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Review

Environmental programming of the gut-brain axis in Multiple Sclerosis: a phase-dependent framework

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Abstract

Research on the gut microbiome in multiple sclerosis (MS) has expanded rapidly but remains limited by two conceptual gaps, insufficient integration of environmental risk factors into gut-brain axis (GBA) models and the tendency to treat microbiome alterations as static disease features. This review proposes an integrated framework in which GBA dysfunction is environmentally programmed and dynamically remodelled across disease progression. We argue that established MS risk factors including *Epstein-Barr* virus exposure, vitamin D deficiency, cigarette smoking, and biological sex, may influence disease susceptibility partly through sustained effects on intestinal immunity, microbial ecology, and host microbial interactions before clinical onset. Dysbiosis is therefore considered a dynamic biological state shaped by cumulative environmental exposure rather than an isolated characteristic of established disease.

We further propose that GBA involvement differs across disease stages, in relapsing-remitting MS, GBA dysfunction may primarily amplify peripheral immune activation, whereas in progressive disease it may contribute to persistent neuroimmune and metabolic stress within the central nervous system. This phase dependent perspective may help explain inconsistencies across microbiome studies and the limited efficacy of current microbiome directed interventions. Future progress will require integrating environmental exposures as biological co-determinants, adopting disease stage stratification, and moving beyond taxonomic profiling toward functional approaches. Such a mechanistic and phase informed framework may improve therapeutic targeting and support earlier intervention strategies in MS.

Keywords:

Gut-brain axis; microbiome; multiple sclerosis; environmental programming; dysbiosis; neuroimmune interactions.

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1. Introduction

Multiple sclerosis (MS) is a chronic immune mediated disorder of the central nervous system (CNS) characterized by inflammatory demyelination, axonal injury, and progressive neurological dysfunction [1]. Although disease modifying therapies have improved control of inflammatory activity, major challenges remain, particularly the limited ability to predict disease evolution and to prevent progressive neurodegeneration [2]. These limitations suggest that important mechanisms linking environmental exposure, immune dysregulation, and long-term CNS injury remain insufficiently understood.

The gut-brain axis (GBA) has emerged as a promising framework to address this gap [3]. Through bidirectional interactions among the intestinal microbiome, immune system metabolism, and the CNS, the GBA provides a biological interface through which peripheral environmental signals may influence neuroinflammatory processes[4]. Studies in MS consistently report alterations in microbial composition and function, including reduced production of short-chain fatty acids (SCFAs), altered microbial metabolism, and disturbed host microbiome interactions [5,6].

However, two conceptual limitations continue to constrain interpretation of this literature. First, microbiome alterations are rarely integrated with established environmental determinants of MS. Factors including *Epstein-Barr* virus (EBV) infection, vitamin D deficiency, cigarette smoking, and biological sex influence both disease susceptibility and intestinal immune-microbial homeostasis [7-9], yet are commonly treated as independent variables rather than biological modulators of GBA function [10]. Second, microbiome alterations are generally interpreted as static disease associated features despite the dynamic nature of MS. Relapsing and progressive disease phases differ substantially in their immunopathology, suggesting that gut derived mechanisms may also evolve during disease progression [2].

This review proposes an integrated framework in which GBA dysfunction is environmentally programmed and dynamically remodelled across disease stages. We first examine how established environmental factors may shape GBA biology before and during disease development. We then discuss a phase dependent model in which gut derived mechanisms contribute differently across relapsing and progressive MS. Together, this framework aims to move beyond descriptive microbiome profiling toward a more mechanistic and clinically informative understanding of host microbiome interactions in MS.

2. Multiple sclerosis from autoimmunity to neurodegeneration

Multiple sclerosis is increasingly understood as a disease involving interconnected inflammatory, immune, and neurodegenerative mechanisms rather than isolated autoimmune demyelination[11]. Acute inflammatory activity and progressive tissue degeneration coexist throughout the disease course and collectively determine long term disability [12].

Disease initiation is thought to result from interactions between genetic susceptibility and environmental exposure that disrupt immune tolerance [13]. Genome-wide association studies have identified more than 200 susceptibility loci, with strongest associations involving immune regulatory pathways, particularly human leukocyte antigen-DRB1*15:01 (HLA-DRB1*15:01) [14]. Loss of tolerance promotes activation of autoreactive T and B cells directed against CNS antigens and facilitates their migration across the blood brain barrier [15].

Within the CNS, inflammatory mediators amplify microglial activation, recruit additional immune populations, and sustain neuroinflammatory signalling [16-19]. Persistent immune activity contributes to demyelination, mitochondrial dysfunction, oxidative stress, and progressive axonal injury [20-23].

Importantly, neurodegeneration in MS progressively becomes partially uncoupled from peripheral immune infiltration and increasingly dependent on compartmentalized CNS processes, including chronic microglial activation and metabolic stress [24]. This transition is particularly relevant for understanding how peripheral systems may differentially influence disease across stages, among these systems, the GBA has emerged as a potential regulator of neuroimmune homeostasis[25,26]. Microbial metabolites, epithelial integrity, and intestinal immune education influence systemic inflammatory tone and may modify CNS vulnerability or resilience [27-29].

This broader perspective provides the rationale for examining the structural and mechanistic organisation of the gut-brain axis in multiple sclerosis [2].

3. Architecture and mechanistic pathways of the gut-brain axis in multiple sclerosis

The gut-brain axis is a bidirectional communication network linking the intestinal environment and the central nervous system through coordinated neural, endocrine, immune, and metabolic pathways [4]. Within this system, the gut microbiota functions as a major regulatory interface that shapes immune homeostasis, neuroinflammatory processes, and CNS function [30]. In MS, microbial dysbiosis is increasingly recognized as a potential contributor to disease progression through disruption of these interconnected signaling pathways.

3.1. Neural regulation of neuroinflammation

Neural communication within the GBA is primarily mediated by the vague nerve, which transmits intestinal and inflammatory signals between the enteric nervous system and the CNS [31]. Beyond regulating gastrointestinal function and barrier integrity, vagal activity exerts anti-inflammatory effects through the cholinergic pathway, in which acetylcholine suppresses pro-inflammatory cytokine production via α7 nicotinic acetylcholine receptors [32]. In MS, reduced parasympathetic activity and impaired vagal tone may weaken peripheral immune regulation and promote sustained neuroinflammatory responses [33].

3.2. Endocrine signalling: HPA axis and hormonal modulation

The endocrine arm of the GBA integrates gut-derived signals with systemic neuroendocrine responses. Enteroendocrine cells respond to microbial activity by releasing hormones involved in metabolism, immune regulation, and CNS function [34]. In MS, dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis contributes to altered glucocorticoid signalling and has been associated with fatigue and neuropsychiatric symptoms [35]. Altered levels of metabolic hormones, including leptin and ghrelin, may further reinforce pro-inflammatory immune polarization and Th17-related responses [36].

3.3. Immune pathways: gut immune education and autoimmune activation

The gut-associated lymphoid tissue (GALT) serves as a central site of host microbiota interaction and immune education[37]. Under physiological conditions, commensal microorganisms support immune tolerance and regulatory responses. In MS, dysbiosis may shift this balance toward inflammatory activation through mechanisms including molecular mimicry between microbial and myelin antigens and increased intestinal permeability, allowing systemic dissemination of microbial products such as lipopolysaccharide (LPS) [38]. These processes enhance peripheral immune activation and favour expansion of autoreactive lymphocytes.

3.4. Metabolic signalling: microbial metabolites as neuroimmune regulators

Microbial metabolites represent a major functional component of the GBA and influence both immune and CNS physiology. Short-chain fatty acids, particularly butyrate and propionate, promote regulatory T-cell differentiation, limit inflammatory responses, and preserve epithelial and blood-brain barrier integrity[31]. Reduced SCFA availability observed in MS may therefore contribute to impaired immune regulation.

In parallel, tryptophan-derived metabolites modulate neuroinflammation through activation of aryl hydrocarbon receptor (AhR)-dependent pathways in astrocytes, while bile acid derivatives contribute to the regulation of immune and microglial activity [39]. Disturbances in these metabolic pathways have been associated with disease activity in MS.

3.5. Gut barrier-blood-brain axis

An emerging concept in MS pathophysiology is the functional coupling between intestinal barrier integrity and the blood-brain barrier (BBB) [28]. Dysbiosis associated barrier disruption increases systemic exposure to microbial and inflammatory mediators, promoting endothelial activation and BBB dysfunction [40].

Peripheral cytokines, particularly IL-17, further facilitate immune-cell trafficking into the CNS, establishing a mechanistic link between intestinal dysfunction and central neuroinflammation [17]. Collectively, disruption of the gut-BBB axis provides a plausible route through which intestinal alterations may contribute to MS progression (**Figure 1**).

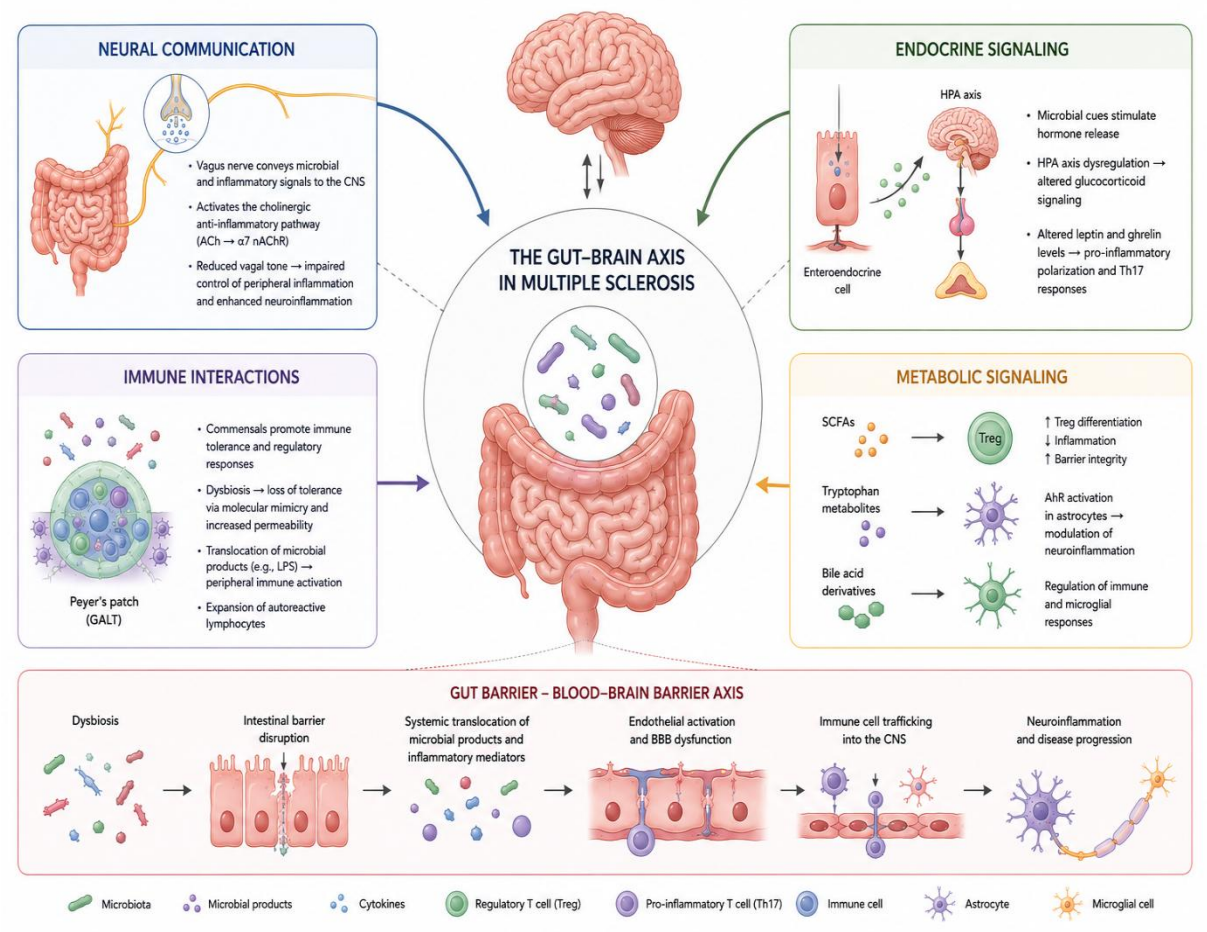

Figure 1. Mechanistic architecture of the gut-brain axis in multiple sclerosis.

4. Mechanistic pathways linking gut dysbiosis to neuroimmune dysfunction in MS

Accumulating evidence indicates that MS is associated with reproducible alterations in gut microbial ecology. However, identifying taxonomic differences alone does not establish biological relevance or causal involvement in disease processes. The central challenge is therefore not simply to determine which microbial communities differ in MS, but to understand how these alterations become translated into host physiological changes capable of influencing neuroimmune function. Current evidence suggests that the gut microbiota may contribute to MS pathophysiology through interconnected mechanisms involving epithelial barrier integrity, microbial metabolic signalling, and immune communication across peripheral and central compartments.

4.1. Gut microbiota alterations in Multiple Sclerosis

Microbiome studies in MS consistently report deviations in microbial composition relative to healthy populations. Among the most recurrent observations are reduced microbial diversity and depletion of taxa associated with immunoregulatory and metabolically beneficial functions, particularly short-chain fatty acid (SCFA)-producing communities within the *Lachnospiraceae* and *Ruminococcaceae* families. In

parallel, enrichment of taxa including *Akkermansia*, *Methanobrevibacter*, and *Blautia* has been described across several cohorts [25].

Despite these recurring observations, microbial signatures remain heterogeneous across studies and no universal disease associated profile has emerged[3]. Variability likely reflects interactions among geography, habitual diet, disease stage, treatment exposure, and methodological differences in sampling and sequencing [5]. Emerging longitudinal and multi-omics studies further suggest that microbiome alterations are dynamic rather than static features of disease. Temporal shifts in microbial composition and metabolic output appear to parallel changes in clinical activity and disease progression[3,41].

Taken together, these findings support the existence of recurrent but context dependent microbial alterations in MS while emphasizing an important limitation: compositional changes alone provide limited insight into functional consequences or causal relevance.

4.2. Gut barrier dysfunction and microbial translocation

Beyond microbial composition, increasing attention has focused on the intestinal barrier as a potential biological interface linking gut alterations to systemic immune responses in MS. Under physiological conditions, the intestinal epithelium acts as a selectively permeable structure that permits nutrient exchange while limiting systemic exposure to luminal microorganisms and their products. Disruption of this barrier may therefore alter host microbe communication and facilitate immune activation.

Clinical studies have reported evidence consistent with altered intestinal permeability in MS. Elevated circulating zonulin concentrations observed in relapsing remitting patients suggest disturbed epithelial homeostasis, although zonulin alone should not be interpreted as a definitive marker of barrier integrity[38]. Mechanistically, disruption of tight junction architecture involving proteins such as occludins and claudins may increase paracellular translocation of microbial derived signals [28].

Among these signals, microbial associated molecular patterns (MAMPs), including lipopolysaccharide (LPS), can activate innate immune pathways through pattern recognition receptors expressed on monocytes, macrophages, and dendritic cells, promoting production of inflammatory mediators including Tumour Necrosis Factor-alpha (TNF-α), Interleukin -6 (IL-6), and Interleukin-1β (IL-1β) [44]. Experimental observations further suggest reciprocal interactions between inflammatory cytokines and barrier integrity, potentially generating self-reinforcing cycles of immune activation[16,17].

Overall, current evidence supports intestinal barrier dysfunction as an intermediate mechanistic layer connecting gut dysbiosis with systemic inflammatory signalling rather than an isolated feature of established disease.

4.3. Microbial metabolites as functional mediators of neuroinflammation

Microbial metabolism represents an additional functional layer through which the gut microbiota may influence neuroimmune homeostasis. Rather than acting solely through compositional changes, intestinal microorganisms generate metabolites capable of regulating immune responses locally and systemically through metabolic, endocrine, and signalling pathways.

Short chain fatty acids

SCFAs, particularly butyrate, propionate, and acetate, are produced through bacterial fermentation of dietary fibre and constitute major mediators of host microbiota communication. SCFAs regulate immune responses through receptor mediated and epigenetic mechanisms and participate in broader gut-brain signalling networks [3,45]. In MS, reduced abundance of SCFA producing communities has been proposed as a functionally relevant consequence of dysbiosis. Among SCFAs, butyrate has received particular attention due to its capacity to suppress inflammatory signalling pathways, including nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) activation and histone deacetylase activity, while supporting regulatory immune responses[46]. Experimental evidence further demonstrates that restoration of butyrate signalling attenuates disease severity and modifies immune responses in experimental autoimmune encephalomyelitis (EAE) models [47].

Tryptophan metabolism and the aryl hydrocarbon receptor pathway

Tryptophan metabolism represents a second major metabolic interface between the gut microbiota and host immunity. Intestinal microorganisms contribute to the conversion of dietary tryptophan into bioactive metabolites, including indole derivatives, while host pathways preferentially generate kynurenine metabolites through indoleamine 2,3-dioxygenase (IDO)-dependent metabolism[43].

Altered tryptophan metabolism has been reported in MS, including shifts in kynurenine-to-tryptophan balance that suggest altered immune metabolic regulation [27]. Mechanistic insight was provided by Rothhammer et al. (2016), who demonstrated that microbiota-derived tryptophan metabolites activate the aryl hydrocarbon receptor (AhR), thereby limiting CNS inflammatory responses in experimental models[42]. These findings identify microbial tryptophan metabolism as a biologically plausible route through which gut derived metabolic signals may influence neuroimmune regulation.

Emerging immunometabolism mediators

Beyond SCFAs and tryptophan metabolism, additional microbial derived metabolic pathways may contribute to neuroimmune regulation. Succinate has been implicated in pro-inflammatory immune activation through SUCNR1-mediated signalling linked to HIF-1α stabilisation and cytokine production [48]. Alterations in branched-chain amino acid (BCAA) metabolism have similarly been proposed to influence immune and metabolic reprogramming, although their contribution to MS remains incompletely defined [49].

Although evidence for these pathways remains less developed than for SCFAs or AhR signalling, their emergence further supports the concept that microbial metabolism constitutes an active regulatory interface between gut ecology and host neuroimmune responses.

4.4. Functional interpretation of microbial alterations

The preceding evidence highlights a central limitation of current microbiome research in MS: taxonomic alterations alone cannot establish biological relevance or causal contribution to disease. Although compositional approaches such as 16S rRNA and metagenomic profiling identify microbial communities associated with MS, they provide limited information regarding metabolic activity, host microbe interactions, or downstream neuroimmune consequences.

Functional approaches offer a more mechanistic perspective. Using germ free transgenic mice colonised with microbiota derived from MS discordant twins, Yoon et al. (2025) demonstrated that disease associated microbial communities can alter neuroimmune outcomes in susceptible hosts [6]. These findings support a transition from descriptive microbial profiling toward integrated frameworks combining microbiomics, metabolomics, immune phenotyping, and mechanistic validation.

Collectively, current evidence suggests that gut dysbiosis acquires neuroimmune relevance through interacting epithelial, metabolic, immune, and CNS resident pathways rather than through isolated mechanisms. Importantly, the relative contribution of these pathways may vary across disease stages, supporting a dynamic interpretation of gut-brain axis involvement and providing the conceptual basis for the phase dependent perspective on disease evolution discussed elsewhere.

5. Environmental programming of the gut-brain axis in MS

The gut-brain axis is increasingly recognized as a biologically relevant component of MS, yet it is most often interpreted as a downstream consequence or amplifier of established neuroinflammation. This view may underestimate a more upstream role of GBA biology in disease susceptibility. Rather than emerging only after immune dysregulation becomes clinically apparent, the GBA may itself be progressively shaped by environmental exposures that act before disease onset and influence the conditions under which neuroimmune responses develop.

Within this perspective, environmental factors are not considered independent risk variables operating in parallel with microbiome associated processes. Instead, they may converge on shared GBA pathways by altering microbial ecology, epithelial homeostasis, and mucosal immune regulation, thereby establishing a

preclinical state of altered neuroimmune responsiveness. Although these influences operate through distinct biological mechanisms, their cumulative effects may reduce immune tolerance and modify host microbe interactions in ways that favor susceptibility to inflammatory disease.

Other environmental exposures, including dietary patterns, psychosocial stress, and lifestyle-related factors, may also contribute to GBA regulation. However, the present section focuses on Epstein-Barr virus infection, vitamin D deficiency, cigarette smoking, and biological sex because these factors combine robust epidemiological support in MS with emerging evidence for direct modulation of gut-brain axis biology.

This perspective positions environmental risk and GBA dysfunction not as competing explanations of MS susceptibility but as interconnected processes that may jointly shape neuroimmune vulnerability before clinical disease onset (**Figure 2**).

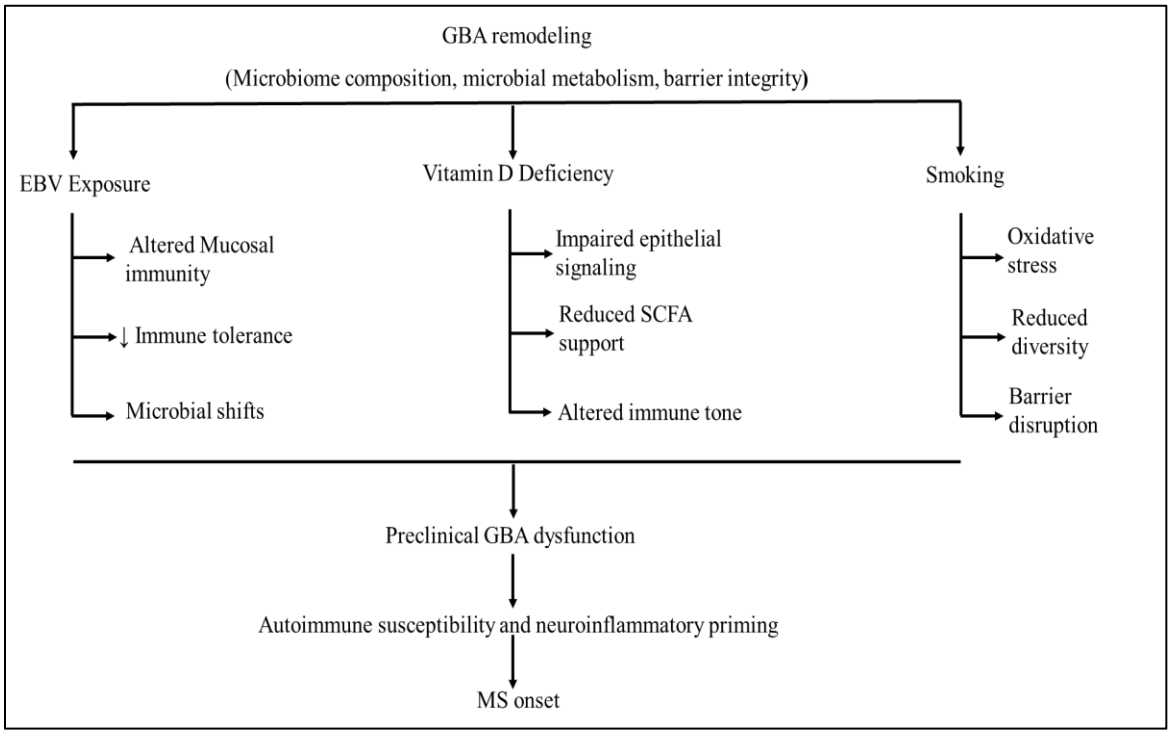

Figure 2. Schematic overview of environmental drivers and shared GBA mechanisms in MS

5.1. *Epstein-Barr* virus: mucosal immune disruption and environmental programming of the gut-brain axis

Epstein-Barr virus is widely regarded as the strongest environmental factor associated with MS, supported by near universal seropositivity among affected individuals and longitudinal evidence linking infection to increased disease risk [50]. Although EBV has primarily been studied through mechanisms involving systemic immune activation and molecular mimicry between Epstein-Barr virus nuclear antigen 1 (EBNA1) and glial cell adhesion molecule (GlialCAM) [51], emerging evidence suggests that its biological influence may extend to the regulation of GBA function.

EBV establishes long term latency within B lymphocytes, including populations associated with gut associated lymphoid tissue (GALT), positioning the virus at an interface between mucosal immunity and host microbiota interactions. Persistent immune perturbation in this compartment may alter secretory IgA responses, reshape microbial surveillance, and modify local immune calibration [7]. Through these mechanisms, EBV has been proposed to influence intestinal homeostasis and favour microbial configurations associated with reduced immunoregulatory capacity.

From this perspective, EBV may contribute to MS susceptibility not only through antigen specific autoimmune mechanisms but also by conditioning the intestinal immune environment in ways that alter host microbe communication before clinical disease onset. This interpretation places EBV within a broader

model of environmental programming in which viral exposure may shape the functional state of the GBA and influence subsequent neuroimmune responsiveness.

5.2. Vitamin D deficiency: Environmental regulation of gut-brain axis resilience

Vitamin D deficiency is among the most consistently associated environmental risk factors for MS, supported by epidemiological, genetic, and mechanistic evidence [52]. Although its contribution to MS has traditionally been interpreted through systemic immunomodulatory effects, vitamin D also plays an important role in maintaining intestinal homeostasis and regulating host microbiota interactions.

The vitamin D receptor (VDR) is highly expressed in the intestinal epithelium, where its activation contributes to epithelial integrity and mucosal immune regulation. Reduced vitamin D signalling has been associated with impaired barrier function and shifts in microbial composition, including reduced representation of SCFA-producing communities[8]. Because microbial metabolites contribute to maintenance of regulatory immune responses, disruption of these pathways may extend the consequences of vitamin D deficiency beyond direct immune effects and alter the functional state of the gut-brain axis.

From this perspective, vitamin D deficiency may represent more than a loss of systemic immune regulation. By influencing epithelial homeostasis, microbial ecology, and immune calibration simultaneously, reduced vitamin D availability may decrease the capacity of the gut-brain axis to maintain neuroimmune resilience and thereby contribute to susceptibility to inflammatory disease.

5.3. Cigarette smoking and gut-brain axis dysregulation in MS

Cigarette smoking is a major modifiable environmental risk factor for MS, associated with increased disease susceptibility and accelerated clinical progression [9]. In addition to its systemic immunological effects, emerging evidence suggests that smoking may influence MS risk through disruption of GBA homeostasis.

Smoke derived compounds, including nicotine and reactive toxicants, can alter intestinal physiology by promoting oxidative stress and impairing epithelial barrier function. Increased intestinal permeability may facilitate exposure to microbial derived inflammatory signals and contribute to sustained immune activation [53].

Smoking has also been associated with reduced microbial diversity and compositional changes that favor loss of SCFA producing communities and expansion of pro-inflammatory taxa. These alterations may weaken mucosal immune regulation and promote a pro-inflammatory intestinal environment. Additional effects on aryl hydrocarbon receptor (AhR)-dependent signalling have been proposed, suggesting potential interactions between smoking and microbiota derived metabolic pathways. These findings support the hypothesis that smoking may contribute to MS susceptibility partly through environmental remodelling of the GBA and enhanced neuroimmune priming.

5.4. Sex differences in gut-immune interactions in MS

Multiple sclerosis occurs approximately three times more frequently in women than in men in the relapsing-remitting phenotype, highlighting the contribution of sex dependent biological factors to disease susceptibility [1]. Beyond established differences in immune responsiveness, growing evidence suggests that host microbiome interactions may participate in this sex bias through modulation of the GBA.

Sex hormones and the gut microbiota interact bidirectionally. Oestrogens influence microbial composition and intestinal physiology, whereas microbial communities regulate circulating oestrogen availability through the oestrobolome, a group of bacterial enzymes involved in oestrogen metabolism [54]. This reciprocal relationship provides a mechanistic interface linking endocrine and immune regulation.

Alterations in microbial composition may influence hormone dependent immune regulation and contribute to sex related differences in neuroinflammatory susceptibility. Clinical observations support this interaction: MS activity declines during pregnancy and increases after delivery, consistent with coordinated effects of hormonal and intestinal changes on immune regulation [53].

Together, these findings suggest that biological sex should be considered an active modifier of GBA function with potential relevance to MS pathogenesis and microbiome-based research.
More broadly, this concept extends to all environmental factors discussed in this section. EBV serostatus, vitamin D levels, smoking history, and biological sex should not be viewed solely as confounding variables but as biological modulators capable of shaping GBA homeostasis. Consequently, microbiome alterations reported in MS cohorts may partly reflect environmental heterogeneity rather than disease specific signatures.

6. Phase-dependent model of gut-brain axis involvement in multiple sclerosis

Conventional GBA research in MS often treats microbiome alterations as relatively static disease associated features. However, MS pathobiology evolves through functionally distinct stages, transitioning from predominantly peripheral immune activation toward increasingly compartmentalized neuroinflammation and neurodegeneration. Within this framework, the biological mechanisms through which the GBA influences MS are unlikely to remain uniform across disease progression.
We propose a phase-dependent model in which GBA mediated mechanisms shift from amplifying peripheral immune responses during relapsing disease to sustaining chronic neuroimmune and metabolic stress during progressive disease.

6.1. Relapsing disease: gut driven immune amplification

In relapsing remitting multiple sclerosis (RRMS), inflammatory activity is driven predominantly by dysregulated peripheral immune responses followed by migration of autoreactive lymphocytes into the central nervous system. Within this phase, the gut-brain axis likely acts less as a primary disease initiator than as an amplifier of immune susceptibility, sustaining conditions that favour relapse occurrence [5].

Immune imbalance and loss of regulatory tone: Rather than generating entirely novel inflammatory pathways, GBA alterations in RRMS appear to reinforce mechanisms already implicated in disease activity. Dysbiosis is consistently associated with impaired regulatory signalling, reduced maintenance of $CD4^+$ regulatory T cells (Tregs), and relative expansion of interleukin-17 (IL-17)-producing helper T cells (Th17) [55]. These alterations are thought to arise partly from reduced production of immunoregulatory microbial metabolites, particularly SCFAs, thereby weakening intestinal immune tolerance and favouring peripheral inflammatory activation.

Barrier dysfunction and immune Propagation: In parallel, disruption of intestinal barrier integrity may facilitate translocation of microbial products into the systemic circulation, enhancing innate immune activation and pro-inflammatory cytokine signalling [38]. Clinical and experimental evidence indicates increased intestinal permeability in RRMS and supports a reciprocal relationship between barrier dysfunction and IL-17 signalling, whereby dysbiosis and Th17 activation sustain a self-reinforcing inflammatory loop that lowers the threshold for CNS directed immune responses[16].

Metabolic dysregulation beyond microbial composition: beyond compositional changes, altered microbial metabolic function may further contribute to RRMS pathology. Impaired microbial tryptophan metabolism and reduced aryl hydrocarbon receptor (AhR) signalling have been associated with diminished barrier support and weakened anti-inflammatory regulation [39], creating conditions that favour sustained Th17 activity and persistent immune activation[56,10]. These observations support a model in which GBA dysfunction during RRMS does not directly trigger relapses but contributes to a permissive peripheral immune environment that facilitates autoreactive T-cell priming and CNS infiltration.

6.2. Progressive disease: Persistent neuroimmune and metabolic stress

As multiple sclerosis evolves into secondary progressive (SPMS) or primary progressive (PPMS) disease, pathological activity shifts from recurrent peripheral immune infiltration toward compartmentalised CNS

inflammation characterised by chronic microglial activation, smouldering lesions, and progressive axonal injury. Within this phase, the contribution of GBA dysfunction is hypothesised to transition from amplifying peripheral immune activation to sustaining chronic neuroimmune and metabolic stress within the CNS.

Persistent neuroimmune activation: Unlike RRMS, where transient immune amplification predominates, progressive MS has been associated with more persistent microbiome alterations and sustained disruption of host-microbial interactions. Rather than promoting continued immune entry into the CNS, these alterations may maintain low grade inflammatory signalling that favours chronic activation of resident microglia and astrocytes[24]. Reduced availability of microbial immunoregulatory metabolites, together with impaired barrier metabolic communication, may contribute to a persistent pro-inflammatory CNS environment and support the maintenance of smouldering lesion activity [5]. However, whether these alterations actively drive disease progression or emerge secondarily to chronic CNS pathology remains unresolved.

Metabolic vulnerability and neurodegeneration: Progressive MS is increasingly recognised as a state of chronic energetic stress in which demyelinated axons operate near their metabolic limits. In this context, prolonged alterations in microbial metabolic outputs, including pathways linked to short-chain fatty acids and tryptophan metabolism, may contribute to mechanisms associated with mitochondrial dysfunction and reduced neuroimmune resilience [22], thereby facilitating the transition from chronic demyelination toward irreversible axonal degeneration.

Clinical Implications: This phase dependent framework suggests that GBA targeted interventions may serve distinct objectives across the disease course: in RRMS, restoring immune regulation and barrier integrity may primarily reduce inflammatory activity, whereas in progressive MS, approaches focused on restoring microbial metabolic homeostasis and limiting chronic neuroimmune activation may offer greater therapeutic relevance [10].

Conclusion

Research on the gut-brain axis in multiple sclerosis has expanded considerably, yet interpretation has often remained constrained by viewing microbiome alterations as static disease features independent of environmental context. This review proposes an alternative framework in which GBA dysfunction is both environmentally programmed and dynamically remodelled across disease progression.

Environmental determinants of MS susceptibility, including *Epstein-Barr* virus exposure, vitamin D deficiency, cigarette smoking, and biological sex, may shape intestinal immunity, microbial ecology, and barrier function before clinical onset, supporting the view that dysbiosis reflects cumulative environmental influences rather than an isolated feature of established disease.

At the same time, GBA involvement appears unlikely to remain mechanistically uniform across disease stages. During relapsing disease, GBA dysfunction may predominantly amplify peripheral immune activation, whereas in progressive disease it may contribute more strongly to persistent neuroimmune and metabolic stress within the CNS. This phase dependent perspective may help explain inconsistencies across microbiome studies and the limited success of current microbiome targeted interventions.

These concepts imply that future research should integrate environmental exposures as biological co-determinants, adopt disease stage stratification, and move beyond descriptive taxonomic profiling toward functional and longitudinal approaches. If confirmed, this framework suggests that the optimal window for GBA directed intervention may occur earlier in the disease course than current strategies assume.

Moving the field from static descriptions of dysbiosis toward a mechanistic and phase informed understanding of the GBA may provide a foundation for the next generation of precision approaches in MS.

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