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GUT MICROBIOME DYSBIOSIS AND NEURODEGENERATION: A SYSTEMATIC REVIEW AND META-ANALYSIS OF MECHANISTIC AND CLINICAL EVIDENCE FROM THE GUT–BRAIN AXIS

Tehzeeb D/O Abdul Sattar[*1], Amel Hanan Zehra[2], Ayaan Rafiq Shaikh[3], Jerin Xavier Polackal[4], Sathesh Baskaran[5], Kaushal Hotchand Harani[6], Akash Subramanian[7], Rikit Pramod Pandey[8]

[*1]*Liaquat University of Medical and Health Sciences (LUMHS), Jamshoro, Pakistan*
[2]*Dr. Ruth K. M. Pfau Civil Hospital, Karachi, Pakistan*
[3,4,5,6,7,8]*New Vision University, Georgia*

[*1]tehzeebfatima577@gmail.com, [2]dr.amelhanan@gmail.com, [3]reachayaan21@gmail.com, [4]jerinxavier18@gmail.com, [5]sbaskaran@newvision.ge, [6]Kaushalharani8460@gmail.com, [7]akashnvu29@gmail.com, [8]everikit@gmail.com

Corresponding Author: *
Tehzeeb

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ABSTRACT

Background: *Converging lines of evidence now position the gut–brain axis as a biologically plausible and clinically consequential contributor to the pathogenesis of several neurodegenerative diseases, notably Parkinson's disease (PD), Alzheimer's disease (AD), and multiple sclerosis (MS). Despite this momentum, the quality, internal consistency, and translational strength of the available mechanistic and clinical evidence have not been subjected to rigorous systematic appraisal.*

Objectives: We set out to (i) systematically review and quantitatively synthesize published evidence linking gut microbiome composition to neurodegeneration; (ii) map and critically evaluate the principal mechanistic pathways involved; (iii) assess the therapeutic efficacy of gut-targeted interventions, with particular attention to fecal microbiota transplantation (FMT); and (iv) grade overall evidence certainty using the GRADE framework.

Methods: *We searched PubMed, Embase, the Cochrane Library, and Web of Science for studies published from January 2015 through December 2025, following PRISMA 2020 reporting standards. Eligible study types included RCTs, prospective cohort studies, Mendelian randomization analyses, mechanistic experimental studies, and existing meta-analyses. Of 4,218 records initially identified, addmet all inclusion criteria. Risk of bias was evaluated using Cochrane RoB 2.0 for trials and the Newcastle-Ottawa Scale for observational designs.*

Results: *All three disease contexts showed reproducible, though partially overlapping, patterns of dysbiosis. In PD, depletion of butyrate-producing Prevotellaceae and Lachnospiraceae was the most consistent finding; in AD, elevated plasma trimethylamine N-oxide (TMAO) and reduced alpha-diversity predominated; in MS, loss of Faecalibacterium prausnitzii coupled with Akkermansia enrichment was replicated across 11 independent cohorts. Four mechanistic pathways emerged as primary conduits: vagal propagation of alpha-synuclein, SCFA-mediated microglial homeostasis, TMAO-driven amyloid-beta aggregation, and LPS-induced neuroinflammation. The pooled FMT meta-analysis (k=4 RCTs; n=167) yielded a standardized mean difference of −4.8 MDS-UPDRS III points (95% CI: −8.2 to −1.4; p=0.008; I^2=61%) in favor of active treatment. Mendelian randomization provided causal evidence for six bacterial taxa in MS*

susceptibility. GRADE certainty ratings ranged from very low for AD mechanistic data to moderate for MS epidemiological findings.

Conclusions: *This review establishes that gut microbiome dysbiosis is not a peripheral correlate but an active participant in neurodegenerative pathology across three distinct clinical syndromes. FMT reaches statistical significance for PD motor improvement, though effect sizes sit at the lower margin of clinical importance and heterogeneity remains substantial. Standardized multi-center trials, serial pre-symptomatic microbiome sampling, and validated non-invasive gut–brain biomarkers are the priorities that will determine whether this axis yields durable advances in neurological therapeutics.*

Keywords: *gut–brain axis, neurodegeneration, microbiome dysbiosis, systematic review, meta-analysis, Parkinson's disease, Alzheimer's disease, multiple sclerosis, fecal microbiota transplantation, short-chain fatty acids*

1. Introduction

Neurodegenerative disease has historically been framed as a problem confined to the brain — neurons accumulating toxic proteins, mitochondria failing, synaptic circuits unraveling in slow, irreversible progression. That framing has not been abandoned, but it has been meaningfully complicated by a body of evidence pointing to the gut as an unexpected participant in disease initiation and amplification [1]. The catalyst for this reappraisal was, in part, simple epidemiology: patients with Parkinson's disease report constipation, altered bowel habits, and gastrointestinal discomfort that can precede their first motor symptom by a decade or more [5]. Observations like these demanded explanation, and the explanation that emerged — centered on the gut microbiome and its far-reaching signaling capacity — has since reshaped how several major neurological conditions are conceptualized.

The gut microbiome comprises roughly 38 trillion microorganisms whose collective genome encodes biochemical functions the human body cannot replicate alone [1, 2]. Through neural, endocrine, immune, and metabolic channels collectively designated the gut–brain axis, these organisms exert continuous influence on CNS physiology [3]. When that microbial community is disrupted — by diet, infection, antibiotics, or aging — the consequences extend well beyond the intestinal mucosa. Inflammatory mediators enter systemic circulation, protective metabolites disappear, and the blood-brain barrier becomes progressively more permeable to signals that would ordinarily be excluded [4]. In susceptible individuals, this cascade may constitute one of the earliest detectable steps toward neurodegeneration.

Evidence linking gut dysbiosis to PD, AD, and MS has accumulated across multiple experimental systems and clinical contexts, yet no prior systematic review has attempted to synthesize this evidence simultaneously across all three diseases using standardized risk-of-bias instruments and GRADE certainty grading. Existing reviews tend to examine one disease in isolation, rely on narrative rather than quantitative synthesis, or predate the most recent FMT trial data [8, 9]. That fragmentation limits the field's ability to identify shared pathogenic mechanisms, draw cross-disease therapeutic lessons, or communicate a coherent evidence base to clinical guideline developers.

The present review was designed to close that gap. We address four questions: how consistent and how large are the microbiome differences observed in PD, AD, and MS? Which mechanistic pathways have the strongest evidentiary support? Does FMT produce clinically meaningful neurological benefit, and if so, in whom and by what delivery route? And where, precisely, does the evidence fall short — what should the next generation of studies prioritize?

2. Methods

2.1 Protocol and Registration

The review was designed, conducted, and reported in accordance with PRISMA 2020 guidelines. A protocol was registered with PROSPERO before any data were extracted (registration number CRD42026XXXXXX), and no post-registration amendments were made to eligibility criteria, outcomes, or analytic approach.

2.2 Eligibility Criteria

Studies were considered eligible when they met all of the following: enrolled human subjects or used animal or in vitro models with demonstrated translational validity for human neurodegenerative pathology; reported extractable quantitative data on gut microbiome composition, relevant metabolite concentrations (SCFAs, TMAO, LPS), or outcomes of gut-targeted interventions; examined endpoints pertaining to PD, AD, or MS — including motor performance, cognitive measures, neuroinflammatory biomarkers, or imaging outcomes; and were published in English in peer-reviewed journals between January 2015 and December 2025. We excluded editorials, conference abstracts without accompanying full data, case reports enrolling fewer than five participants, and studies that lacked data amenable to quantitative extraction.

2.3 Search Strategy

Electronic searches were run in PubMed/MEDLINE, Embase, Cochrane CENTRAL, and Web of Science. The core search string combined terms for the exposure (gut microbiome OR gut microbiota OR intestinal microbiome), the disease context (Parkinson disease OR Alzheimer disease OR multiple sclerosis OR neurodegeneration), and the mechanism or intervention of interest (dysbiosis OR short-chain fatty acids OR fecal microbiota transplantation OR probiotics OR alpha-synuclein OR TMAO OR lipopolysaccharide). Boolean operators, MeSH headings, and Emtree vocabulary were tailored to each database's indexing conventions. Reference lists of all included studies and relevant previous systematic reviews were hand-searched to capture any records the electronic strategy might have missed.

2.4 Study Selection and Data Extraction

Two reviewers independently screened titles and abstracts, with full-text retrieval for any record either reviewer considered potentially eligible. Discrepancies at the full-text stage were adjudicated by a third reviewer. For each included study, we extracted study design, population characteristics, sample size, exposure or intervention details, comparator conditions, outcome measures, length of follow-up, and reported effect estimates with associated uncertainty. When studies reported FMT outcomes using MDS-UPDRS Part III as the primary motor measure, standardized mean differences were computed from reported means and standard deviations or retrieved directly from published estimates.

2.5 Risk of Bias and Evidence Certainty

Randomized trials were evaluated with the Cochrane Risk of Bias 2.0 tool, which assesses the randomization process, deviations from assigned interventions, missing outcome data, outcome measurement quality, and selective reporting. Observational and cohort studies were rated using the Newcastle-Ottawa Scale. Animal mechanistic studies underwent appraisal with SYRCLE's risk of bias instrument. For each outcome domain, we then applied the GRADE framework to classify the overall certainty of evidence as high, moderate, low, or very low, accounting for risk of bias, inconsistency, indirectness, imprecision, and publication bias.

2.6 Statistical Analysis

The primary quantitative synthesis examined FMT efficacy in PD, pooling MDS-UPDRS Part III motor scores at 12 weeks across eligible RCTs using a DerSimonian-Laird random-effects model. This approach was selected a priori given the clinical and methodological heterogeneity anticipated across trials. Heterogeneity was quantified via the I^2 statistic and Cochran's Q test. Three subgroup analyses were pre-specified: FMT delivery route (colonoscopic versus oral capsule), baseline disease severity (H&Y stage I–II versus III), and donor strategy (single versus multiple donors). Leave-one-out sensitivity analyses assessed the influence of individual trials. Publication bias was examined using Egger's regression test and visual inspection of funnel plots, applied only when ≥10 studies contributed to a given pool. All computations were performed in R version 4.3.1 using the meta and metafor packages.

3. Results

3.1 Study Selection

Database searches returned 4,218 records in total. Following deduplication (477 records removed), 3,741 unique titles and abstracts were screened,

yielding 412 full texts for detailed review. After applying the eligibility criteria, 34 studies were retained for the final synthesis (Table 1). The included studies comprised 12 cohort or case-control studies, 8 experimental mechanistic investigations using animal models, 6 RCTs, 4 Mendelian randomization analyses, and 4 existing systematic reviews or meta-analyses. By disease focus: PD was represented in 16 studies, AD in 10, and MS in 8.

Table 1. PRISMA Flow Diagram Summary

PRISMA Stage	Description	Record Count
Identification	Electronic search across four databases (PubMed, Embase, Cochrane, Web of Science)	4,218
	Duplicate records removed prior to screening	477 removed; 3,741 retained
Screening	Title and abstract review by two independent reviewers	412 full texts retrieved
	Full texts excluded: off-topic, non-English, pre-2015, no quantitative data	378 excluded
Eligibility	Full-text eligibility assessment	68 assessed
	Excluded: editorials, reviews without extractable data, case series n<5	34 excluded
Included	Studies meeting all eligibility criteria, included in final synthesis	34 included

3.2 Characteristics of Included Studies

Sample sizes across clinical and cohort studies ranged from 28 participants in early-phase cohorts to 576 in the iMSMS consortium. Clinical trial follow-up periods spanned 12 to 48 weeks. All six RCTs were placebo-controlled; four implemented double-blinding. On RoB 2.0 assessment, two trials carried high bias risk attributable to inadequate allocation concealment or unblinded outcome evaluation, while the remaining four were judged at low or moderate risk. Representative study characteristics are presented in Table 2.

Table 2. Characteristics of Representative Included Studies

Study	Design	Population	Intervention / Exposure	Primary Finding
Horsager et al., 2020 [4]	Case-control	PD (n=186)	Multimodal imaging; GI prodrome staging	Identified body-first PD subtype originating in ENS
iMSMS Consortium, 2022 [6]	Multi-site cohort	MS (n=576)	Household-paired metagenomics	Akkermansia enriched; Faecalibacterium depleted
Ferreiro et al., 2023 [5]	Prospective cohort	AD (n=164)	Microbiome profiling vs. PET/CSF biomarkers	Dysbiosis detectable ~3.2 yrs before amyloid positivity

Study	Design	Population	Intervention / Exposure	Primary Finding
Seo et al., 2023 [22]	Murine experimental	ApoE knock-in mice	FMT cross-transfer; tauopathy induction	ApoE isoform modulates microbiome–neurodegeneration link
Bruggeman et al., 2024 [9]	RCT Phase 2	PD (n=46)	Single-dose FMT vs. placebo, 12 weeks	Positive motor trend; primary endpoint not reached
Yang et al., 2024 [19]	Mechanistic cohort	PD (n=112)	Erythrocytic α-syn tracking; vagal pathway	RBC-carried α-syn shown to migrate via gut-brain route
Zancan et al., 2024 [26]	Mendelian randomization	MS GWAS cohort	Causal inference; gut taxa as exposure	Six taxa causally associated with MS risk (FDR <0.05)
Lin et al., 2024 [24]	Meta-analysis	MS (k=11)	Cross-cohort microbiome signature analysis	Reproducible dysbiosis profile across independent cohorts
Chen et al., 2025 [27]	Systematic review	PD (n=104; 6 studies)	FMT: UPDRS, non-motor scales	Motor improvement observed; considerable between-study variation
Waseem et al., 2025 [28]	Systematic review + MA	PD RCTs (k=4)	Cochrane RoB 2.0; pooled motor analysis	FMT favored over placebo; pooled effect below p<0.05

3.3 Gut Microbiome Dysbiosis Signatures

3.3.1 Parkinson's Disease

Across the 16 PD-focused studies, one finding stood out for its cross-cohort reproducibility: the near-universal depletion of two butyrate- and propionate-producing families — Prevotellaceae (diminished in 7 of 10 cohort studies) and Lachnospiraceae (diminished in 9 of 10) — occurring in parallel with expansion of Akkermansia muciniphila and Bifidobacterium species [10, 11]. The functional significance of losing these taxa is straightforward: both families anchor the intestinal production of short-chain fatty acids, whose absence has downstream consequences for microglial activity, neuroinflammatory tone, and the structural integrity of the gut epithelium [12, 13].

Metagenomic profiling added a second layer to this picture. Enrichment of Escherichia and Shigella species — paired with elevated fecal LPS concentrations — was documented in PD patients relative to age-matched controls, reflecting a shift toward gram-negative-predominant communities capable of sustaining heightened TLR4-mediated inflammatory signaling [14]. Notably, these patterns held across studies conducted in Europe, North America, and East Asia, though the magnitude of individual taxon changes was modulated by local dietary habits, antibiotic exposure history, and the severity of concomitant constipation [10].

3.3.2 Alzheimer's Disease

The ten AD-focused studies converged on a picture of reduced microbial diversity and phylum-level reorganization, most commonly manifest as Firmicutes depletion alongside Bacteroidetes enrichment relative to cognitively normal older adults [15, 16]. A prospective cohort of 164 participants provided particularly striking timing data: gut microbiome dysbiosis — captured by 16S rRNA and shotgun sequencing — antedated PET-

confirmed amyloid positivity by a mean of 3.2 years, raising the possibility that the gut signature is not merely coincident with early AD pathology but may precede its cerebral expression [5].

TMAO, produced when gut bacteria metabolize dietary choline and L-carnitine and subsequently oxidized hepatically by FMO3, emerged as the most consistently elevated metabolite in AD. Pooling five studies, the standardized mean difference in plasma TMAO between AD cases and controls was 0.68 (95% CI: 0.41–0.96; I^2=43%), with concentrations correlating inversely with CSF amyloid-beta 42/40 ratios and positively with phospho-tau levels [17]. ApoE genotype further structured these associations: ε4 carriers harbored a distinctly pro-inflammatory microbial profile enriched in LPS-producing Proteobacteria, a finding replicated in ApoE humanized mouse models [18].

3.3.3 Multiple Sclerosis

The iMSMS study, drawing on 576 household-paired MS patients and healthy controls across multiple international sites, described what is currently the most rigorously characterized neurological microbiome dysbiosis signature: consistent enrichment of Akkermansia muciniphila and Blautia, with simultaneous loss of Faecalibacterium prausnitzii, Prevotella copri, and Butyricimonas species [6]. An independent meta-analysis spanning 11 cohorts confirmed these findings were not cohort-specific artifacts but a genuine, reproducible feature of the MS gut microbiome [19].

What elevates the MS dysbiosis evidence above that in PD and AD is the availability of Mendelian randomization data. Using genome-wide association study instruments, Zancan and colleagues identified six bacterial taxa whose abundance was causally linked to MS susceptibility at a false discovery rate below 0.05 — including Faecalibacterium as a protective factor and Akkermansia as a risk-augmenting one [20]. The seemingly paradoxical risk-increasing role of Akkermansia in MS — a species celebrated for its gut barrier-protective properties in metabolic disease — underscores how microbial effects are fundamentally disease- and context-dependent, and why generalizing findings across conditions should be done with caution.

3.4 Mechanistic Pathways

3.4.1 Vagal Alpha-Synuclein Propagation

The Braak staging hypothesis proposed, now more than two decades ago, that the pathological cascade of PD might originate not in the substantia nigra but in the enteric nervous system, ascending via the vagus nerve through the dorsal motor nucleus before eventually reaching midbrain dopaminergic structures [21, 22]. Five included mechanistic studies collectively provided substantial support for this route. In rodent models, stereotaxic injection of preformed alpha-synuclein fibrils into the duodenal wall triggered dose-dependent Lewy body pathology at the dorsal motor nucleus of the vagus within 10–12 weeks — pathology that was entirely prevented by prior subdiaphragmatic vagotomy, confirming the nerve as the necessary conduit [22].

Danish registry data brought this mechanism into human epidemiology. Individuals who had undergone complete truncal vagotomy showed a 42% reduction in subsequent PD incidence relative to non-vagotomized controls (HR: 0.58; 95% CI: 0.36–0.94), an effect that was absent following partial vagotomy — a dose-response relationship that is difficult to explain without vagal propagation playing a genuine role [21]. More recently, erythrocyte-derived extracellular vesicles, which carry alpha-synuclein in abundance, have been shown to transport the protein from gut to microglia under conditions of compromised blood-brain barrier integrity, extending the propagation mechanism beyond purely axonal routes [23].

3.4.2 SCFA-Mediated Neuroimmune Modulation

Short-chain fatty acids — chiefly butyrate, propionate, and acetate, generated by anaerobic fermentation of dietary fibre — act at multiple nodes of the gut-brain interface. Butyrate fuels colonocytes, upholds tight-junction architecture via occludin and ZO-1 upregulation, inhibits histone deacetylases to reshape neuroimmune gene expression, and stimulates enteroendocrine cells to release GLP-1 and PYY [24, 25]. In isolation these properties seem broadly neuroprotective, and they often are: butyrate supplementation in AD mouse models reduced soluble Aβ1-42 concentrations by 38% through a combination of NF-κB suppression and increased neprilysin expression, while propionate supplementation in a 90-day MS trial expanded

peripheral Treg populations by 26% and was associated with lower annualized relapse rates [25, 26].

The picture is not, however, uniformly protective. When alpha-synuclein is overexpressed, SCFAs — particularly in higher concentrations — appear to prime rather than suppress microglial activation, promoting reactive oxygen and nitrogen species generation and contributing to dopaminergic neuronal death [13]. This dual character means that SCFA-based therapeutic strategies will need careful dose titration and likely patient stratification, rather than blanket supplementation.

3.4.3 TMAO and Amyloid Pathology

Trimethylamine N-oxide represents a gut-derived metabolic signal with particular relevance to AD. The biosynthetic pathway begins in the intestinal lumen, where bacteria convert dietary choline, betaine, and L-carnitine into trimethylamine; hepatic FMO3 then oxidizes this intermediate to TMAO, which has sufficient lipophilicity to cross the blood-brain barrier and reach hippocampal tissue [17]. Once there, TMAO promotes Aβ oligomerization, accelerates tau phosphorylation, and impairs mitochondrial function. Clinically, individuals with plasma TMAO in the top quartile showed a 2.4-fold elevated risk of cognitive decline over five years compared to those in the lowest quartile (HR: 2.43; 95% CI: 1.61–3.67) [17]. The pharmacological implication is encouraging: FMO3 inhibitors and choline-restricted dietary protocols have each demonstrated TMAO lowering in experimental models, providing a concrete therapeutic rationale for AD-focused trials.

3.4.4 LPS, Gut Permeability, and Microglial Priming

The fourth pathway links microbiome composition to neuroinflammation through the physical barrier of the intestinal epithelium. Dysbiosis downregulates the tight-junction proteins occludin and claudin-5, increasing paracellular permeability and permitting gram-negative bacterial lipopolysaccharide to enter the portal and subsequently systemic circulation — the so-called 'leaky gut' phenomenon [14, 27]. Circulating LPS engages TLR4 receptors on monocytes and microglia, activating NF-κB–dependent transcription of IL-1β, TNF-α, and IL-6. This proinflammatory microglial phenotype has now been documented across all three diseases in the present review, and fecal calprotectin — a pragmatic, non-invasive surrogate of intestinal mucosal inflammation — was significantly elevated in PD and AD patient groups relative to controls in three cohort studies, suggesting increased gut permeability is not a sporadic finding but a consistent feature of the neurodegenerative gut environment [14].

3.5 Meta-Analysis: FMT Efficacy in Parkinson's Disease

Four RCTs comparing FMT to placebo in patients with mild-to-moderate PD contributed to the primary quantitative synthesis, collectively enrolling 167 participants (FMT: n=85; placebo: n=82). Using a random-effects pooling model, the mean between-group difference in MDS-UPDRS Part III score at 12 weeks favored FMT by 4.8 points (95% CI: −8.2 to −1.4; Z=2.67; p=0.008; I^2=61%) [9, 28, 29, 30]. This represents a statistically significant, small-to-moderate effect that sits at the lower boundary of the estimated minimum clinically important difference for this scale.

Pre-specified subgroup analyses revealed that colonoscopic delivery produced a larger motor benefit than oral capsule administration (SMD: −6.1 versus −3.2; p for subgroup difference=0.04), and that participants at H&Y stage II derived more benefit than those at stage III (SMD: −5.8 versus −2.9; p=0.06). Sensitivity analysis omitting the GUT-PARFECT trial — the single largest contributor — attenuated the pooled estimate to −3.6 points (95% CI: −7.1 to −0.1; p=0.043), confirming that the finding is directionally robust but somewhat dependent on that trial's weight. Non-motor outcomes also improved under FMT (pooled SMD: −3.1; 95% CI: −5.4 to −0.8; k=3 studies), with constipation and sleep quality showing the strongest response [27, 28].

Eighteen point eight percent of FMT recipients and 12.2% of placebo recipients experienced at least one adverse event; all were gastrointestinal and self-limiting (bloating, transient cramping, loose stools), and no serious events attributable to the intervention were recorded in any trial. Given the high heterogeneity, limited trial count, and variable

blinding quality, GRADE certainty for FMT motor outcomes in PD was rated as LOW.

4. Discussion

4.1 Principal Findings in Summary

Drawing together 34 studies spanning experimental models, observational cohorts, Mendelian randomization analyses, and randomized trials, this review produces several findings that we believe are sufficiently robust to guide future research design and, more cautiously, clinical thinking. First, dysbiosis is a reproducible feature of PD, AD, and MS — not an epiphenomenon, but a patterned shift in microbial community composition with predictable downstream biochemical effects. Second, at least four mechanistic pathways connect gut ecology to central neurological injury; none operates in isolation, and several amplify one another. Third, FMT produces a statistically significant improvement in PD motor scores at 12 weeks — a result that, while modest and heterogeneous, is the first quantitative signal of sufficient magnitude to justify Phase 3 investigation.

4.2 Interpreting the Evidence

The depletion of SCFA-producing bacteria — particularly F. prausnitzii and Lachnospiraceae members — across all three disease contexts is, in our view, the most clinically interpretable finding in this review. It points to a shared neuroimmune vulnerability rooted in the loss of butyrate-mediated microglial homeostasis and Treg support — mechanisms sufficiently general that they operate across autoimmune (MS), proteinopathic (PD), and amyloidogenic (AD) backgrounds [12, 31]. That the same taxa are depleted in pre-symptomatic microbiome studies opens the possibility — not yet confirmed prospectively — that SCFA-producer abundance could serve as an early risk stratification marker.

The causal inference achievable in MS — through Mendelian randomization — remains ahead of what is possible in PD and AD, where the genetic instruments for gut taxa are not yet sufficiently powered [20]. This is partly a function of the stronger GWAS data available for MS susceptibility loci, and partly reflects the more clearly autoimmune (and thus immunologically tractable) disease mechanism. Analogous MR studies in PD and AD are actively being pursued and represent arguably the highest methodological priority for establishing causality in those conditions.

On the therapeutic side, contextualizing the FMT meta-analysis requires honesty about what the data can and cannot support. The pooled SMD of −4.8 MDS-UPDRS III points lands at the lower bound of estimated clinical importance (MCID: 3.25–4.5 points), and the I^2 of 61% signals meaningful between-trial variation that cannot be explained by the available subgroup data alone [9, 29]. Differences in donor selection, delivery route, number of transplants, concomitant levodopa dose, and baseline microbiome composition all likely contribute to this heterogeneity — and none of these variables was standardized across the four included trials.

4.3 Therapeutic Implications

Short of FMT, two other intervention classes emerge from this synthesis with meaningful, if preliminary, support. Multi-strain probiotic supplementation using SCFA-producing Lactobacillus and Bifidobacterium species has shown consistent, if modest, benefits on constipation, inflammatory markers, and motor trajectory in PD across several RCTs — effects that are biologically coherent with the dysbiosis signatures described above, even if the effect sizes are small and trial durations insufficient to assess disease modification [32]. Dietary fibre supplementation, which augments SCFA biosynthesis prebiotically, is supported by mechanistic reasoning and observational data and carries essentially no safety burden, making it a reasonable adjunct to existing management even in advance of definitive trial data [24].

Looking further ahead, the postbiotic category — defined by the International Scientific Association for Probiotics and Prebiotics as preparations of inanimate microorganisms and their components that confer a health benefit — offers a degree of mechanistic precision that live cultures cannot match. Enteric-coated butyrate formulations optimized for colonic delivery, targeted FMO3 inhibitors to reduce TMAO burden in AD patients, and psychobiotics engineered for specific neuroactive metabolite production are all in early clinical development [33, 34]. These approaches represent the third therapeutic generation of gut–

brain axis medicine, and their entry into Phase 2 trials in PD and AD over the next three to five years will substantially clarify the field's translational trajectory.

4.4 Limitations

This review has several limitations that should inform interpretation. The FMT meta-analysis encompasses only four trials and 167 participants — sufficient to detect a statistically significant effect but inadequate to characterize the subgroup interactions or long-term durability that would be needed to support clinical guidelines. The mechanistic evidence base remains predominantly preclinical; while rodent gut–brain axis studies have been informative, extrapolation to humans is constrained by meaningful differences in microbiome composition, intestinal transit time, and neuroinflammatory signaling between species. Publication bias in observational microbiome research — where studies finding no between-group differences are rarely published — cannot be fully excluded, notwithstanding the non-significant Egger's test in our quantitative pool. Finally, the methodological heterogeneity in microbiome profiling across included studies (variable 16S rRNA hypervariable region targeting, inconsistent DNA extraction protocols, differing bioinformatic pipelines) prevents precise taxon-level data pooling and introduces a degree of measurement noise that no statistical correction can entirely resolve.

4.5 Future Research Directions

Five priorities stand out. First, multicenter Phase 3 RCTs of FMT in PD — and exploratory Phase 2 trials in AD — are needed urgently, with standardized donor selection criteria, consistent colonoscopic delivery, and neurologically meaningful co-primary endpoints that include both motor and cognitive outcomes. Second, prospective cohort studies with serial microbiome sampling in genetically at-risk, pre-symptomatic individuals will be essential to establish whether dysbiosis precedes neuropathological change or merely accompanies it. Third, Mendelian randomization studies in PD and AD should be accelerated using the enlarged GWAS instruments now available. Fourth, multi-omics integration — linking metagenomics to plasma metabolomics, host transcriptomics, and CNS biomarkers in the same individuals — is necessary to move from association to mechanistic attribution. Fifth, non-invasive gut–brain axis biomarkers (stool metagenomics, plasma TMAO and SCFA quantification, fecal calprotectin) need prospective validation as stratification and response-monitoring tools in therapeutic trials.

5. Conclusions

What this systematic review makes plain is that the gut is neither a spectator nor a mere symptom generator in neurodegeneration — it is, at minimum, a co-conspirator in pathological cascades that ultimately injure the brain. The dysbiosis signatures documented across PD, AD, and MS are too consistent to dismiss, the mechanisms too coherent to ignore, and the early therapeutic signals too promising to leave unstudied. None of this justifies clinical overreach; the evidence is, in places, still thin, and the tools for gut-targeted neurological therapy remain immature.

Yet the trajectory is clear. A pooled FMT effect that crosses both statistical and clinical significance thresholds — even narrowly — in a four-trial meta-analysis of a disease as refractory as Parkinson's would have seemed improbable a decade ago. Mendelian randomization placing specific gut bacteria in a causal relationship with MS susceptibility has shifted the evidentiary standard in that disease. And a microbiome signature detectable in pre-symptomatic individuals years before cerebral amyloid accumulates in AD suggests a diagnostic window that current neuroimaging approaches cannot easily match for cost or accessibility.

The work now is to consolidate these signals through larger, more rigorous, better-standardized trials — and to do so with the awareness that the gut's accessibility, relative to the brain, is itself a clinical advantage. Dietary modification, probiotic supplementation, and FMT are interventions that can be deployed widely, monitored non-invasively, and adjusted iteratively. That is not a small thing in a field where the biological complexity of the target has so often outpaced the tools available to engage it.

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