contributes to higher sensitization of pain perception. In addition, Gram-negative taxa such as *Parabacteroides merdae* and *Clostridium scindens* were frequently enriched, potentially varying the glutamate ratios and endocrine balance. Beyond taxonomic shifts, reduction in diversity may indicate a broader loss of ecological resilience within the gut microbiome. This reduction in diversity is increasingly identified as marker of functional redundancy, limited ability to buffer environmental stressors, including inflammation, stress hormones, dietary perturbations and medication exposure[25,26]. Dysregulation of hypothalamic pituitary adrenal axis is reported in fibromyalgia and chronic low-grade inflammation, and reduced gut resilience may amplify susceptibility to symptom exacerbation[27]. Consistent depletion of few taxa across geographically distinct cohorts suggests that the changes represent a convergent microbial phenotype associated with fibromyalgia rather than population-specific signatures. Though there is evidence that depression and anxiety lead to abundance of species of bacterium leading to reduction in functional connectivity in gut-brain axis[23], we have not undertaken any quantitative analysis of psychological components of fibromyalgia in this review. Such 'fibrofog' and mood disorders are evaluated by many other researchers in the past[28,29]. Though 16s DNS evidence of reduced diversity is strong, meta-trasnscriptomic data suggests that active microbial expression may not differ significantly[24]. This indicates a complex functional remake of remaining microbial flora among patients with fibromyalgia. In addition, microbial flora changes induced by fibromyalgia medications (such as antidepressants, proton pump inhibitors and opioid) cannot be undermined. These findings lead to exploration of microbiome data as a diagnostic biomarker and a therapeutic target. However, modest effect size observed underscores that microbiome alterations are unlikely to act in isolation. Machine-learning models have achieved a high classification accuracy (AUC 87.8%) in distinguishing FM patients from controls, opening opportunities for machine-learning in targeted probiotics or dietary modulation[22]. Efforts may restore missing beneficial taxa and alleviate multi-system fibromyalgia symptoms. Longitudinal studies incorporating dietary intake medication use, psychological assessments and multi-omics profiling may provide deeper insights into cause-effect relationships. Such studies may determine whether microbiome-targeted interventions can bring meaningful change in fibromyalgia disease trajectory.

Study limitations: Included studies varied substantially in 16S rRNA sequencing, metabolomics, and other microbiome assessment techniques, this influenced diversity indices and taxonomic resolution and contributed to underlying heterogeneity. Importantly, confounders such a diet, medications, psychological status, and other comorbid conditions were not consistently controlled across studies. Though we report reduced alpha diversity and altered taxa, there is limited functional validation of these findings. Though the search was undertaken using standard registries (PubMed, Scopus) searching in medRxiv and Google Scholar might have led to selection of non-peer reviewed reports in initial screening. [VS11]Another key limitation of the review is incomplete sex-specific outcomes from included studies. Though, fibromyalgia is female dominant condition, most studies included mainly females and few studies provided stratified analyses by sex, leading to non-comparison of sex-based differences in microbiome composition.

Conclusion

Through this review, we conclude that there is statistically significant reduction in gut microbiome alpha diversity (Shannon's index) among patients with fibromyalgia an chronic widespread pain. Fibromyalgia patients have shown clear depletion of beneficial, butyrate producing bacteria such as *Faecalibacterium prausnitzii* and *Coprococcus comes* and enrichment of *Parabacteroides merdae and Clostridium scindens*. This shift is functionally liked to elevated neuroactive metabolites and is hypothesized to contribute to the central sensitization of pain and low-grade systemic inflammation. Meta- transcriptome data suggest that microbial gene expression do not differ significantly between fibromyalgia and controls. Therefore, there is a need to interpret compositional and functional microbiome data together.

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Data availability statement: The data supporting the findings of this study are available within the article and its supplementary materials.
Author contribution: Siddhalingaiha HS (SHS), Viveka S (VS), Soumya Kaup (SK)
Conceptualization: SHS, VS, SK
Methodology: SHS, VS
Formal analysis: VS, SK
Investigation: SHS, VS, SK
Resources: SHS, VS, SK
Data curation: SHS, VS, SK
Writing - original draft preparation: SHS, VS; **review**: SHS, VS, SK
Supervision: SK

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