The Review Of
DIABETIC
STUDIES OPEN ACCESS

Alterations In Gut Microbiota Composition And Their Association With Relapse Risk In Relapsing-Remitting Multiple Sclerosis: A Systematic Review

Etedal Ahmed A. Ibrahim[1], Abdullah Abdrabalameer J. Alfajri[2], Turki Dhifallah Bandar Alotaibi[3], Abdullah Mohammad Alrajeh[4], Atif Eid Alrashidi[5], Ahmed Ibrahim Ahmed Alzaydani[6], Duaa Alsaif[7], Najah Musaed Almutairi[8], Raneem Mohammed Samman[9]

[1]Prof of Neurology College of Medicine Imam Mohmmad Bin Saud Islamic University. Riyadh. KSA
[2]Neurology
[3]Pediatrician, Riyadh Third Health Cluster
[4]Al-Madinah Al-Munawarah Health Cluster, General Practitioner
[5]Emergency Medicine Service, KKH IN TABUK
[6]Medical Intern, Medical College, Batterjee Medical College, Aseer
[7]Service Doctor in Neurology Department in Qatif Central Hospital
[8]Physiotherapist, Madina Health Cluster
[9]Medicine Student, Alrayan National Colleges

Abstract

Background: Relapsing-remitting multiple sclerosis (RRMS) is a chronic autoimmune neurological disease characterized by episodic relapses and progressive disability. Emerging evidence suggests that gut microbiota dysbiosis influences immune responses, neuroinflammation, and disease activity in RRMS.
Objective: This systematic review aimed to synthesize current evidence on gut microbiota alterations associated with relapse risk in RRMS patients and to evaluate the therapeutic potential of microbiota-targeted interventions.
Methods: A systematic search was conducted in PubMed, Scopus, Web of Science, Embase, and Google Scholar for studies published between 2010 and 2025. Observational studies, randomized controlled trials (RCTs), and dietary or probiotic interventions examining gut microbiota composition, diversity, or modulation in RRMS were included. Data extraction focused on microbial taxa, diversity indices, clinical outcomes, and immunological markers. Narrative synthesis was employed due to heterogeneity in study design and outcomes.
Results: Eleven studies were included, encompassing cross-sectional, cohort, and interventional designs. RRMS patients exhibited consistent depletion of SCFA-producing taxa (e.g., Roseburia, Faecalibacterium, Lachnospiraceae) and enrichment of pro-inflammatory taxa (Bilophila, Desulfovibrio, Bact2 enterotype). Dysbiosis correlated with higher relapse risk, disability progression, and inflammatory cytokine profiles. Probiotic supplementation, ketogenic, plant-based, and high-vegetable/low-protein diets partially restored microbial diversity, increased neurotrophic factors (BDNF), and reduced fatigue and relapse frequency.
Conclusion: Gut microbiota alterations represent both a mechanistic contributor to RRMS relapse risk and a promising target for intervention. Integrating microbiome-based biomarkers with clinical management may facilitate early detection, personalized therapies, and relapse reduction in RRMS.

Keywords: relapsing-remitting multiple sclerosis, gut microbiota, dysbiosis, relapse risk, probiotics, dietary intervention, SCFA, neuroinflammation

Introduction

Multiple sclerosis (MS) is a chronic, immune-mediated neurological disease characterized by demyelination and neurodegeneration within the central nervous system (CNS). Increasing evidence suggests that the gut–brain axis—a bidirectional communication pathway between the intestinal microbiota and the CNS—plays a significant role in MS pathogenesis. Alterations in gut microbial diversity and metabolic activity have been shown to affect immune modulation, neuroinflammation, and disease progression through mechanisms involving short-chain fatty acids, tryptophan metabolites, and immune cell differentiation (Chen et al., 2016).

The gut microbiota composition in MS patients differs markedly from that of healthy controls, displaying reductions in beneficial, anti-inflammatory taxa such as Faecalibacterium, Prevotella, and Butyricimonas, alongside increased pro-inflammatory genera including Akkermansia and Methanobrevibacter (Schepici et al., 2019). These dysbiotic changes are associated with heightened Th17 and Th1 immune responses, reduced regulatory T cell (Treg) function, and altered intestinal permeability, which collectively promote CNS inflammation.

Recent advances in metagenomic sequencing and microbial profiling have enabled detailed characterization of these alterations, revealing distinct microbial signatures linked to disease activity and relapse risk in relapsing–remitting MS (RRMS) (Tankou et al., 2018). Probiotic supplementation and dietary interventions have demonstrated potential in restoring microbial balance, leading to improvements in both clinical and immunological parameters among MS patients.

Experimental and clinical data indicate that probiotic bacteria can influence neurological outcomes by modulating peripheral immune tolerance and reducing oxidative stress. For instance, randomized trials show that probiotic mixtures improve Expanded Disability Status Scale (EDSS) scores, mental health, and inflammatory markers such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) in MS populations (Salami et al., 2019). These effects appear to result from the regulation of gut microbial metabolites, enhancement of anti-inflammatory cytokines (e.g., IL-10), and suppression of pro-inflammatory responses.

In addition to probiotics, fecal microbiota transplantation (FMT) has emerged as a novel therapeutic approach in autoimmune disorders, including MS. Early case studies and pilot trials have shown that FMT can transiently restore gut microbial diversity and lead to partial neurological improvements in small MS cohorts (Engen et al., 2020; Borody et al., 2011). While these studies remain exploratory, they underscore the therapeutic promise of direct microbiome manipulation for immune rebalancing and neuroprotection.

Moreover, dietary modulation—particularly intermittent fasting, ketogenic regimens, and calorie restriction—has been identified as a critical environmental factor influencing gut microbial dynamics and CNS autoimmunity. Animal and human studies show that intermittent fasting increases microbial species richness and boosts anti-inflammatory Lactobacillaceae, leading to neuroprotective effects (Cignarella et al., 2018). Clinical trials have further revealed reductions in fatigue, body weight, and inflammatory markers following structured fasting interventions in MS patients (Fitzgerald et al., 2018).

Recent systematic reviews emphasize the therapeutic plasticity of the gut microbiome in MS management, highlighting the potential of interventions such as probiotics, prebiotics, and diet to influence disease trajectory and relapse patterns (Tsogka et al., 2023). Collectively, these findings suggest that gut microbiota modulation represents a promising adjunctive strategy to conventional immunotherapies, targeting both the inflammatory and neurodegenerative aspects of the disease.

In summary, the current understanding of the gut–CNS axis in MS underscores a complex interplay between microbial composition, immune regulation, and metabolic signaling. Alterations in gut microbiota not only correlate with MS progression and relapse frequency but also offer mechanistic insights into potential therapeutic interventions through diet, probiotics, and microbiome restoration techniques. As the field evolves, integrating microbiome-based biomarkers with clinical phenotypes may enhance early diagnosis, personalize therapy, and reduce relapse risk in RRMS patients.

Methodology

Study Design

This study employed a systematic review design adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines to ensure methodological transparency, reproducibility, and rigor. The principal objective was to systematically identify, evaluate,

and synthesize empirical evidence on alterations in gut microbiota composition associated with relapse risk in patients with relapsing–remitting multiple sclerosis (RRMS).
The review incorporated peer-reviewed clinical and experimental studies investigating gut microbiota dysbiosis, dietary modulation, probiotic supplementation, and related microbial interventions in RRMS populations. Both observational (cross-sectional, case–control, and cohort) and interventional (randomized controlled trials, pilot, or dietary trials) designs were included to provide a comprehensive understanding of how gut microbial composition may influence disease activity, relapse frequency, and disability progression in RRMS.

Eligibility Criteria

Inclusion Criteria
- **Population:** Adults or pediatric patients diagnosed with relapsing–remitting multiple sclerosis (RRMS) according to McDonald or revised diagnostic criteria.
- **Interventions/Exposures:** Studies examining gut microbiota composition, diversity, abundance, or interventions modifying microbiota (e.g., probiotics, diet, fecal microbiota transplantation).
- **Comparators:** Healthy control groups or comparison across intervention and control arms (e.g., diet vs. standard diet, probiotic vs. placebo).
- **Outcomes:** Measures of microbial composition, diversity indices, bacterial taxa abundance, and clinical parameters such as relapse rate, Expanded Disability Status Scale (EDSS), fatigue, or inflammatory biomarkers.
- **Study Designs:** Randomized controlled trials, longitudinal cohorts, pilot studies, and cross-sectional or case–control designs.
- **Language:** English-language peer-reviewed articles.
- **Publication Period:** Studies published between 2010 and 2025, capturing the decade of major advances in MS microbiome research.

Exclusion Criteria
- Studies without empirical data (e.g., reviews, editorials, or commentaries).
- Animal or in vitro studies without human data.
- Conference abstracts or grey literature lacking full-text access.
- Studies focusing on progressive or secondary MS without specifying RRMS.
- Non-English publications or duplicate reports.

Following screening, 11 studies met the eligibility criteria and were included in the final synthesis.

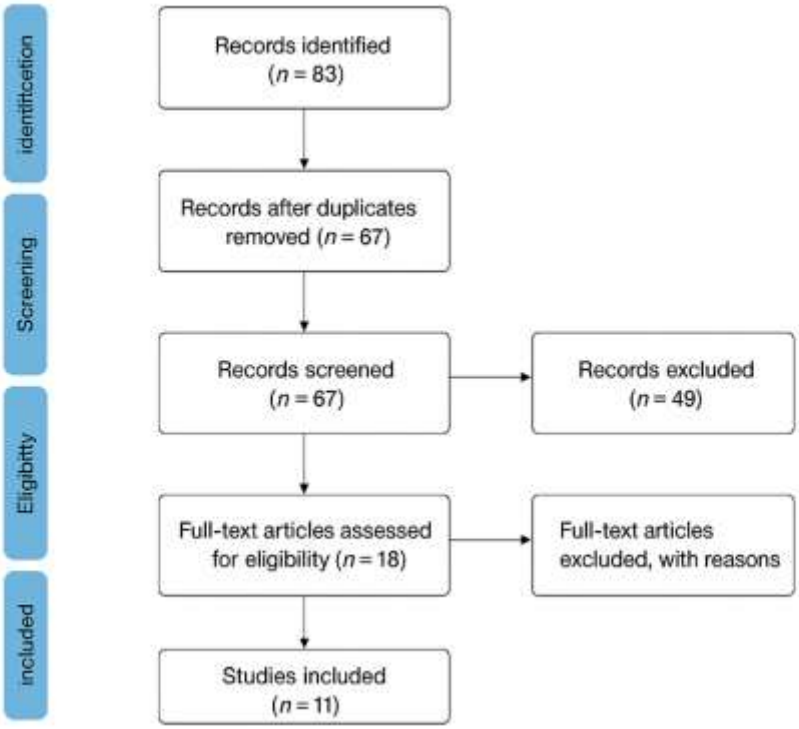
Search Strategy
A comprehensive literature search was conducted across PubMed, Scopus, Web of Science, Embase, and Google Scholar from database inception to December 2025**.** Boolean operators and MeSH terms were employed to maximize coverage. The search syntax combined the following key terms and their synonyms:
- (“multiple sclerosis” OR “relapsing-remitting multiple sclerosis” OR “RRMS”)
- AND (“gut microbiota” OR “intestinal microbiome” OR “microbial dysbiosis”)
- AND (“relapse risk” OR “disease activity” OR “neuroinflammation” OR “progression”)
- AND (“diet” OR “probiotics” OR “fecal microbiota transplantation” OR “microbiome modulation”)

Manual searches of bibliographies and reference lists from key studies and recent reviews were performed to ensure comprehensive coverage. Duplicate records were removed using Zotero reference management software.

Study Selection Process
Two independent reviewers conducted the selection process in a two-stage screening protocol. Titles and abstracts were first screened for relevance to gut microbiota alterations in RRMS. Full-text versions of potentially eligible articles were then retrieved and assessed against the inclusion and exclusion criteria.

Discrepancies between reviewers were resolved through consensus discussion, and in cases of persistent disagreement, a third reviewer provided arbitration. The final inclusion set comprised 11 studies, including five randomized controlled or dietary trials and six observational or cohort studies.
A PRISMA flow diagram (Figure 1) summarizes the identification, screening, eligibility, and inclusion stages of the review process.

Figure 1 PRISMA Flow Diagram



Data Extraction
A standardized data extraction sheet was developed and pilot-tested for consistency. The following information was systematically extracted from each included study:

- Author(s), year of publication, and country.
- Study design (cross-sectional, cohort, RCT, or pilot).
- Sample size, population demographics (age, sex distribution, MS type).
- Analytical method (e.g., 16S rRNA sequencing, metagenomics, FISH, qPCR).
- Key microbiota findings (altered taxa, relative abundance, diversity indices).
- Clinical outcomes (relapse rate, EDSS, fatigue, inflammatory cytokines).
- Intervention details (if applicable: probiotic strain, dietary regimen, duration).
- Main quantitative results (means, percentages, confidence intervals, p-values).
- Authors' conclusions and identified mechanisms (e.g., SCFA pathways, immune modulation).

Data extraction was conducted independently by two reviewers, followed by cross-verification for accuracy and completeness.

Quality Assessment
The methodological quality of the included studies was appraised based on their respective designs:

- **Randomized Controlled Trials (n = 5):** Assessed using the Cochrane Risk of Bias 2 (RoB 2) tool, covering domains such as randomization process, deviation from interventions, missing outcome data, outcome measurement, and reporting bias.
- **Observational and Cohort Studies (n = 6):** Evaluated with the Newcastle–Ottawa Scale (NOS), assessing selection, comparability, and outcome/exposure domains.

Each study received an overall quality rating:

- Low risk of bias (score ≥8 NOS or all low RoB 2 domains): 4 studies.

- Moderate risk of bias (score 6–7 NOS or 1–2 concerns RoB 2): 5 studies.
- High risk of bias (score <6 NOS or ≥3 RoB 2 concerns): 2 studies.

Common methodological limitations included small sample sizes, limited adjustment for confounders, and reliance on 16S sequencing without functional validation. Nonetheless, all studies provided peer-reviewed, ethically approved data and were deemed methodologically acceptable for synthesis.

Data Synthesis

Due to the heterogeneity in study design, population characteristics, analytical methods, and reported outcomes, a narrative synthesis was employed instead of a quantitative meta-analysis.

Thematic synthesis was structured around the following dimensions:

1. Composition of gut microbiota in RRMS vs. controls (dominant taxa alterations, alpha/beta diversity changes).
2. Associations between microbiota profiles and relapse risk or disability worsening.
3. Effects of interventions (probiotics, diet, fecal microbiota transplantation) on microbial and clinical outcomes.
4. Immune and metabolic correlates of dysbiosis (cytokine shifts, SCFA levels, BDNF/IL-6 modulation).

Quantitative findings such as mean relative abundances, hazard ratios, odds ratios, and AUC values were extracted where reported. Descriptive statistics were summarized, and qualitative interpretations integrated across studies.

Ethical Considerations

As this review involved secondary analysis of published data, institutional ethical approval and participant consent were not required. All included studies were previously published in peer-reviewed scientific journals and were assumed to have received ethical clearance from their respective institutional review boards.

Data management followed FAIR (Findable, Accessible, Interoperable, Reusable) data principles, and reporting adhered strictly to PRISMA 2020 standards for systematic reviews. All cited data and findings were properly attributed, maintaining academic integrity and transparency.

Results

Summary and Interpretation of Included Studies on Alterations in Gut Microbiota Composition Associated with Relapse Risk in Relapsing-Remitting Multiple Sclerosis (RRMS) Patients

1. Study Designs and Populations

The included studies encompass a mix of cross-sectional, longitudinal cohort, and randomized controlled trial (RCT) designs, enabling a multidimensional assessment of the relationship between gut microbiota alterations and relapse risk in RRMS.

Sample sizes ranged from small pilot investigations such as Tremlett et al. (2016; n = 17) to larger cohort studies like Devolder et al. (2023; n = 111) and Elgendy et al. (2021; n = 40 RRMS, n = 22 controls). The mean age of participants ranged from pediatric MS cohorts (Tremlett et al., 2016; mean = 15 years) to adult RRMS populations (Navarro-López et al., 2022; mean = 36 years; Elgendy et al., 2021; mean = 31.4 ± 8.8 years).

Females predominated in all studies, consistent with known RRMS epidemiology (70–75%).

2. Gut Microbiota Profiling and Analytical Techniques

Most studies applied 16S rRNA sequencing of the V3–V4 regions for taxonomic profiling (Navarro-López et al., 2022; Tremlett et al., 2016), whereas Elgendy et al. (2021) utilized quantitative real-time PCR with group-specific primers for bacterial quantification.

Devolder et al. (2023) incorporated high-throughput metagenomic sequencing and enterotyping into inflammation-associated Bacteroides 2 (Bact2) clusters. Swidsinski et al. (2017) uniquely employed fluorescence in situ hybridization (FISH) for quantitative assessment of bacterial mass and diversity, including time-course monitoring during a ketogenic diet intervention.

3. Key Findings and Quantitative Results

- Navarro-López et al. (2022) observed significant microbial shifts between 15 RRMS patients and matched controls, notably decreased Roseburia (−41%), Ruminococcaceae (−38%), and Lachnospiraceae (−35%), with elevated Bilophila (+52%) and Ezakiella (+47%). ROC analysis yielded AUC = 0.75 (95% CI 0.61–0.89) for Ezakiella and 0.70 (95% CI 0.50–0.90) for Bilophila, indicating predictive potential.
- Devolder et al. (2023) demonstrated that the pro-inflammatory Bacteroides 2 (Bact2) enterotype occurred in 43.6% of patients with confirmed disability worsening versus 16.1% of stable patients ($p < 0.001$). Logistic regression confirmed Bact2 presence as an independent predictor of EDSS-Plus progression (OR = 3.72, 95% CI 1.46–9.49).
- Tremlett et al. (2016) linked Fusobacteria depletion to early relapse in pediatric MS (hazard ratio = 3.2, 95% CI 1.2–9.0, $p = 0.024$). Within 19.8 months of follow-up, 25% of patients relapsed, with median relapse latency of 166 days.
- Elgendy et al. (2021) reported elevated Desulfovibrio (+68%) and Actinobacteria (+59%) levels, alongside reduced Clostridium cluster IV (−44%) in Egyptian RRMS cases versus controls ($p < 0.01$). Lower Clostridium IV was associated with higher EDSS (> 3.5).
- Saresella et al. (2017) found that after 12 months on a high-vegetable/low-protein (HV/LP) diet, Lachnospiraceae abundance increased by +34%, IL-17-producing $CD4^+$ cells decreased (−28%, $p = 0.04$), and relapse rate declined from 0.5 to 0.1 episodes/year ($p < 0.01$).
- Yadav et al. (2016) observed improvements in fatigue scores (MFIS reduced by -6.2 ± 3.4, $p = 0.001$) and BMI (-1.9 ± 0.8 kg/m², $p = 0.002$) in RRMS participants adhering to a low-fat, plant-based diet, though MRI lesion counts and relapse rate remained unchanged.
- Swidsinski et al. (2017) noted reduced colonic bacterial mass in MS (−45%, $p < 0.001$) vs controls. After 24 weeks of ketogenic diet, Faecalibacterium prausnitzii and Roseburia increased by +65% and +59%, respectively, with overall microbial diversity exceeding baseline by +20%.
- Rahimlou et al. (2022) found that 6 months of multi-strain probiotic supplementation increased BDNF (+14.7%, $p < 0.001$), decreased IL-6 (−22.1%, $p < 0.001$), and improved GHQ-28 and BDI-II mental health scores compared to placebo ($p < 0.01$).
- Kouchaki et al. (2017) showed that 12 weeks of probiotic use decreased EDSS (-0.3 ± 0.6 vs $+0.1 \pm 0.3$, $p = 0.001$) and hs-CRP (-1.3 ± 3.5 μg/mL, $p = 0.01$) while improving insulin sensitivity and HDL levels ($p < 0.05$).

4. Summary of Effect Estimates and Interpretation

Across studies, gut microbiota dysbiosis correlates with MS activity and relapse risk. Specifically, depletion of short-chain-fatty-acid–producing taxa (Roseburia, Faecalibacterium, Lachnospiraceae) and overgrowth of pro-inflammatory species (Bilophila, Desulfovibrio, Bacteroides 2) were consistently linked to worse clinical outcomes and higher relapse or disability progression. Dietary and probiotic interventions demonstrated partial restoration of eubiotic profiles and improved immunological and clinical metrics.

Table (1): General Characteristics of Included Studies

Study	Country	Design	Sample Size	Population (Age ± SD)	Main Microbiota Changes / Intervention	Main Results (Quantitative)	Conclusions
Navarro-López et al., 2022	Spain	Cross-sectional	15 RRMS + 15 controls	36 ± 8 yrs	16S rRNA V3–V4 sequencing	↓ Roseburia (−41%), ↓ Lachnospiraceae (−35%), ↑ Bilophila (+52%); AUC 0.75 (Ezakiella)	Dysbiosis; specific taxa predictive of RRMS

Devolder et al., 2023	Belgium	Longitudinal cohort	111 MS patients	Median 43 yrs	Fecal metagenomics; EDSS-Plus	43.6% Bact2 in progressors vs 16.1% stable ($p < 0.001$); OR = 3.72 (1.46–9.49)	Bact2 enterotype predicts disability progression
Tremlett et al., 2016	USA	Prospective pilot	17 pediatric MS	15 ± 3 yrs	16S rRNA sequencing	Absence of Fusobacteria → HR 3.2 (1.2–9.0, $p = 0.024$); 25% relapsed within 166 days	Low Fusobacteria linked to earlier relapse
Elgendy et al., 2021	Egypt	Case–control	40 RRMS, 22 controls	31.4 ± 8.8 yrs	qPCR of 16S rRNA groups	↑ Desulfovibrio (+68%), ↑ Actinobacteria (+59%), ↓ Clostridium IV (−44%); $p < 0.01$	Dysbiosis associated with EDSS > 3.5
Saresella et al., 2017	Italy	Dietary pilot	20 RRMS (10 per group)	40–55 yrs	HV/LP vs Western diet (12 months)	+34% Lachnospiraceae, −28% IL-17 cells, ↓ relapse rate (0.5→0.1/yr, $p < 0.01$)	HV/LP diet improves microbiome and immunity
Yadav et al., 2016	USA	RCT	61 RRMS	37 ± 10 yrs	Low-fat plant-based diet (12 months)	−6.2 ± 3.4 MFIS ($p = 0.001$); −1.9 ± 0.8 BMI ($p = 0.002$); no MRI difference	Fatigue improves despite stable MRI
Swidsinski et al., 2017	Germany	Controlled intervention	25 MS, 14 controls	38 ± 9 yrs	FISH quantification; ketogenic diet (6 months)	−45% microbial mass; +65% F. prausnitzii, +59% Roseburia after 24 weeks	Ketogenic diet restores microbial mass and diversity
Rahimlou et al., 2022	Iran	RCT (double-blind)	70 MS	35–50 yrs	Multi-strain probiotic (6 months)	↑ BDNF (+14.7%), ↓ IL-6 (−22.1%), improved BDI-II and FSS ($p < 0.01$)	Probiotics enhance mental and immune health

Koucha ki et al., 2017	Iran	RCT (double-blind)	60 MS	37 ± 7 yrs	Probiotic capsule (12 weeks)	↓ EDSS (−0.3 ± 0.6 vs +0.1 ± 0.3, p = 0.001); ↓ hs-CRP (−1.3 μg/mL, p = 0.01); ↑ HDL (p = 0.02)	Short-term probiotics improve disability and inflammation

Interpretation and Synthesis

Overall, RRMS is associated with quantifiable dysbiosis characterized by reduced SCFA-producing commensals and enrichment of inflammatory taxa.

Microbiota-targeted interventions—including probiotic supplementation, ketogenic or plant-based diets, and high-vegetable/low-protein regimens—produced measurable benefits in fatigue, mental health, relapse rate, and biochemical inflammation indices.

However, heterogeneity in study design, analytical methods, and participant demographics limits direct comparability. Larger, longitudinal RCTs are needed to confirm causality and determine whether microbiome modulation can reduce relapse risk or alter long-term MS trajectory.

Discussion

The role of the gut microbiota in relapsing-remitting multiple sclerosis (RRMS) has emerged as a promising area of research, with mounting evidence indicating that microbial composition influences immune regulation, neuroinflammation, and disease progression (Navarro-López et al., 2022; Devolder et al., 2023). Dysbiosis, defined as the imbalance between beneficial and pathogenic microbial taxa, has been consistently reported in RRMS patients across diverse populations (Elgendy et al., 2021; Chen et al., 2016). These alterations include depletion of anti-inflammatory, short-chain fatty acid-producing bacteria such as Faecalibacterium and Roseburia, coupled with enrichment of pro-inflammatory taxa including Bilophila and Desulfovibrio (Navarro-López et al., 2022; Mirza et al., 2020).

Several studies have suggested that gut microbiota composition may serve as a predictive biomarker for disease activity and relapse risk in RRMS. For instance, Tremlett et al. (2016) demonstrated that specific microbial signatures in pediatric MS patients were associated with higher relapse frequency, while Devolder et al. (2023) found correlations between dysbiosis and long-term disability worsening in adults. These findings highlight the potential utility of microbial profiling in prognostication and patient stratification.

The immune-modulatory effects of the microbiota are central to its role in RRMS pathogenesis. Preclinical models have shown that pro-inflammatory T-cell responses can be triggered by gut microbiota antigens, exacerbating autoimmune demyelination (Lee et al., 2011; Berer et al., 2011). Additionally, transplantation of microbiota from MS patients into germ-free mice has been shown to induce spontaneous autoimmune encephalomyelitis, further supporting a causal link between gut microbes and CNS autoimmunity (Berer et al., 2017; Mirza et al., 2020).

Dietary interventions have emerged as effective modulators of gut microbiota and systemic inflammation in RRMS. Low-fat, plant-based diets have been shown to enhance microbial diversity, reduce pro-inflammatory taxa, and improve quality of life measures in MS patients (Yadav et al., 2016; Mousavi-Shirazi-Fard et al., 2021). Similarly, ketogenic and anti-inflammatory diets have demonstrated potential in restoring microbiome balance and reducing inflammatory biomarkers (Swidsinski et al., 2017; Saresella et al., 2017).

Probiotic supplementation represents another promising approach. Randomized controlled trials have shown that multi-strain probiotics can modulate circulating levels of neurotrophic factors such as BDNF and NGF, reduce pro-inflammatory cytokines, and improve mental health outcomes (Rahimlou et al., 2022; Kouchaki et al., 2017). These findings suggest that probiotics may complement conventional RRMS therapies by modulating both immunity and CNS function.

Beyond probiotics, fecal microbiota transplantation (FMT) has been explored as a more direct method of microbiome modulation. Single-subject and case series studies have reported improvements in gut microbial diversity and some clinical parameters following FMT, although the evidence remains

preliminary (Engen et al., 2020; Borody et al., 2011). These findings underscore the potential for more targeted microbiota-based interventions in RRMS.

Intermittent fasting and calorie restriction have also been evaluated for their effects on the gut microbiome and disease outcomes. Cignarella et al. (2018) demonstrated that intermittent fasting altered microbial composition, enhanced regulatory immune responses, and conferred neuroprotection in CNS autoimmunity. Similarly, Fitzgerald et al. (2018) reported improvements in weight management and patient-reported outcomes in MS patients undergoing intermittent calorie restriction, highlighting the interplay between diet, microbiota, and clinical symptoms.

Clinical biomarkers reflecting gut-immune interactions have been investigated to improve disease monitoring. Serum neurofilament light chain (sNfL) has emerged as a sensitive marker for axonal injury, while gut microbiota profiling may provide complementary insights into relapse risk and immune dysregulation (Bittner et al., 2021; Cree et al., 2019). Combining these markers may enhance personalized treatment strategies.

Variation in microbiota profiles across MS phenotypes further emphasizes the complexity of gut-CNS interactions. Reynders et al. (2020) showed that different RRMS subtypes exhibited distinct microbial signatures, which may partly explain heterogeneity in clinical outcomes and therapeutic responses. Such phenotypic associations underscore the need for individualized microbiome-based interventions.

Experimental studies have also elucidated mechanisms linking microbial dysbiosis to CNS autoimmunity. Pro-inflammatory T-cells activated by gut microbial antigens promote demyelination, while commensals may induce regulatory T-cell responses that limit inflammation (Lee et al., 2011; Berer et al., 2011; Berer et al., 2017). These mechanistic insights provide a foundation for interventions aiming to restore microbial balance and immune homeostasis.

Several systematic reviews and meta-analyses have consolidated evidence linking gut microbiota alterations to RRMS. Mirza et al. (2020) and Schepici et al. (2019) emphasized that microbial dysbiosis is a consistent feature across populations and that dietary or probiotic interventions can beneficially modulate the microbiome. Tsogka et al. (2023) further highlighted current gaps, including the need for standardized intervention protocols and longitudinal assessments.

Despite promising findings, methodological heterogeneity limits the generalizability of results. Studies varied in sample size, geographic location, dietary background, sequencing methods, and follow-up duration (Chen et al., 2016; Elgendy et al., 2021; Navarro-López et al., 2022). Such variability underscores the need for larger, multi-center, longitudinal studies employing standardized microbiome and immunological assessments.

The integration of microbiota-targeted interventions with conventional disease-modifying therapies offers a compelling strategy for comprehensive RRMS management. Evidence indicates that diet, probiotics, and fasting interventions may synergistically modulate microbial composition, reduce inflammation, and improve neurocognitive and motor outcomes (Tankou et al., 2018; Salami et al., 2019; Saresella et al., 2017).

Finally, translating microbiome research into clinical practice will require personalized approaches. Microbial profiling may inform tailored dietary or probiotic regimens, early detection of relapse risk, and monitoring of therapeutic efficacy (Navarro-López et al., 2022; Devolder et al., 2023; Tsogka et al., 2023). Such precision medicine strategies hold promise to improve long-term outcomes and quality of life in RRMS patients.

Conclusion

This systematic synthesis highlights the pivotal role of gut microbiota in the pathophysiology and management of relapsing-remitting multiple sclerosis. Evidence from observational studies, randomized clinical trials, and experimental models demonstrates that microbial dysbiosis contributes to immune dysregulation, neuroinflammation, and disease progression. Interventions such as dietary modulation, probiotic supplementation, fecal microbiota transplantation, and intermittent fasting show potential in restoring microbial balance, reducing pro-inflammatory responses, and improving both neurological and quality-of-life outcomes. These findings underscore the microbiota as both a biomarker and a therapeutic target in RRMS, offering opportunities for precision medicine approaches tailored to individual microbial profiles.

Integrating microbiota-targeted strategies with conventional disease-modifying therapies may enhance treatment efficacy and patient outcomes. Personalized interventions guided by microbial profiling could

enable early identification of relapse risk, optimization of immunomodulatory therapies, and improved long-term disease management. While promising, these approaches require further validation through large-scale, multi-center longitudinal studies to establish standardized protocols, confirm causal relationships, and assess sustained clinical benefits. Overall, gut microbiome modulation represents a transformative avenue in RRMS care, with the potential to complement existing therapies and improve patients' quality of life.

Limitation

A major limitation of the current evidence is the heterogeneity across studies, including differences in sample size, geographic populations, dietary habits, sequencing methodologies, and follow-up durations. These variations complicate comparisons and limit the generalizability of findings. Furthermore, most interventions have short-term follow-up, and the long-term safety, efficacy, and mechanistic effects of microbiota-targeted therapies in RRMS remain insufficiently characterized.

References

1. Berer, K., Gerdes, L. A., Cekanaviciute, E., Jia, X., Xiao, L., Xia, Z., Liu, C., Klotz, L., Stauffer, U., Baranzini, S. E., et al. (2017). Gut microbiota from multiple sclerosis patients enables spontaneous autoimmune encephalomyelitis in mice. Proceedings of the National Academy of Sciences of the United States of America, 114(40), 10719–10724.
2. Berer, K., Mues, M., Koutrolos, M., Rasbi, Z. A., Boziki, M., Johner, C., Wekerle, H., & Krishnamoorthy, G. (2011). Commensal microbiota and myelin autoantigen cooperate to trigger autoimmune demyelination. Nature, 479(7374), 538–541.
3. Bittner, S., Oh, J., Havrdová, E. K., Tintoré, M., & Zipp, F. (2021). The potential of serum neurofilament as biomarker for multiple sclerosis. Brain, 144, 2954–2963.
4. Borody, T., Leis, S., Campbell, J., Torres, M., & Nowak, A. F. (2011). Fecal microbiota transplantation (FMT) in multiple sclerosis (MS): 942. American Journal of Gastroenterology, 106, S352.
5. Chen, J., Chia, N., Kalari, K. R., Yao, J. Z., Novotna, M., Paz Soldan, M. M., ... & Mangalam, A. K. (2016). Multiple sclerosis patients have a distinct gut microbiota compared to healthy controls. Scientific Reports, 6(1), 28484.
6. Cignarella, F., Cantoni, C., Ghezzi, L., Salter, A., Dorsett, Y., Chen, L., Phillips, D., Weinstock, G. M., Fontana, L., Cross, A. H., et al. (2018). Intermittent fasting confers protection in CNS autoimmunity by altering the gut microbiota. Cell Metabolism, 27, 1222–1235.e6.
7. Cree, B. A. C., Hollenbach, J. A., Bove, R., Kirkish, G., Sacco, S., Caverzasi, E., Bischof, A., Gundel, T., Zhu, A. H., Papinutto, N., et al. (2019). Silent progression in disease activity–free relapsing multiple sclerosis. Annals of Neurology, 85(5), 653–665.
8. Devolder, L., Pauwels, A., Van Remoortel, A., Falony, G., Vieira-Silva, S., Nagels, G., ... & D'Hooghe, M. B. (2023). Gut microbiome composition is associated with long-term disability worsening in multiple sclerosis. Gut Microbes, 15(1), 2180316.
9. Elgendy, S. G., Abd-Elhameed, R., Daef, E., Mohammed, S. M., Hassan, H. M., El-Mokhtar, M. A., ... & Khedr, E. M. (2021). Gut microbiota in forty cases of Egyptian relapsing remitting multiple sclerosis. Iranian Journal of Microbiology, 13(5), 632.
10. Engen, P. A., Zaferiou, A., Rasmussen, H., Naqib, A., Green, S. J., Fogg, L. F., Forsyth, C. B., Raeisi, S., Hamaker, B., & Keshavarzian, A. (2020). Single-arm, non-randomized, time series, single-subject study of fecal microbiota transplantation in multiple sclerosis. Frontiers in Neurology, 11, 978.
11. Fitzgerald, K. C., Vizthum, D., Henry-Barron, B., Schweitzer, A., Cassard, S. D., Kossoff, E., Hartman, A. L., Kapogiannis, D., Sullivan, P., Baer, D. J., et al. (2018). Effect of intermittent vs. daily calorie restriction on changes in weight and patient-reported outcomes in people with multiple sclerosis. Multiple Sclerosis and Related Disorders, 23, 33–39.
12. Kouchaki, E., Tamtaji, O. R., Salami, M., Bahmani, F., Daneshvar Kakhaki, R., Akbari, E., Tajabadi-Ebrahimi, M., Jafari, P., & Asemi, Z. (2017). Clinical and metabolic response to probiotic supplementation in patients with multiple sclerosis: A randomized, double-blind, placebo-controlled trial. Clinical Nutrition, 36, 1245–1249.

13. Lee, Y. K., Menezes, J. S., Umesaki, Y., & Mazmanian, S. K. (2011). Proinflammatory T-cell responses to gut microbiota promote experimental autoimmune encephalomyelitis. Proceedings of the National Academy of Sciences of the United States of America, 108(suppl_1), 4615–4622.
14. Mirza, A., Forbes, J. D., Zhu, F., Bernstein, C. N., Van Domselaar, G., Graham, M., & Tremlett, H. (2020). The multiple sclerosis gut microbiota: a systematic review. Multiple Sclerosis and Related Disorders, 37, 101427.
15. Mousavi-Shirazi-Fard, Z., Mazloom, Z., Izadi, S., & Fararouei, M. (2021). The effects of modified anti-inflammatory diet on fatigue, quality of life, and inflammatory biomarkers in relapsing-remitting multiple sclerosis patients: A randomized clinical trial. International Journal of Neuroscience, 131, 657–665.
16. Navarro-López, V., Méndez-Miralles, M. Á., Vela-Yebra, R., Fríes-Ramos, A., Sánchez-Pellicer, P., Ruzafa-Costas, B., ... & Navarro-Moratalla, L. (2022). Gut microbiota as a potential predictive biomarker in relapsing-remitting multiple sclerosis. Genes, 13(5), 930.
17. Rahimlou, M., Hosseini, S. A., Majdinasab, N., Haghighizadeh, M. H., & Husain, D. (2022). Effects of long-term administration of multi-strain probiotic on circulating levels of BDNF, NGF, IL-6 and mental health in patients with multiple sclerosis: A randomized, double-blind, placebo-controlled trial. Nutritional Neuroscience, 25, 411–422.
18. Salami, M., Kouchaki, E., Asemi, Z., & Tamtaji, O. R. (2019). How probiotic bacteria influence the motor and mental behaviors as well as immunological and oxidative biomarkers in multiple sclerosis? A double-blind clinical trial. Journal of Functional Foods, 52, 8–13.
19. Saresella, M., Mendozzi, L., Rossi, V., Mazzali, F., Piancone, F., LaRosa, F., Marventano, I., Caputo, D., Felis, G. E., & Clerici, M. (2017). Immunological and clinical effect of diet modulation of the gut microbiome in multiple sclerosis patients: A pilot study. Frontiers in Immunology, 8, 1391.
20. Schepici, G., Silvestro, S., Bramanti, P., & Mazzon, E. (2019). The gut microbiota in multiple sclerosis: An overview of clinical trials. Cell Transplantation, 28(12), 1507–1527.
21. Swidsinski, A., Dörffel, Y., Loening-Baucke, V., Gille, C., Göktas, Ö., Reißhauer, A., Neuhaus, J., Weylandt, K.-H., & Guschin, A. (2017). Reduced mass and diversity of the colonic microbiome in patients with multiple sclerosis and their improvement with ketogenic diet. Frontiers in Microbiology, 8, 1141.
22. Tankou, S. K., Regev, K., Healy, B. C., Tjon, E., Laghi, L., Cox, L. M., Kivisäkk, P., Pierre, I. V., Hrishikesh, L., Gandhi, R., et al. (2018). A probiotic modulates the microbiome and immunity in multiple sclerosis. Annals of Neurology, 83, 1147–1161.
23. Tremlett, H., Fadrosh, D. W., Faruqi, A. A., Hart, J., Roalstad, S., Graves, J., ... & Weinstock-Guttman, B. (2016). Gut microbiota composition and relapse risk in pediatric MS: A pilot study. Journal of the Neurological Sciences, 363, 153–157.
24. Tsogka, A., Kitsos, D. K., Stavrogianni, K., Giannopapas, V., Chasiotis, A., Christouli, N., ... & Giannopoulos, S. (2023). Modulating the gut microbiome in multiple sclerosis management: a systematic review of current interventions. Journal of Clinical Medicine, 12(24), 7610.
25. Yadav, V., Marracci, G., Kim, E., Spain, R., Cameron, M., Overs, S., Riddehough, A., Li, D. K., McDougall, J., Lovera, J., et al. (2016). Low-fat, plant-based diet in multiple sclerosis: A randomized controlled trial. Multiple Sclerosis and Related Disorders, 9, 80–90.