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THE ROLE OF THE MICROBIOTA-GUT-BRAIN AXIS IN THE PATHOGENESIS AND TREATMENT OF MULTIPLE SCLEROSIS – A REVIEW OF THE LITERATURE

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ABSTRACT

This review examines the bidirectional relationship between the gut microbiome and multiple sclerosis (MS). Analyzing current literature from PubMed and Google Scholar, the paper confirms that MS patients consistently display gut dysbiosis. This is characterized by reduced microbial diversity, a depletion of anti-inflammatory, short-chain fatty acid-producing bacteria, and an overabundance of pro-inflammatory taxa. This imbalance contributes to intestinal barrier dysfunction ("leaky gut"), systemic inflammation, and the activation of neurotoxic T cells, which exacerbates neuroinflammation. Notably, the interaction is reciprocal; common disease-modifying therapies also influence gut microbiota composition. The review concludes that these complex interactions present new opportunities for adjunctive therapies. Emerging evidence supports the potential of microbiome-targeted strategies, including probiotics, prebiotics, dietary changes, and butyrate supplementation, to reduce inflammation and alleviate symptoms, paving the way for more personalized MS management.

Introduction: Multiple sclerosis (MS) is a chronic, immune-mediated disorder of the central nervous system and a leading cause of neurological disability in young adults. Its pathogenesis involves a complex interplay between genetic susceptibility and modifiable environmental factors. In recent years, the gut microbiota has emerged as a critical regulator of systemic immunity and a potential key modulator of neuroinflammation via the microbiota-gut-brain axis.

Purpose of the work: This review aims to synthesize current evidence on the bidirectional relationship between gut microbiota and multiple sclerosis. It focuses on the molecular mechanisms linking dysbiosis to neuroinflammation, the clinical impact of microbiota alterations in MS patients, and the therapeutic potential of microbiome-targeted interventions.

Materials and methods: A comprehensive analysis of scientific articles available on PubMed and Google Scholar was conducted. The search strategy included combinations of keywords such as "multiple sclerosis", "gut microbiota", "dysbiosis", "short-chain fatty acids", "microbiota-gut-brain axis", "immunomodulation", and "probiotics". Studies published in peer-reviewed journals, including original research, meta-analyses, and clinical trials, were selected for review.

Results: The review confirms that MS patients exhibit significant gut dysbiosis characterized by reduced microbial diversity, depletion of short-chain fatty acid (SCFA)-producing bacteria (e.g., Faecalibacterium, Butyricicoccus), and an increase in pro-inflammatory taxa (e.g., Prevotella). This dysbiosis contributes to increased intestinal permeability ("leaky gut"), systemic low-grade inflammation, and activation of encephalitogenic T cells (Th1/Th17), which exacerbate neuroinflammation and demyelination. Clinical data indicate that over 75% of MS patients report gastrointestinal symptoms, correlating with microbiota alterations. Importantly, the review highlights that standard disease-modifying therapies (e.g., interferon-beta, dimethyl fumarate, ocrelizumab) can themselves modulate gut microbiota composition, suggesting a bidirectional drug-microbiome interaction. Furthermore, emerging evidence supports the therapeutic potential of microbiota-targeted strategies: probiotic supplementation (Lactobacillus, Bifidobacterium) reduces inflammatory markers and improves disability scores; prebiotic fibers (e.g., inulin) enhance SCFA production and attenuate experimental autoimmune encephalomyelitis; dietary interventions alleviate fatigue and improve quality of life; and butyrate, a key SCFA, promotes remyelination. Fecal microbiota transplantation has shown promise in achieving long-term disease stabilization in isolated cases.

KEYWORDS

Multiple Sclerosis, Gut Microbiota, Dysbiosis, Microbiota-Gut-Brain Axis, Short-Chain Fatty Acids, Neuroinflammation, Disease-Modifying Therapies, Immunomodulation, Probiotics, Prebiotics, Fecal Microbiota Tranplantation, Autoimmunity, Central Nervous System

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1. Multiple Sclerosis: Pathogenesis, Risk Factors, Epidemiology, Symptoms, Diagnostic Tools and Therapeutic Approach

1.1 Pathogenesis and Risk Factors

Multiple sclerosis (MS) is a chronic, immune-mediated disorder of the central nervous system (CNS) and a leading cause of neurological disability in young adults, significantly impairing quality of life [1]. Its pathogenesis involves a loss of immune tolerance to myelin antigens, driven by aberrant activation of autoreactive lymphocytes. $CD4^+$ T cells of the pro-inflammatory Th1 and Th17 lineages are central players, secreting cytokines like interferon-γ and interleukin-17 that sustain neural inflammation. These activated cells cross the blood-brain barrier and, along with B lymphocytes and innate immune cells (microglia, macrophages), drive demyelination and axonal injury. Over time, this inflammatory process evolves into progressive neurodegeneration [2].

MS aetiology involves an interplay between genetic predisposition and environmental factors. The genetic contribution is polygenic and relatively modest (estimated at 18–24%), with the HLA region on chromosome 6 accounting for approximately 20% of this risk. The *HLA-DRB1*15:01* allele confers the strongest susceptibility, while HLA-A02:01* is protective [2, 3, 4]. Genome-wide studies have identified over 200 associated genetic loci [5]. Key environmental risk factors include Epstein-Barr virus (EBV) infection, vitamin D deficiency, smoking, and adolescent obesity. Their mechanisms, such as molecular mimicry (EBV) and chronic low-grade inflammation (obesity), highlight the role of immune dysregulation and environmental interactions in disease susceptibility [6, 7, 8, 9].

In addition to EBV, other herpesviruses (HHV-6, VZV) and other viral infections (e.g., measles) have been associated with increased MS risk, potentially through mechanisms like molecular mimicry or non-specific immune activation that can expose hidden myelin antigens and trigger epitope spreading [10]. Other implicated environmental factors include severe psychological stress, occupational exposure to organic solvents or ionizing radiation, and season of birth (spring in the northern hemisphere), the latter likely linked to prenatal vitamin D levels. Conversely, protective factors include high sun exposure, prolonged breastfeeding, regular fish consumption, and a generally healthier lifestyle [11].

Table 1. Risk factors of developing multiple sclerosis

Risk factor	Mechanism	Comment
Epstein-Barr virus (EBV)	Molecular mimicry between viral antigens (especially EBNA-1) and CNS autoantigens, chronic immune stimulation resulting from latent infection and EBV reactivation in B lymphocytes, or direct CNS infection.	The strongest known risk factor.
Vitamin D deficiency	Vitamin D induces the formation of Treg lymphocytes with anti-inflammatory function and inhibits the pro-inflammatory response. By maintaining immune homeostasis, it inhibits the initiation of autoimmunity and promotes tolerance.	Low OH(25)D levels increase the risk of disease by up to >60%, with the strongest effect in childhood and youth.
Obesity (especially in youth)	Immunomodulatory effect of adipose tissue – causes chronic low-grade inflammation, increases the level of pro-inflammatory cytokines (TNF-a, IL-6, leptin) and may impair the function of the blood-brain barrier and the functioning of regulatory T cells.	A twofold increase in risk in obese individuals (BMI ≥30) aged around 20 years. The association is independent of vitamin D levels (although obesity often correlates with vitamin D levels). Importantly, there are immunosuppressive effects of UV radiation that are independent of vitamin D: inhibition of cellular response, induction of regulatory T cells and a shift in response towards Th2.

Risk factor	Mechanism	Comment
Smoking (active and passive)	Irritation of the lungs by tobacco smoke may promote permeability of the pulmonary epithelial barrier, facilitating antigen presentation, activating Th1 lymphocytes, and promoting a pro-inflammatory response and their migration to the CNS via smoke chemicals that may damage the blood-brain barrier.	The risk increases with time and intensity of smoking. Current smokers have an approximately 40% higher risk (up to 60% for heavy smokers).
Shift work	Disruption of the circadian rhythm and melatonin secretion, which has an immunomodulatory effect and inhibits the differentiation of pathogenic T lymphocytes.	
Changes in the gut microbiota	An imbalance in the microbiota can affect the immune system through the production of metabolites, modulation of T cell responses, and the integrity of the intestinal barrier.	

1.2 Epidemiology

MS affects approximately 1.89 million people globally, with a rising prevalence trend worldwide, particularly in Europe [12]. The disease exhibits a distinct geographical and demographic pattern. Prevalence is highest in North America and Western Europe (e.g., Sweden: 219/100,000) and lowest in Asia and Africa, reflecting a pronounced latitude gradient strongly associated with sunlight exposure and vitamin D deficiency [12, 13]. Within countries, subnational disparities exist, such as higher incidence in northern versus southern US states [13]. A hallmark of MS epidemiology is a 2–3 times higher incidence in women than in men, with a peak age of onset between 30–34 years. Higher healthcare expenditure per capita is also a significant predictor of prevalence, likely indicating better diagnostic ascertainment in wealthier nations [12, 14].

1.3 Symptoms and Disease Course

MS is clinically heterogeneous. The most common initial course is relapsing-remitting MS (RRMS; ~85% of cases), characterized by acute neurological attacks followed by remission. Many patients later transition to secondary progressive MS (SPMS), marked by gradual, irreversible decline. A minority present with primary progressive MS (PPMS), featuring steady progression from onset [15, 16]. Symptoms arise from CNS demyelination and axonal injury, varying by lesion location [15-17]:

- **Fatigue**: A common and debilitating symptom, with thalamic dysfunction implicated as a key biomarker [18].
- **Cognitive impairment**: Affects 45-70% of patients, impacting processing speed, memory, and executive functions, necessitating regular assessment [19].
- **Psychiatric disorders**: Depression and anxiety are prevalent, sharing neuroanatomical correlates with MS pathology and worsening overall burden [20].
- **Optic neuritis**: A frequent visual manifestation, often causing acute unilateral vision loss and potential residual deficits [21].
- **Motor and cerebellar dysfunction**: Includes ataxia, tremor, dysarthria, and weakness, predicting faster disability accumulation [22].
- **Brainstem dysfunction**: Causes diverse symptoms (e.g., impaired eye movements, dysphagia) and autonomic dysregulation [23].
- **Sensory disturbances**: Common initial symptoms include paresthesia, Lhermitte's sign, and underrecognized olfactory dysfunction linked to cognitive decline [15, 16, 17, 24].
- **Pain**: Affects over half of patients, often neuropathic, and significantly reduces quality of life [25, 26].
- **Urinary and sexual dysfunction:** Highly prevalent complications stemming from neurological damage and requiring integrated management [27, 28].
- **Motor, brainstem/cerebellar, or multifocal symptoms** at onset typically predict a faster accrual of disability compared to sensory or visual onset [15, 16].

1.4 Diagnosis

Diagnosing multiple sclerosis (MS) remains challenging due to the disease's clinical and radiological heterogeneity, the lack of a single definitive biomarker, and a broad differential diagnosis. The process is multifaceted, requiring the integration of clinical assessment, neuroimaging, and laboratory findings to demonstrate dissemination of CNS lesions in time (DIT) and space (DIS) while excluding other explanations [29, 30]. The evaluation begins with clinical judgment to determine if the presentation is typical for an MS-related demyelinating attack. Typical syndromes include optic neuritis, brainstem syndromes (e.g., internuclear ophthalmoplegia), cerebellar syndromes, and transverse myelitis. A clinical attack is defined as an episode of neurological dysfunction lasting at least 24 hours without fever or infection, and must be corroborated by objective signs on neurological examination [30, 31]. It is important to note that the diagnostic criteria are validated for these typical presentations; their use in atypical cases is not recommended and reduces specificity.

Table 2. The 2017 McDonald Diagnostic Criteria for MS

Number of Clinical Attacks	Number of Lesions with Objective Clinical Evidence	Additional Data Needed for MS Diagnosis
≥2	≥2	None. (Clinical evidence alone demonstrates DIS and DIT).
≥2	1 (with historical evidence of a prior attack in a different location)	None.
≥2	1	DIS demonstrated by: (1) a second clinical attack at a different site or (2) MRI
1	≥2	DIT demonstrated by: (1) A second clinical attack or (2) MRI (simultaneous enhancing/ non-enhancing lesions or new lesion on follow-up) or (3) CSF-specific oligoclonal bands
1	1	DIS (by a second clinical attack or MRI) **and** DIT (by a second clinical attack or MRI or CSF-specific oligoclonal bands)

Essential Prerequisites for Applying the Criteria:

- The patient must present with a syndrome **typical of MS** (e.g., optic neuritis, myelitis),
- There must be "**no better explanation**" for the clinical and paraclinical findings, necessitating a thorough consideration of the differential diagnosis,
- **Symptomatic brainstem and spinal cord lesions** can be included for demonstrating both DIS and DIT.

Neuroimaging, primarily magnetic resonance imaging (MRI), is the most sensitive tool for confirming dissemination in space (DIS) and time (DIT), often enabling diagnosis before a second clinical attack. Per the 2017 McDonald criteria, DIS is demonstrated by T2-hyperintense lesions in ≥2 of four characteristic CNS regions: periventricular, cortical/juxtacortical, infratentorial, or spinal cord. DIT is confirmed by the simultaneous presence of gadolinium-enhancing (active) and non-enhancing lesions on a single scan, or a new lesion on a follow-up scan. Spinal cord imaging is particularly valuable for increasing diagnostic specificity [30, 31]. Laboratory tests provide crucial supportive evidence and help exclude mimics. Cerebrospinal fluid (CSF) analysis for oligoclonal bands (OCBs), indicating intrathecal IgG synthesis, is a key finding. The presence of CSF-specific OCBs can substitute for DIT evidence, allowing for earlier diagnosis. Conversely, atypical CSF findings (e.g., pleocytosis >50 cells/mm³) are red flags. Serological testing for AQP4-IgG and MOG-IgG antibodies is mandatory to exclude neuromyelitis optica spectrum disorder (NMOSD) and MOG antibody-associated disease, the primary differential diagnoses [29, 30]. The diagnostic principle of "no better explanation" necessitates the systematic exclusion of these and other MS mimics.

Table 3. Major Categories of MS Mimics

Category	Key examples	Distinguishing Features "Red Flags"
Other Inflammatory CNS Disorders	NMOSD- neuromyelitis optica spectrum disorders (AQP4-IgG+)	Longitudinally extensive transverse myelitis (≥3 vertebral segments), severe/bilateral optic neuritis, area postrema syndrome (hiccups/nausea). Brain lesions in AQP4-rich areas (diencephalon, periependymal).
	MOG Antibody-Associated Disease	Often presents with acute disseminated encephalomyelitis (ADEM)- (especially in children), optic neuritis, or myelitis. May have confluent or fluffy lesions. Longitudinally extensive transverse myelitis (LETM) often with central cord edema.
	Acute Disseminated Encephalomyelitis (ADEM)	Predominantly in children. Encephalopathy (required for diagnosis). Multifocal, often large, ill-defined lesions. Usually monophasic.
	Neurosarcoidosis, CNS Vasculitis, Behçet's Disease	Meningeal enhancement, systemic symptoms (e.g., fever, weight loss, skin/oral lesions, uveitis), pulmonary findings (sarcoid).
Infectious Diseases	Lyme Disease, CNS Syphilis, HIV, HTLV-1	Exposure history, systemic symptoms, specific serological testing, prominent CSF pleocytosis.
Metabolic & Nutritional	Vitamin B12 / Copper Deficiency	Progressive myelopathy, peripheral neuropathy, macrocytic anemia (B12), T2 hyperintensity in dorsal columns.
Genetic / Vascular	Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL)	History of migraines with aura, early-onset strokes, family history. Temporal pole involvement on MRI is characteristic.
	Susac's Syndrome	Clinical triad: encephalopathy, branch retinal artery occlusions, hearing loss. "Snowball" lesions in the corpus callosum.
Structural / Compressive	Cervical Spondylotic Myelopathy, Tumors	Insidiously progressive myelopathy, lack of typical brain lesions, MRI evidence of compression.
Progressive Disorders	Hereditary Spastic Paraplegia	Family history, pure progressive spastic paraparesis, often minimal or no brain MRI abnormalities.
	Primary Lateral Sclerosis	Progressive upper motor neuron syndrome without sensory or other CNS findings atypical for MS.
Functional & Other	Migraine, Fibromyalgia, Functional Neurological Disorder	Lack of objective neurological signs, MRI lesions not corresponding to symptoms, non-anatomical sensory patterns, high burden of non-specific symptoms.

Prominent "Red Flags" warranting consideration of an alternative diagnosis include: onset after age 50, progressive course from onset without relapses, systemic symptoms (fever, weight loss), peripheral neuropathy, movement disorders, seizures, meningismus, longitudinally extensive spinal cord lesions, persistent or nodular gadolinium enhancement, meningeal enhancement, and CSF findings atypical for MS (as noted above) [29,30,31].

1.5 Basics of MS Treatment

MS treatment consists of managing acute relapses and long-term disease modification.

Acute Relapse Management: High-dose intravenous glucocorticosteroids (e.g., methylprednisolone) are first-line therapy to accelerate recovery by reducing inflammation, though they do not alter disease progression. Treatment decisions, including the need for hospitalization, are based on severity. A full return to baseline function is the optimal response. In cases of steroid-refractory exacerbations (affecting ~50% of patients), second-line options like plasmapheresis or intravenous immunoglobulins may be considered [32, 33].

Disease-Modifying Therapies (DMTs): These are the cornerstone of long-term management for relapsing forms of MS. They are broadly categorized into immunomodulators and immunosuppressants, with efficacy measured by reductions in annualized relapse rate, disability progression, and MRI activity [32, 34, 35]. DMTs are often stratified:

First-line DMTs: Include interferon-β, glatiramer acetate, dimethyl fumarate, and teriflunomide.

Higher-efficacy DMTs: Include natalizumab, fingolimod, and anti-CD20 monoclonal antibodies (e.g., ocrelizumab). These are used for active disease and carry a more complex risk profile.

Treatment Strategies- two main philosophies guide DMT initiation:

- Escalation Approach: Begins with first-line, moderate-efficacy DMTs, escalating to higher-efficacy agents only if breakthrough disease occurs.
- Early High-Efficacy Approach: Advocates for initiating potent immunosuppressive/immunomodulatory therapy at diagnosis to maximally suppress inflammatory activity from the outset, with evidence suggesting greatest benefit in younger patients with early, active disease [36].

Treatment options for progressive MS forms remain substantially limited and focus primarily on symptom management.

2. Gut Microbiota- Functions, Influencing Factors, Microbiota-Immunity-Brain Axis, Probiotic Role

As outlined above, the pathogenesis of MS involves a complex interplay of genetic susceptibility and modifiable environmental factors. Among these environmental determinants, the gut microbiota has emerged in recent years as a critical regulator of systemic immunity and a potential key modulator of neuroinflammation. The bidirectional communication along the gut-brain axis provides a plausible mechanism through which intestinal dysbiosis could influence the initiation and progression of MS. The following sections will delve into the physiology of this axis, examine the evidence for gut microbiota alterations in MS patients, and discuss the potential of microbiome-targeted interventions as a novel therapeutic avenue.

2.1 About Gut Microbiota- What Should We Know?

2.1.1 The Symbiosis and Stability of Gut Microbiota

The human gut hosts a complex community of microorganisms, primarily bacteria, in a state of symbiosis. This means both parties benefit: the microbes receive a protected habitat and nutrients, while they are indispensable for our health. In a healthy adult, this gut microbiota composition remains relatively stable over time. However, this stability is not rigid; it naturally changes with age, diet, and health status. Maintaining this equilibrium is crucial, as significant and persistent disruption, known as dysbiosis, is strongly associated with various gastrointestinal and systemic diseases [37].

What to eat to keep microbiota in a good shape?

A well-balanced and diverse gut microbiota is essential for overall health, influencing digestion, immunity, metabolism, and even cognitive function. Dietary choices play a pivotal role in shaping the composition and functionality of the gut microbiome. Based on current evidence, the following dietary recommendations are proposed to support a healthy gut microbiota:

- Prioritize Soluble Dietary Fibers (SDFs), which are readily fermented by gut bacteria and serve as the primary substrate for beneficial microbial metabolism, leading to the production of short-chain fatty acids (SCFAs) such as acetate, propionate, and butyrate. Most important sources of SDFs are:
- Fructo-oligosaccharides (FOS) and Galacto-oligosaccharides (GOS), found in onions, garlic, leeks, asparagus, bananas, and legumes,
- Inulin, abundant in chicory root, Jerusalem artichokes, asparagus, and bananas,
- Beta-glucans, present in oats, barley, and mushrooms,
- Pectins, rich in apples, citrus fruits, carrots, and berries,
- Gums (e.g., acacia gum, guar gum): Found in legumes and certain plant exudates

- Incorporate Resistant Starches (RS). which escapes digestion in the small intestine and undergoes fermentation in the colon, acting similarly to soluble fibers
- sources are: potatoes (cooked and cooled), green bananas, legumes and whole grains
- Emphasize Dietary Diversity- consume a wide range of fruits, vegetables, whole grains, nuts, and seeds to provide an array of microbiota-accessible carbohydrates (MACs)
- Limit Western Diet Patterns- high in saturated fats, refined sugars, and low in fiber are associated with dysbiosis, reduced microbial diversity, and increased risk of metabolic and inflammatory diseases. It is important to avoid excessive intake of processed foods, red meat, and sugar-sweetened beverages.
- Consider Prebiotic and Probiotic Synergy- while SDFs act as prebiotics, incorporating probiotic-rich foods can introduce beneficial live microorganisms (yogurt, kefir, sauerkraut, kimchi, kombucha, and other fermented foods) [49].

The Influence of Sleep and Physical Exercise on the Gut Microbiota.

Both sleep and physical exercise are fundamental lifestyle regulators of gut microbiota composition and function, with significant implications for intestinal and systemic health. Adequate, quality sleep is essential for maintaining gut microbial balance. Sleep disturbances, such as fragmentation or deprivation, disrupt circadian rhythms and reduce microbial diversity. This often leads to an unfavorable increase in the Firmicutes/Bacteroidetes ratio, associated with enhanced energy harvest, inflammation, and metabolic risk. Conditions like obstructive sleep apnea, through intermittent hypoxia, further alter the gut environment, favoring mucin-degrading bacteria and increasing intestinal permeability ("leaky gut"), which can trigger systemic inflammation. Regular, moderate physical exercise exerts a profoundly positive influence. It increases microbial diversity, enriches beneficial bacteria (e.g., Faecalibacterium prausnitzii, Akkermansia muciniphila), and boosts the production of anti-inflammatory short-chain fatty acids (SCFAs). Exercise improves gut barrier function, reduces systemic inflammation, and modulates immune responses via the gut-muscle axis. However, this relationship is dose-dependent. Excessive, exhaustive training without proper recovery can induce stress, promote dysbiosis, increase intestinal permeability, and temporarily suppress immunity, negating the benefits. In summary, balanced sleep and appropriate exercise synergistically promote a healthy, resilient gut microbiota. Conversely, disturbances in either can lead to dysbiosis, highlighting their critical role in a holistic approach to health [50, 51].

2.1.2 Diversity Across the Intestinal Tract

The diversity and density of gut bacteria are not uniform throughout the digestive system. They increase dramatically from the stomach to the colon. The stomach and duodenum, due to high acidity and rapid content flow, contain very few microorganisms. Further along, the jejunum and ileum (small intestine) host a moderate number of mostly fast-growing, oxygen-tolerant bacteria like Lactobacillus. The highest density and diversity are found in the colon (large intestine), which contains an extremely dense, anaerobic community dominated by groups such as Bacteroidetes and Firmicutes. This is the main site of microbial fermentation [37].

2.1.3 Factors Influencing the Gut Microbiota and vice versa

The composition of the gut microbiota is dynamic and shaped by complex interactions between genetic, environmental and lifestyle factors. The influence of these factors varies significantly at different stages of life, from the crucial period of infancy to old age. Table 4 summarises the most important factors influencing the gut microbiota depending on age [37,38].

Table 4. Factors modifying the gut microbiota

Age range	Factors shaping the gut microbiota
Infancy	- Method of delivery (natural delivery ensures the transfer of bacteria from the mother's reproductive tract and intestines) - Exposure to antibiotics: may significantly disrupt early colonisation and maturation of the microbiota - Environmental factors: presence of siblings, pets, family lifestyle (e.g., rural vs. urban)
Childhood (from 3 to approx. 5 years of age) and adulthood	- Long-term dietary patterns (a high-fibre diet promotes microbial diversity and the production of short-chain fatty acids [SCFA]) - Host genetics - Physiological factors (intestinal transit time, intestinal pH, oxygen level) - Geographical location
Old age	- Proper diet - Supplementation
Age range	**Factors disrupting the gut microbiota**
Infancy	- Caesarean section delivery reduces or delays colonisation by immunomodulatory Bacteroides and Bifidobacterium species, while increasing the risk of colonisation by opportunistic pathogens (e.g. Enterococcus, Clostridioides difficile), - Antibiotic therapy: Particularly early and broad-spectrum therapy can permanently disrupt the maturation process of the microbiota and reduce its diversity, - Feeding with formula without HMO: Leads to faster growth in diversity, but with characteristics different from the microbiota of breastfed children, with greater abundance of Bacteroides, Clostridium and Enterobacteriaceae
Childhood (from 3 to approx. 5 years of age) and adulthood	- Long-term use of medicines: in addition to antibiotics, also proton pump inhibitors, non-steroidal anti-inflammatory drugs, metformin, etc. - Drastic, short-term dietary changes (e.g., elimination diets) may cause temporary shifts, but the microbiota exhibits resilience and a tendency to return to its previous state if the change is not maintained in the long term, - chronic stress - inflammatory diseases (e.g. inflammatory bowel disease)
Old age	- Age-related physiological changes: decreased muscle function (slowed bowel motility), reduced production of digestive enzymes, altered feelings of hunger and thirst lead to changes in diet, often lacking in nutrients and fibre. - Hormonal changes: in women, menopause has a profound effect on the composition of the microbiota. - 'Inflammaging': chronic low-grade inflammation associated with age, which is influenced by and itself influences the microbiota. - Comorbidities - Progressive frailty and associated nutritional limitations - Polypharmacy (polypharmacy): the simultaneous use of multiple drugs is common in older people and has a strong cumulative negative effect on the microbiota.

Importantly, it should be remembered that although not directly related, lifestyle diseases have a significant impact on the condition of the gut microbiota: the most important and most frequently discussed of these are obesity and metabolic syndrome, type 2 diabetes, cardiovascular diseases and mental disorders.

Obesity and the metabolic syndrome

Obesity and the metabolic syndrome are closely linked to distinct alterations in the gut microbiota that directly impact host physiology. Analysis of the literature indicates that a key characteristic is dysbiosis, manifesting as a decreased relative abundance of Bacteroidetes (Bacteroidota) and an increase in Firmicutes (Bacillota). This shift in ratio is not merely a statistical correlation but entails significant functional consequences. The obesity-associated microbiome is enriched in genes responsible for the breakdown of complex carbohydrates (starch, sucrose) and pathways leading to the production of short-chain fatty acids (SCFAs), primarily butyrate and acetate. In practical terms, this altered bacterial community extracts more energy from the same diet, a fact corroborated by the lower energy content found in the feces of obese subjects. This enhanced energetic efficiency operates through several interconnected mechanisms. The increased SCFA production, particularly acetate and butyrate, provides additional substrates for host metabolism. Acetate serves as a precursor for hepatic de novo lipogenesis, while butyrate is a primary energy source for colonocytes, contributing to gut barrier integrity. Simultaneously, the dysbiotic microbiota influences host energy storage regulation. It suppresses intestinal expression of angiopoietin-like 4 (ANGPTL4), a circulating inhibitor of lipoprotein lipase (LPL). The subsequent increase in adipocyte LPL activity promotes fatty acid uptake and triglyceride accumulation within fat cells. Importantly, this trait of "increased energetic harvest" is transmissible. Experiments transplanting microbiota from obese mice into germ-free recipients demonstrated a significantly greater gain in body fat compared to transplants from lean donors, despite identical food intake. This provides direct evidence for a causal role of the microbiota in obesity pathogenesis. Furthermore, the disrupted microbiota in obesity affects a broader health context, fostering the development of metabolic diseases. Beyond energy harvest, dysbiosis compromises gut barrier function. The reduction in protective SCFAs, especially butyrate, weakens tight junctions between intestinal epithelial cells. This, coupled with shifts in microbial composition, facilitates the translocation of bacterial components such as lipopolysaccharide (LPS) into circulation, triggering a chronic, low-grade systemic inflammation. This metabolic endotoxemia is a critical mechanism linking obesity to insulin resistance, type 2 diabetes, and cardiovascular complications. Inflammation impairs insulin signaling in adipose tissue, liver, and muscle, while also promoting hepatic steatosis [39, 40, 41].

Type 2 diabetes

Type 2 Diabetes Mellitus (T2DM) exerts a profound "top-down" influence on the gut microbiota, driving it into a state of dysbiosis that reciprocally exacerbates the disease. The primary mechanisms of this influence are multifaceted. Chronic hyperglycemia alters the luminal nutrient environment, selectively favouring bacteria adept at utilizing simple sugars. Concurrently, T2DM-associated systemic inflammation and metabolic endotoxemia, driven by elevated lipopolysaccharide (LPS) levels, increase intestinal permeability and create an inhospitable mucosal environment for beneficial commensals like Faecalibacterium and Akkermansia muciniphila. Furthermore, T2DM alters host bile acid metabolism, and since bile acids possess antimicrobial and signaling properties (via FXR and TGR5 receptors), these changes directly shape microbial survival and community structure. Pharmacological management, particularly with metformin, is a major exogenous modulator, inducing significant and often beneficial shifts in microbial composition, such as increased abundance of A. muciniphila and short-chain fatty acid producers. Complications like diabetic enteropathy and non-alcoholic fatty liver disease (NAFLD) further disrupt the gut ecosystem. Crucially, this diabetic-induced dysbiosis—characterised by reduced diversity, loss of protective taxa, and expansion of pro-inflammatory species—actively perpetuates disease pathology by worsening glucose homeostasis, inflammation, and barrier dysfunction, establishing a vicious cycle. Therefore, the gut microbiota in T2DM is both a consequence of the metabolic disorder and a contributing factor to its progression [42,43].

CVD

Cardiovascular diseases (CVD) and the gut microbiota are linked through a bidirectional relationship in which cardiovascular pathology both alters and is influenced by microbial composition and activity. Patients with CVD commonly exhibit gut dysbiosis marked by reduced microbial diversity, depletion of short-chain fatty acid (SCFA)–producing bacteria, and enrichment of pro-inflammatory taxa. These changes are driven by systemic inflammation, impaired intestinal perfusion, and neurohormonal activation associated with CVD, which together compromise gut barrier integrity and increase intestinal permeability. The resulting translocation of microbial products, such as lipopolysaccharides, amplifies systemic inflammation and accelerates vascular dysfunction. In turn, the gut microbiota contributes directly to CVD progression through the production of bioactive metabolites. Reduced SCFA availability impairs vascular regulation, immune balance, and endothelial function, favoring hypertension and atherosclerosis. Dysbiotic microbial communities

also enhance the generation of pro-atherogenic metabolites, including trimethylamine N-oxide (TMAO), which is linked to endothelial dysfunction, platelet activation, and increased cardiovascular risk. Altered microbial bile acid metabolism further disrupts lipid homeostasis and inflammatory signaling. Diet critically modulates this gut–heart axis: fiber- and polyphenol-rich dietary patterns promote beneficial microbial functions and cardioprotective metabolite profiles, whereas Western diets exacerbate dysbiosis and cardiovascular risk. Together, these findings highlight a self-reinforcing loop between CVD and gut microbiota, positioning the gut–heart axis as a promising therapeutic target [44,45,46].

Mental disorders

The gut microbiome has emerged as a critical area of research in understanding the pathophysiology of anxiety and depressive disorders. This systematic review by Simpson et al. (2020) consolidates evidence from 26 studies, providing the first dedicated synthesis for anxiety disorders and an updated review for depression. The analysis reveals that while gut microbial diversity metrics—such as alpha and beta diversity—show inconsistent differences between clinical and control groups, specific taxonomic shifts are more reliably observed. These microbial alterations suggest shared underlying mechanisms between these highly comorbid conditions, potentially mediated through inflammation, intestinal permeability, and gut-brain-axis communication. Notably, the composition of the gut microbiota in individuals with depression and anxiety shows a tendency toward an increase in proinflammatory bacterial groups, such as Enterobacteriaceae and certain Actinobacteria, alongside a decrease in anti-inflammatory, short-chain fatty acid (SCFA)-producing genera like Faecalibacterium and Coprococcus. These changes may contribute to a proinflammatory state, compromise intestinal barrier integrity, and promote systemic and central nervous system inflammation, which is increasingly implicated in mood disorder pathogenesis. Importantly, the review highlights significant methodological heterogeneity and confounding factors across studies—including variations in sequencing techniques, insufficient control for psychotropic medications and diet, and lack of longitudinal design—which limit causal inference and generalizability. Despite these challenges, the gut microbiota represents a promising target for future therapeutic interventions. However, the current evidence is not yet sufficient to recommend specific microbiome-based treatments. Future research must prioritize standardized methodologies, longitudinal and experimental designs, and a greater focus on microbial function—rather than mere taxonomy—to elucidate causal pathways and identify viable clinical applications for microbiome modulation in mental health [47,48].

2.1.4 Functions of microbiota in human body.

Participation in digestion and absorption – breaks down substances indigestible to humans (e.g., resistant starch, oligosaccharides, mucins).

Vitamin synthesis – produces vitamins K, B1, B6, B12, and folic acid.

Metabolism of compounds – breaks down sloughed epithelial cells, bile components, xenobiotics, drugs, and potential carcinogens.

Support of the intestinal barrier – stimulates the proper functioning of the intestinal barrier, improves the absorption of minerals (sodium, potassium, magnesium, calcium).

Production of short-chain fatty acids (SCFAs) – fermentation yields butyric, propionic, and acetic acids, which:

- Nourish and regenerate colonocytes (intestinal epithelial cells),
- Have anti-inflammatory effects,
- Inhibit the development of colon cancer cells.

Modulation of the immune system – activates GALT cells (gut-associated lymphoid tissue), stimulates the production of secretory IgA, maintains the Th1/Th2 lymphocyte balance.

Protection against pathogens – competes with pathogens for nutrients and adhesion sites on the epithelium, produces bacteriostatic substances (e.g., hydrogen peroxide, organic acids).

Impact on metabolic health – maintaining a balanced microbiota is associated with a lower risk of obesity, type 2 diabetes, and hypertension.

Impact on mental and neurological health – the microbiota participates in the synthesis of serotonin and neurotransmitter precursors, and its disturbances are linked to depression, schizophrenia, and autism.

Regulation of body weight – certain bacteria (e.g., Akkermansia muciniphila) correlate with maintaining a healthy body weight [52].

Modulation of insulin resistance and influence on its secretion – Microbial metabolites can affect tissue sensitivity to insulin and the function of pancreatic beta cells.

Influence on gut-brain axis communication – The microbiota is a key component of the bidirectional gut-brain axis. It influences the host's neurological and psychological functions through:

- Synthesis of neurotransmitters (e.g., GABA – gamma-aminobutyric acid)
- Impact on the integrity of the blood-brain barrier (BBB) by increasing the production of tight junction proteins
- Production of substances (e.g., LPS, lipoproteins) that stimulate cytokine release from immune cells; these cytokines can cross the BBB and affect neuronal function, mood, and behavior

Shaping the response to anti-cancer immunotherapy – The composition and diversity of the microbiota can influence the effectiveness of cancer treatments, e.g., anti-PD1 immunotherapy. Patients who respond better to treatment typically have a more diverse microbiota, richer in certain beneficial species (e.g., Faecalibacterium, Bifidobacterium, Akkermansia) [53].

2.1.5 Pro- and prebiotics.

Probiotics are defined as live microorganisms which, when administered in adequate amounts, confer health benefits to the host, primarily through modulation of the composition and activity of the gut microbiota. The most commonly studied probiotic strains include bacteria of the Lactobacillus and Bifidobacterium genera, which demonstrate the ability to strengthen the intestinal barrier, regulate immune responses, and produce bioactive metabolites such as short-chain fatty acids (SCFAs).

Prebiotics, in contrast, are selectively fermentable dietary components that stimulate the growth and activity of beneficial gut microorganisms, leading to favorable changes in the gut microbiota composition. Their effects are primarily indirect and involve modulation of the gut–brain axis through increased SCFA production, regulation of the hypothalamic–pituitary–adrenal (HPA) axis, and modulation of inflammatory responses.

Synbiotics are formulations that combine probiotics and prebiotics, allowing for synergistic interactions between these components. The use of synbiotics promotes improved colonization of the gastrointestinal tract by probiotic strains and enhances their biological effects, including their influence on central nervous system function.

The effectiveness of probiotics, prebiotics, and synbiotics in neurological and psychiatric disorders is associated with the existence of the microbiota–gut–brain axis, a complex bidirectional communication system linking the gastrointestinal tract and the central nervous system. Gut microorganisms influence brain function through several key mechanisms, including neural (vagus nerve), endocrine, immune, and metabolic pathways. Intestinal bacteria are capable of synthesizing or modulating the levels of neurotransmitters such as serotonin, dopamine, gamma-aminobutyric acid (GABA), and noradrenaline, which play a crucial role in the regulation of mood, cognitive functions, and stress responses. Moreover, probiotics exhibit anti-inflammatory properties by reducing the levels of pro-inflammatory cytokines and enhancing anti-inflammatory responses. This is particularly important in the pathogenesis of neurological disorders such as Alzheimer's disease, depression, and anxiety disorders, in which chronic inflammation and gut dysbiosis play a significant role. Alterations in gut microbiota composition have also been observed in patients with neurodegenerative diseases, further supporting the rationale for dietary and probiotic interventions as adjunctive therapeutic strategies. Indications for the use of probiotics, prebiotics, and synbiotics primarily include depressive disorders, anxiety disorders, and chronic stress, as well as selected neurodegenerative diseases in which a relationship between gut dysbiosis and symptom severity has been demonstrated. Increasingly, these preparations are considered as complementary to standard pharmacological treatments rather than as alternatives, due to their favorable safety profile and multifaceted mechanisms of action [54, 55, 56].

2.1.7 Microbiota-gut-brain axis.

The microbiota–gut–brain axis is a bidirectional, integrated communication system in which signals are transmitted through multiple overlapping neurophysiological, immunological, endocrine and metabolic pathways. Although the full map of these interactions is still under investigation, current knowledge allows us to distinguish the following key mechanisms:

Neuroanatomical pathways: Direct communication occurs mainly through the vagus nerve, whose afferent fibres detect signals from the intestines (e.g. bacterial metabolites, cytokines) and transmit them to the brain stem centres. It plays a key role in the so-called inflammatory reflex, modulating the immune response. At the same time, the enteric nervous system (ENS) functions as a local processor, integrating signals from the mucosa, microbiota and immune cells, directly influencing motility, secretion and communication with the CNS.

Hypothalamic–pituitary–adrenal (HPA) axis: Microbiota is essential for the proper maturation and regulation of the HPA axis, the main stress axis. In turn, activation of the HPA axis (e.g., under psychosocial stress) significantly alters the composition and function of the gut microbiota, increasing intestinal barrier permeability and driving low-grade inflammation, thus creating a positive feedback loop.

Modulation of the immune system: Microbiota is fundamental to the development and homeostasis of both innate and adaptive immune responses. Immune cells in the intestinal lamina propria (including dendritic cells, macrophages, and T lymphocytes) constantly monitor the microbial environment. The mediators they produce (cytokines, chemokines) can enter the systemic circulation and influence inflammation in the CNS, activating, among others, microglia cells. In recent years, particular attention has been paid to the role of neutrophils and IL-17A+ cells in the pathogenesis of neurodevelopmental and neurodegenerative disorders.

Synthesis of neuroactive metabolites: Gut bacteria produce a range of signalling molecules capable of directly or indirectly modulating CNS activity. These include:

- Short-chain fatty acids (SCFA), such as butyrate, propionate and acetate, which regulate intestinal barrier function, regulatory T cell differentiation, and microglia maturation and function.
- Neurotransmitters and their precursors, including serotonin (5-HT), GABA, dopamine, and metabolites of the tryptophan pathway (e.g., indoles, kynurenine), which may influence neurogenesis, synaptic plasticity, and mood.
- Bacterial enzymes (e.g. β-glucuronidases) that affect the metabolism of endogenous compounds and xenobiotics.

Integrity of physiological barriers: A key element of the axis is the state of the intestinal barrier. Its increased permeability ('leaky gut') facilitates the translocation of pro-inflammatory bacterial components (e.g. LPS) into the circulation, causing low-grade systemic inflammation. These factors can then disrupt the function of the blood-brain barrier (BBB), allowing greater infiltration of cytokines and immune cells into the CNS and leading to neuroinflammation [57].

3. Links between gut microbiota and Multiple sclerosis.

3.1 Molecular mechanisms.

Changes in the composition of the microbiome – functional dysbiosis:

Reduction of bacteria with anti-inflammatory potential:

Ruminococcaceae family (reduced in patients) – responsible for the production of short-chain fatty acids (SCFA), mainly butyrate, which has anti-inflammatory properties and supports the integrity of the intestinal barrier.

Faecalibacterium genus (reduced) – the main producer of butyrate; its deficiency may exacerbate inflammation.

Akkermansia muciniphila (reduced) – crucial for maintaining the intestinal mucus layer; its reduction may lead to 'leaky gut'.

Increase in bacteria with pro-inflammatory or ambiguous potential:

The Prevotellaceae family and Prevotella genus – their increased abundance may be associated with Th17 lymphocyte activation and increased inflammatory response.

The Fusobacterium genus – associated with inflammatory processes in the intestines [58].

As mentioned above, the composition of the gut microbiota is influenced by many different factors, which is why gut dysbiosis may not only be the result of the disease itself, but also the result of many other factors.

Disruption of short-chain fatty acid (SCFA) production

SCFAs (butyrate, propionate, acetate) are key bacterial metabolites that regulate:

- Intestinal barrier integrity – through enterocyte nutrition.
- In animal models, SCFA deficiency (e.g., in germ-free mice) leads to increased BBB permeability and exacerbation of EAE (experimental autoimmune encephalomyelitis).
- Immune regulation – induction of regulatory T cells (Treg) and inhibition of Th17 responses.

The meta-analysis observed a reduction in SCFA-producing species (e.g. Faecalibacterium, Butyricicoccus), which may lead to: Increased intestinal permeability → translocation of bacterial products (LPS) into the circulation → activation of the immune system and exacerbation of neuroinflammation [58,59].

Impact on immune response – relationship with disease activity

- Subgroup analysis showed that microbiome diversity decreases during active MS (Shannon index).
- This suggests that dysbiosis may be dynamic and correlate with disease exacerbations, possibly through:
- Activation of Th17 lymphocytes (associated with Prevotella and other bacteria) – key in the pathogenesis of MS.
- A reduction in Tregs (dependent on SCFA) – leading to a loss of immune tolerance.
- Changes in the microbiome may modulate the response to immunomodulatory treatment (e.g. dimethyl acetate), indicating a bidirectional interaction between therapy and microbiota.

Intestinal barrier dysfunction and bacterial translocation

- A decrease in Akkermansia muciniphila and Bifidobacterium may weaken the mucosal barrier and increase intestinal permeability.
- Translocation of bacterial components (e.g. lipopolysaccharide – LPS) into the circulation may:
- Activate peripheral immune cells (monocytes, lymphocytes).
- Induce the production of pro-inflammatory cytokines (TNF-α, IL-6, IL-17).
- Promote the penetration of immune cells through the blood-brain barrier and exacerbate demyelination

Modulation of the gut–brain axis via the vagus nerve and metabolites

- Gut bacteria produce neuroactive metabolites (e.g. GABA, serotonin, dopamine) that can affect:
- Signalling via the vagus nerve – a direct connection between the intestine and the brain stem.
- Microglia activity – immune cells in the brain that are overactive in MS and contribute to myelin damage.
- In animal models, SCFAs (acetate) can directly modulate microglia maturation and function.
- Potential molecular mimicry and activation of autoreactive lymphocytes
- Some gut bacteria can express antigens that are structurally similar to myelin proteins (e.g. myelin basic protein – MBP).
- Activation of T lymphocytes specific for bacterial antigens may lead to cross-reactivity with CNS antigens – this mechanism is considered one of the key mechanisms in the initiation of the autoimmune response in MS [60].

3.2 Clinical and social dimension.

A survey conducted among MS patients (n=55) reveals:

- A high frequency of gastrointestinal symptoms (constipation, bloating, diarrhoea) – approx. 75% of respondents.
- Awareness of the existence of probiotics (67.3%) and their use (58.2%).
- Willingness to use probiotics with proven efficacy (83%).
- Long diagnosis time – a significant problem delaying intervention.

3.3 A broader spectrum of therapeutic interventions targeting the microbiota

This paper lists four main strategies:

Direct manipulation (probiotics, antibiotics):

Probiotics (e.g. Lactobacillus reuteri, mixtures of Lactobacillus and Bifidobacterium)

Twelve weeks of probiotic supplementation (containing Lactobacillus acidophilus, L. casei, L. fermentum, Bifidobacterium bifidum) significantly reduced inflammatory markers (hs-CRP, IL-6, IL-8, TNF-α) and improved EDSS and BSFS scores [61].

Administration of Prevotella histicola bacteria (isolated from healthy humans) to mice with EAE inhibited disease progression, reduced Th1/Th17 cell infiltration in the CNS and induced Treg cells. This demonstrates the potential of specific probiotic species [62].

The commercial probiotic VSL#3 (a mixture of 8 strains) alleviated EAE by inducing tolerogenic dendritic cells and T cells, reducing neuroinflammation [63].

Antibiotics (with caution)

Indirect manipulation – diet (prebiotics, fibre), lifestyle

In a clinical study a 12-week personalised anti-inflammatory diet (rich in fibre, vegetables, fruit, whole grains, healthy fats and spices) significantly reduced fatigue and improved quality of life in patients with RRMS. At the same time, it increased levels of the anti-inflammatory interleukin-4 (IL-4), indicating beneficial

modulation of the immune response. This diet is therefore an effective non-pharmacological adjunctive intervention that can alleviate symptoms and support MS treatment [64].

Administration of the prebiotic inulin to mice with EAE (a model of multiple sclerosis) alleviated the symptoms of the disease and reduced inflammation and demyelination in the central nervous system. This worked by modulating the gut microbiota – increasing the amount of beneficial bacteria (e.g. Lactobacillus, Dubosiella) and raising the level of short-chain fatty acids (mainly butyric acid). This, in turn, inhibited the activity of pro-inflammatory Th17 cells, which are key in the pathology of MS. The effect was dependent on the microbiome – it disappeared after administration of antibiotics and was transferred by microbiota transplantation from treated mice. The results suggest that prebiotics may be a promising adjunctive strategy in the treatment of MS by acting on the gut-immune axis [65].

Faecal microbiota transplantation (FMT)

A single FMT from a healthy donor in a patient with secondary progressive MS (SPMS) was associated with 10 years of disease stabilisation without progression of disability [66].

The enormous potential of SCFA (especially butyrate)

Butyrate (sodium butyrate) not only inhibited demyelination but also strongly promoted remyelination in the EAE model. It acted directly on oligodendrocyte precursor cells (OPCs), accelerating their maturation. Mechanism: inhibition of histone deacetylase (HDAC) [67].

3.4 Impact of standard MS treatment on gut microbiota

Standard disease-modifying therapies (DMTs) used in multiple sclerosis — including immunomodulatory and immunosuppressive agents — are increasingly recognized not only as regulators of peripheral and central immune responses, but also as modulators of the gut microbial ecosystem. While the primary goal of these therapies is to reduce neuroinflammation and prevent disease progression, accumulating evidence suggests that their therapeutic effects may be partially mediated or influenced by alterations in the composition and function of the gut microbiota [68–71]. Immunosuppressive treatment in MS can affect the gut microbiota through both direct and indirect mechanisms. Orally administered drugs, such as dimethyl fumarate (DMF) or high-dose steroids, may come into direct contact with intestinal microorganisms, thereby influencing bacterial growth, metabolic activity, and community structure [69, 71]. In contrast, parenterally administered biologics, such as ocrelizumab, exert their effects systemically, yet they too are associated with shifts in gut microbial composition, likely through immune-mediated feedback loops involving the gut-associated lymphoid tissue (GALT) and systemic modulation of cytokine networks [70]. Importantly, the relationship between DMTs and the microbiota appears to be bidirectional. On one hand, treatment can partially reverse MS-associated dysbiosis by increasing the abundance of short-chain fatty acid (SCFA)-producing bacteria (e.g., Roseburia, Prevotella) and reducing pro-inflammatory taxa, thereby contributing to the restoration of immune homeostasis [68, 70]. On the other hand, certain therapies may reduce microbial diversity or promote the expansion of opportunistic taxa, depending on the drug, route of administration, and individual patient factors [69, 71]. Emerging data also highlight the potential of baseline microbiota composition to predict treatment outcomes or adverse effects. For instance, the presence of specific bacterial taxa prior to DMF initiation has been associated with an increased risk of drug-induced lymphopenia, suggesting that microbiome profiling could inform personalized treatment decisions [69]. Similarly, in ocrelizumab-treated patients, a favorable clinical response (NEDA-3 status) correlates with increased microbial diversity and enrichment of SCFA producers, while non-responders exhibit persistent dysbiosis and elevated markers of intestinal barrier dysfunction [70]. These findings underscore that the gut microbiota is not a passive bystander but an active participant in the response to immunosuppressive therapy in MS. Understanding these complex interactions may open new avenues for adjunctive microbiome-targeted interventions—such as probiotics, prebiotics, or dietary modifications—that could enhance treatment efficacy, mitigate side effects, and ultimately improve long-term outcomes for MS patients.

Table 5. Impact of selected disease-modifying therapies (DMTs) used in MS on the gut microbiota and clinical implications.

DRUG	Mechanism of Interaction with Microbiota	Observed Microbiome Changes	Clinical Implications / Bidirectionality
IFN-β (+GA)	Mainly indirect, through modulation of the systemic immune response, which may affect the intestinal environment (e.g. cytokine levels, barrier status).	An increase in the relative abundance of potentially beneficial Prevotella and Sutterella species and a decrease in Sarcina compared to untreated individuals. This may suggest a partial normalisation of the microbiota profile.	This suggests that first-line treatment may contribute to restoring the balance of the microbiota. However, other studies suggest that IFN-β may be associated with lower microbiome richness in some patients, highlighting the complexity of the response.
DIMETHYL FUMARATE	Direct (contact with the intestinal mucosa after oral administration) and indirect (effect on systemic metabolism).	Significant taxonomic changes: decrease in Coprococcus eutactus and Enterococcus gilvus, increase in Lactobacillus pentosus. An effect on bacterial metabolism was also observed (increase in Krebs cycle metabolites).	A key example of bidirectionality: The composition of the initial microbiota is a risk factor for DMF-induced lymphopenia. The presence of Akkermansia muciniphila and the absence of Prevotella copri prior to treatment is associated with a >6-fold higher risk of lymphopenia. The microbiome profile may therefore be a biomarker for risk stratification.
OCRELIZUMAB	Indirect, mainly through B-cell depletion and associated changes in immune signalling that affect GALT and systemic inflammation.	Temporary reduction in microbiome diversity (lowest after 6 months), returning to normal after 12 months. In individuals responding to treatment (NEDA-3), an increase in diversity and abundance of SCFA-producing bacteria (e.g., Roseburia) was observed, accompanied by a decrease in markers of intestinal barrier damage (LBP, MBL).	Microbiota as a biomarker of efficacy: In individuals who do not respond to treatment, profound dysbiosis with SCFA bacterial deficiency persists. The microbiome profile can help predict response to therapy, and effective treatment promotes restoration of the microbiome profile of a healthy individual.
HIGH-DOSE STEROIDS	Dependent on the route of administration: Oral corticosteroids have a direct effect on the composition of the microbiome. Intravenous/intramuscular administration has mainly an indirect (systemic) effect.	An increase in the abundance of Blautia and Collinsella species and a reduction in Sutterella wadsworthensis (pro-inflammatory) and Dysosmobacter welbonis. These changes are accompanied by an increase in markers of insulin resistance and inflammation.	Steroid-induced changes in the microbiota correlate with systemic metabolites associated with metabolic disorders. This suggests that the microbiota may mediate the metabolic side effects of steroid therapy, which is important in the treatment of acute MS relapses.

4. Discussion

The presented literature review confirms that intestinal microflora plays an important role in the pathogenesis and course of multiple sclerosis, and that disturbances in its composition (dysbiosis) are a constant feature associated with this disease [58, 59]. The results of the analyses clearly indicate that people with MS experience significant quantitative and qualitative changes in the composition of their microflora, characterised by a reduction in microbial diversity, a decrease in the number of bacteria producing short-chain fatty acids (SCFA) from the Faecalibacterium and Butyricicoccus genera, and an increase in potentially pro-inflammatory taxa such as Prevotella [58, 59, 68]. These data are consistent with reports from other authors who emphasise that this dysbiosis leads to increased intestinal barrier permeability ("leaky gut"), systemic low-grade inflammation and activation of pro-inflammatory T lymphocytes (Th1/Th17), which in turn exacerbates neuroinflammation and the demyelination process in the CNS [1, 59, 60]. One of the key conclusions from recent studies, fully confirmed in this paper, is the bidirectional nature of the interaction between MS treatment and gut microbiota [68–72]. On the one hand, standard disease-modifying therapeutics (DMTs) are not neutral to the gut ecosystem. As demonstrated in section 3.4, both older generation drugs (interferon-beta) and modern therapies (dimethyl fumarate, ocrelizumab) as well as steroids used in disease relapses have a significant impact on the composition and function of microflora [68–73]. This effect depends on the route of administration, the mechanism of action of the drug and the individual characteristics of the patient. For example, oral dimethyl fumarate (DMF) has direct contact with the intestinal mucosa, while intravenous ocrelizumab acts on the microflora indirectly by modulating the systemic immune response, which affects the intestinal environment [69, 70, 72, 73]. On the other hand, more and more data indicate that the initial composition of the microflora may determine the response to treatment and the risk of adverse effects. Observations concerning DMF are of groundbreaking importance here, where the presence of Akkermansia muciniphila and the simultaneous absence of Prevotella copri prior to treatment is associated with a more than six-fold increase in the risk of lymphopenia [69, 72]. Similarly, in the case of ocrelizumab, responders (achieving NEDA-3 status) show an increase in microflora diversity and an increase in the number of SCFA-producing bacteria (e.g., Roseburia) after 12 months, while non-responders continue to experience profound dysbiosis accompanied by elevated markers of intestinal barrier damage (LBP, MBL) [70, 73]. These findings, confirmed in a systematic review from 2025, suggest that the microbiome profile may serve as a biomarker for risk stratification and prediction of treatment efficacy in the future [72, 83]. This work also points to the promising, albeit still experimental, potential of microflora-targeting interventions as adjunctive therapies in MS. Data from randomised clinical trials confirm that probiotic supplementation (especially with Lactobacillus and Bifidobacterium species) can lead to a reduction in inflammatory markers (hs-CRP, IL-6, TNF-α) and improvement in disability scales (EDSS) and bowel function [61, 72]. Dietary interventions, such as a personalised anti-inflammatory diet rich in fibre, also bring measurable benefits in the form of reduced fatigue and improved quality of life for MS patients, which correlates with an increase in the level of anti-inflammatory interleukin-4 (IL-4) [64, 72]. Particularly promising, albeit preliminary, are the results of studies on animal models (EAE) using prebiotics (e.g. inulin) and sodium butyrate. It has been demonstrated that prebiotics, by modulating the composition of microflora and increasing SCFA production, are able to inhibit the activity of pro-inflammatory Th17 lymphocytes and alleviate disease symptoms [65, 73]. Furthermore, sodium butyrate not only inhibits demyelination but also promotes remyelination by directly affecting oligodendrocyte precursor cells (OPCs), which opens up completely new therapeutic perspectives in the context of neuroprotection and damage repair [67, 73]. Single reports of faecal microbiota transplantation (FMT) from a healthy donor, which led to 10 years of disease stabilisation in a patient with secondary progressive multiple sclerosis (SPMS), require confirmation in controlled clinical trials, but provide evidence of the enormous potential of this strategy [66, 72]. In addition to its therapeutic potential, increasing attention is being paid to the microbiota as a potential source of biomarkers in MS. According to recent reviews, specific taxonomic profiles of the microbiota may be helpful not only in predicting response to treatment, but also in early diagnosis and monitoring of disease progression [72, 73]. Changes in the composition of microflora are already observed in patients with clinically isolated syndrome (CIS), and the degree of dysbiosis may correlate with disease activity. This suggests that microbiome analysis could become a non-invasive tool to support clinical decisions in the future. However, further prospective studies using metagenomics and metabolomics are needed to identify specific, functional microbiome signatures with real predictive value [73, 74].

Conclusions

This study confirms that gut microbiota is an important link between environmental factors and the immune response in MS. Gut dysbiosis is common in MS patients and correlates with disease activity and gastrointestinal symptoms. Crucially, drugs used in MS significantly modulate the composition of the microflora, and the composition of the initial microbiota itself may affect the efficacy and tolerability of treatment.. Interventions targeting the microflora, although still in the early stages of research, offer real hope for the development of effective, safe and personalised strategies to support MS therapy, improve patients' quality of life and potentially modify long-term prognosis. Further research in this rapidly evolving field is not only justified but essential.

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