

## SYSTEMATIC REVIEW

## OPEN



# The usefulness of microbiome profiling for geriatric patients with neuropsychiatric conditions: a scoping review

Emma Tanevska<sup>1</sup>, Cristian E. Leyton<sup>1,2</sup> and Richard Seamark<sup>3</sup>

© The Author(s) 2025

**INTRODUCTION:** Neuropsychiatric disorders encompass psychiatric and neurodegenerative diseases. These conditions are particularly challenging to diagnose in the elderly due to their overlapping cognitive, affective, and behavioural symptoms. Recent studies indicate microbiota imbalances exist in both psychiatric and neurodegenerative conditions, suggesting potential biomarkers for diagnosis and prognosis. The objective of this scoping review is to provide a comprehensive overview of how microbiome profiling has been used in research to develop diagnostic and prognostic models for elderly patients with neuropsychiatric conditions.

**METHODS:** Following JBI guidelines, a comprehensive search was conducted across four electronic databases (MEDLINE, PsycINFO, SCOPUS, EMBASE) with strategies developed alongside academic librarians. Two independent reviewers screened titles, abstracts, and full texts based on pre-specified inclusion criteria. Data was extracted focusing on participants, study methods, and key findings.

**RESULTS:** Thirty-one studies employing microbiome-based predictive models were identified, primarily targeting Alzheimer's and Parkinson's diseases, with limited research on psychiatric conditions which was only found for depression and schizophrenia. Most studies used 16S rRNA gene sequencing and machine learning models. Findings highlight the potential of gut microbiota data to enhance predictions of neuropsychiatric conditions, though limitations included small, non-diverse cohorts and a lack of methodological standardisation. The review highlights the need for larger, longitudinal, multicenter studies to validate models and improve clinical applicability.

**DISCUSSION:** Microbiome-based predictive models for neuropsychiatric conditions in the elderly show promise. Future research should focus on longitudinal studies and expanding profiling methods to validate findings in larger, diverse cohorts.

*Translational Psychiatry* (2025)15:420; <https://doi.org/10.1038/s41398-025-03685-w>

## INTRODUCTION

As the global population ages, the prevalence of neuropsychiatric conditions such as dementia, Parkinson's disease (PD), and geriatric depression has dramatically increased [1], posing substantial challenges to healthcare systems. In addition, neuropsychiatric disorders, which includes psychiatric and neurodegenerative diseases, have overlapping cognitive, affective, and behavioural symptoms, making accurate diagnosis in the elderly challenging [2]. Current diagnostic approaches are limited by the lack of reliable biomarkers and can rely on costly, invasive procedures such as neuroimaging and cerebrospinal fluid (CSF) analysis for neurodegenerative conditions [3]. This can delay appropriate diagnoses which can make treatment less effective [4]. These limitations highlight the need for innovative, less invasive diagnostic tools that can improve the accuracy, accessibility and timeliness of diagnoses for neuropsychiatric conditions in the elderly. Furthermore, we need reliable prognostic biomarkers that can predict disease progression and guide personalised treatment strategies for these conditions [3].

Gut microbiome profiling could be a promising tool in this space, offering non-invasive, faecal-based sampling to explore the dynamic relationship between gut microbes and the brain.

Increasing evidence suggests that gut microbes produce metabolites and neurotransmitters that influence brain function and immune responses [5], such that disruptions in the balance of gut microbiota may be linked to various diseases. There is extensive research which shows gut microbiota imbalances in neuropsychiatric conditions including Alzheimer's disease, Parkinson's disease, and psychiatric disorders [6]. A meta-analysis on AD found 10 bacterial genera linked to AD and high-risk AD genes [7], while another study found significantly lower levels of Firmicutes in AD patients [8]. For PD, constipation is one of the earliest and most common symptoms, affecting 90% of patients [9] and sometimes appearing 20 years before motor symptoms [10]. This suggests early gut changes, supported by evidence that  $\alpha$ -synuclein might appear in the enteric nervous system before the brain, which has led to the hypothesis that Parkinson's could originate in the gut and spread to the brain via the vagus nerve [11, 12]. However, this hypothesis has been challenged by neuropathological evidence showing that some PD cases display a pattern of neuroanatomical pathological progression incompatible with the entero-cephalic transmission mechanism [13]. Psychiatric conditions including depression, bipolar disorder, schizophrenia, and anxiety have been shown to share a

<sup>1</sup>University Centre for Rural Health, Faculty of Medicine and Health, The University of Sydney, Sydney, NSW, Australia. <sup>2</sup>Brain and Mind Centre, The University of Sydney, Sydney, NSW, Australia. <sup>3</sup>Lismore Community Mental Health. Northern NSW Local Health District, Lismore, NSW, Australia. ✉email: [cristian.leyton@sydney.edu.au](mailto:cristian.leyton@sydney.edu.au)

Received: 11 April 2025 Revised: 10 September 2025 Accepted: 2 October 2025

Published online: 20 October 2025

transdiagnostic gut microbiota pattern with reduced butyrate-producing bacteria and increased pro-inflammatory, lactic acid-producing, and glutamate- and GABA-metabolizing bacteria [6, 14]. Despite mounting evidence that microbiota changes are linked to neuropsychiatric conditions, there is no consensus on the extent to which microbiome data can reliably inform diagnostic or therapeutic decisions.

This scoping review synthesizes existing research on the application of microbiome profiling in developing diagnostic and prognostic models for neuropsychiatric conditions in the elderly. By mapping the current scope of research, including methodologies, findings, and limitations, it aims to evaluate the potential of microbiome profiling to enhance clinical decision-making. To achieve this, the review explores several key questions: What is the current scope of research on microbiome profiling in diagnostic and prognostic models for geriatric patients presenting with neuropsychiatric conditions? Specifically, which conditions have these models studied, and what outcomes have they aimed to predict? Are there similarities among the models, or do they vary significantly? Furthermore, what is the current extent of research in this field, what are its limitations, and how applicable are the findings so far? By addressing these questions, this review provides an overview of the current landscape, identifying opportunities to advance the integration of microbiome data into clinical practice for managing neuropsychiatric conditions in the elderly.

## METHODS

This review adheres to the JBI methodology for scoping reviews [15]. The reporting is conducted in accordance with PRISMA guidelines for scoping reviews (see Supplementary Material 1). A protocol was uploaded to Open Science Framework [16]: <https://osf.io/crwum>.

### Literature retrieval, inclusion and exclusion

A systematic search was conducted in MEDLINE, PsycINFO, SCOPUS, EMBASE databases to identify relevant articles using a PCC (Population, Concept, Context) research strategy. The search strategy (See Supplementary Material 2) was limited to studies published in English since 2014 according to the following criteria: [1] participants are human patients with neuropsychiatric conditions, including psychiatric and neurodegenerative disorders. Studies on only MCI were included if it was formally diagnosed and defined as an early stage of AD but excluded if based only on a cognition score; [2] the study uses microbiome profiling in diagnostic or prognostic models, although models were allowed to include additional data beyond microbiome alone; [3] focus is on elderly patients, without setting a specific age limit [4] the study is a primary study or meta-analysis that has been published in a peer reviewed journal. We excluded studies that explore the relationship between diseases and gut microbiota without applying it to predictive models, those using only metabolites in predictive models, animal studies, or unavailable full text (See Supplementary Material 3 for full inclusion and exclusion criteria).

Citations were managed using Endnote for deduplication and uploaded into Covidence [17]. Two independent reviewers screened the articles at two stages: title and abstract review, followed by full-text screening. Disagreements were resolved through discussion or by an additional reviewer. Sources of evidence that did not meet the inclusion criteria at the full-text stage were recorded and reported in the scoping review. The results of the search and screening process are detailed in this review and depicted in a PRISMA flow diagram (Fig. 1).

### Data extraction

Data from a sample of six included studies were extracted by two independent reviewers. The remaining studies were extracted by the lead reviewer and reviewed by others. We extracted the

following data: [1] Characteristics of included studies (Authors, Year, Country, Journal, Study Design); [2] Characteristics of study populations (Sample size, Gender, Age, Source of Participants); [3] Neuropsychiatric condition studied and Diagnostic criteria used; [4] Gut microbiome analysis technique; [5] Characteristics and performance of the model (Disease of focus, Whether diagnostic or prognostic, Predictive goals of models, Type of model used, Inputs to model, Validation methods and Model performance); [6] Results (Key findings about the model, Other key findings, Strengths and limitations, and Recommendations/areas for future research).

Results are self-reported by the studies. The performance of the models was evaluated using the Area Under the Curve (AUC) as it was the most frequently reported metric. Our interpretation of AUC values was guided by a paper by Carter et al. [18].

## RESULTS

### Selection of sources of evidence

A total of 1501 citations were identified through database searches. After removing 409 duplicates, 1092 records were screened based on their titles and abstracts. The remaining full-text documents ( $n = 90$ ) were reviewed in detail, and 31 papers were included in the final review (Fig. 1).

### Characteristics of sources of evidence

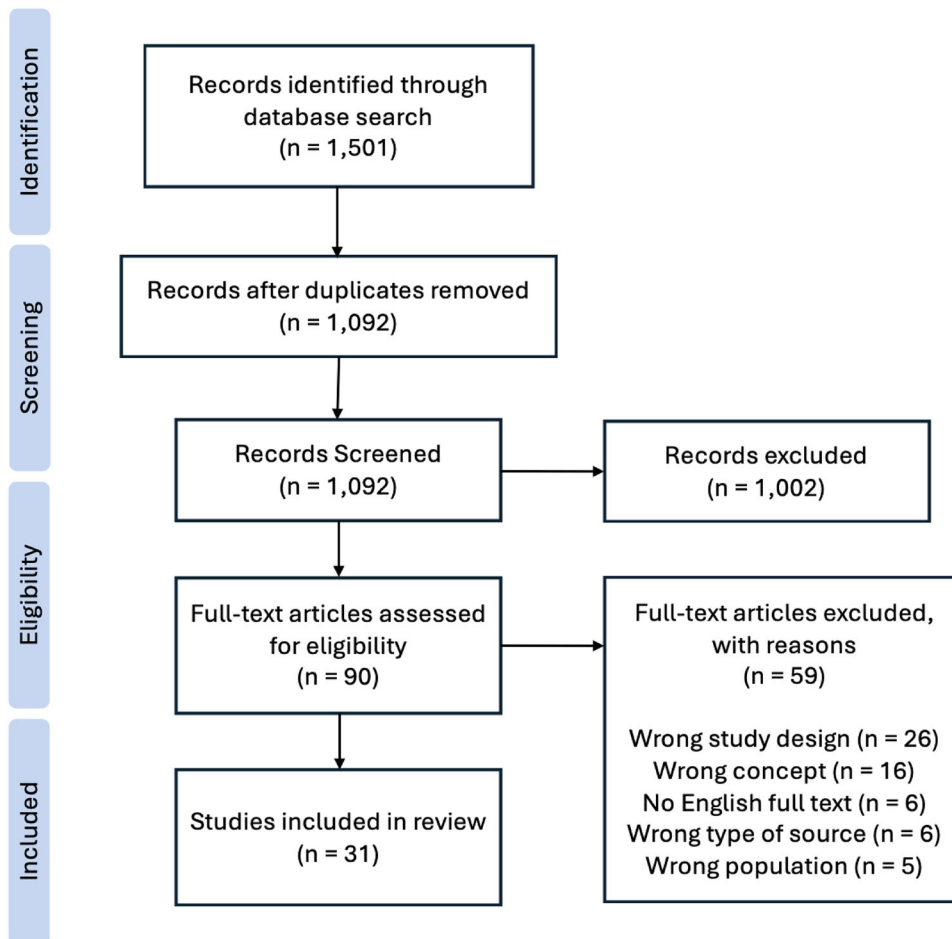
We found 31 studies investigating the use of microbiome data to predict the diagnosis or prognosis of elderly patients with neuropsychiatric diseases. Most studies had a cross-sectional design ( $n = 13$ ), followed by case-control ( $n = 9$ ), longitudinal ( $n = 6$ ), and meta-analyses ( $n = 3$ ). Participants were predominantly recruited from outpatient clinics ( $n = 21$ ). Two studies recruited from the community and one study focused on hospitalized in-patients with Schizophrenia. There were 16 studies from China, the rest were from the USA ( $n = 3$ ), Japan ( $n = 3$ ), Germany ( $n = 3$ ), Finland ( $n = 2$ ), Italy ( $n = 1$ ), South Korea ( $n = 1$ ), Australia ( $n = 1$ ), and the Netherlands ( $n = 1$ ). The oldest cohort was a dementia cohort with a mean age of 88, and the youngest was 61 in a study on MSA.

16S rRNA gene sequencing was used in 22 studies, shotgun metagenomic sequencing in 10, and real-time PCR in two. Twenty of the studies used machine learning for their predictive modelling; the most common method was random forest analysis ( $n = 12$ ). Twenty-five studies predicted diagnosis and the remaining six predicted prognosis. Among the diagnostic studies, 22 compared patients with healthy controls (HCs), and seven included comparisons to subgroups with diverse clinical statuses.

### Alzheimer's disease, MCI and other dementias

The review included 12 studies on Alzheimer's disease and mild cognitive impairment (MCI), along with one study on general dementia (Tables 1, 2). Sample sizes ranged from 21 AD patients [19] to meta-analyses involving 2758 samples [20]. Six studies focused on differentiating AD patients from healthy controls (HCs), achieving AUCs between 0.77 [20] and 0.96 [19]. The highest-performing model (AUC = 0.96) used two gut bacterial genera and four metabolites in a small cohort, while other models, some in larger cohorts and with validation, incorporated functional and clinical variables with microbiome data. Direct comparisons of AUCs across studies remain challenging due to differences in study design, sample sizes, validation methods, and the inclusion of additional model inputs.

Two studies explored the use of gut microbiota to predict biomarker status in AD, with one achieving an AUC of 0.90 for PET amyloid status [21], while another struggled to predict CSF amyloid and tau markers (AUCs = 0.63–0.64) [22]. Three studies aimed to distinguish early stages of Alzheimer's disease from healthy controls [23–25], and found that including microbiome features improved



**Fig. 1** PRISMA flow diagram illustrating the progression of information through the various stages of the scoping review.

performance [23]. Two prognostic models showed exceptional accuracy, with one predicting MCI progression to AD over four years ( $AUC = 0.97$ ) [26] and another predicting rapid MCI progression over two years with perfect accuracy ( $AUC = 1.00$ ) [27].

#### Parkinson's disease and other parkinsonism syndromes

The review included 12 studies on Parkinson's disease (PD) and 3 on related disorders (Tables 3, 4). Ten focused on differentiating PD from healthy controls (HCs), with AUCs ranging from 0.63 [20]–0.97 [28]. Models used diverse inputs, including phage abundance [28], biosynthetic gene clusters [29], and clinical factors like constipation severity [30] and carbohydrate intake [31]. Two studies with external validation showed strong predictive accuracy, with one identifying a set of 25 gut microbial gene markers that could distinguish PD from healthy controls and other conditions like MSA and Alzheimer's disease ( $AUCs = 0.83$ – $0.91$ ) using real time PCR [32].

Two prognostic studies investigated PD progression and levodopa responsiveness. Microbiota-based models were superior to clinical models for predicting early but not advanced stage PD progression ( $AUC = 0.80$ ) [33], and the *tyrDC* gene was a strong biomarker for levodopa responsiveness ( $AUC = 0.95$ ) [34]. Studies on related disorders demonstrated the utility of microbiota in differentiating multiple system atrophy (MSA) [35], dementia with Lewy bodies (DLB) [36], and essential tremor (ET) [37] from HCs and PD.

#### Depression

Three studies focused on depression in the elderly, all using 16S RNA sequencing (Tables 5, 6). One was excellent at differentiating

late-life depression from healthy controls using gut microbiota and serum inflammatory cytokines ( $AUC = 0.96$ ) [38]. Another study predicted current and future cognitive scores (MMSE) and depression severity (MARDS, SGDS-K) [39]. The third study predicted remission after antidepressant treatment based on pre-treatment microbiome profiles ( $AUC = 0.86$ ), observing significant genus-level changes in remitters but not in non-remitters [40].

#### Schizophrenia

A single study on schizophrenia accurately distinguished hospitalised schizophrenia patients from healthy controls using only five bacterial genera ( $AUC = 0.96$ ) [41] (Tables 5, 6).

#### DISCUSSION

This scoping review identifies a growing body of research employing microbiome profiling in prognostic and diagnostic models for elderly neuropsychiatric patients. The studies collectively demonstrate the potential of microbiome data as a non-invasive method for clinical testing in neuropsychiatric conditions. Most of the current research focuses on AD and PD, with a limited number of studies focusing on psychiatric conditions such as depression and schizophrenia.

The gut microbiome can influence brain function and mediate neuropsychiatric alterations through multiple mechanisms, including modulation of the immune system and proinflammatory mediators, vagal activity, tryptophan metabolism, and the release of microbial metabolites such as short-chain fatty acids, branched

**Table 1.** Key characteristics of predictive studies focusing on Alzheimer's Disease and related conditions.

Authors	Year	Location	Type of Study	Sample size	Sequencing platform	Disease of Focus	Predictive Goal of Model	Type of model	Validation	Results of model
Ferreiro A, Choi J, et al.	2023	USA	Cross-sectional	44 Preclinical AD patients, 115 Healthy Controls	Shotgun metagenomic sequencing	Alzheimer's Disease	Predict preclinical Alzheimer's disease status	Random forest analysis	10-fold cross-validation on 100 random subsets of the training cohort	Adding microbiome data to clinical features increased accuracy from 0.67–0.75 and specificity from 0.85–0.97 for differentiating AD from HC. Combining microbiome data, clinical features, and other biomarkers achieved 1.00 accuracy (0.99 without microbiome data).
Haran J, Bhattarai S, et al.	2019	USA	Longitudinal cohort	24 AD patients, 33 patients with other dementias, 51 patients with no dementia	Shotgun metagenomic sequencing	Alzheimer's Disease	To discriminate between AD, other dementias, and no dementia	Random forest analysis	Leave-one-out cross-validation, out of bag analysis	Models accurately differentiated nursing home elders with AD, other dementias, and no dementia using microbial and clinical data.
Laske C, Müller S, et al.	2024	Germany	Longitudinal cohort	27 patients converted from MCI to AD, 22 with stable MCI	Shotgun metagenomic sequencing	Alzheimer's Disease	Predict conversion from MCI to AD	Logistic regression models and ensemble learning model	Apparent performance	In individuals with MCI, the gut microbiome predicted progression to AD over 4 years, with highest accuracy from a combined taxonomic, functional, and clinical model (AUC = 0.97).
Laske C, Müller S, et al.	2022	Germany	Cross-sectional	75 Alzheimer's Disease (AD) patients and 100 Healthy Controls (HC)	Shotgun metagenomic sequencing	Alzheimer's Disease	Discriminate amyloid-positive AD patients from healthy controls	Machine learning applying logistic regression techniques. In this training phase further feature selection was achieved. Best performing models were joined in an	Split-sample validation approach	Diagnostic performance for discriminating amyloid-positive AD from controls improved from taxonomic to functional data, and was highest when combining taxonomic, functional, and clinical data (AUC = 0.92)

Table 1. continued

Authors	Year	Location	Type of Study	Sample size	Sequencing platform	Disease of Focus	Predictive Goal of Model	Type of model	Validation	Results of model
Li B, He Y, et al.	2019	China	Cross-sectional	30 AD, 30 MCI, 30 HC	16S rRNA gene sequencing of the V3-V4 regions	Mild Cognitive Impairment	Identification of MCI	ensemble learning model	Apparent performance	training; 0.80 validation)
Li Z, Zhou J, et al.	2022	China	Meta-analysis	2758 subjects (1469 patients with various neurological diseases and 1289 controls)	16S rRNA gene sequencing	Alzheimer's Disease, Parkinson's Disease	Predict AD and PD patients from HCs	Statistical analysis models	Apparent performance	Microbiota genera predicted MCI with Sensitivity = 93% and AUC = 0.78.
Ling Z, Zhu M, et al.	2021	China	Case-control	100 AD patients, 71 Healthy Controls (HC)	16S rRNA gene sequencing of the V3-V4 regions	Alzheimer's Disease	Discriminate between AD patients and controls	Logistic regression analysis	Apparent performance	Alpha diversity could predict AD (Shannon index AUC = 0.77), but it was a poor predictor for PD.
Liu P, Li W, et al.	2019	China	Cross-sectional	33 AD patients, 32 Amnesic Mild Cognitive Impairment (aMCI) patients, 32 HC	16S rRNA gene sequencing of the V3-V4 region	Alzheimer's Disease	Distinguish AD and aMCI from healthy controls (HC). Distinguish AD from aMCI.	Multivariable logistic regression analysis	Apparent performance	Combining multiple genera distinguished AD from healthy controls with AUC = 0.84. The best individual genus achieved AUC = 0.80.
Saji N, Niida S, et al.	2019	Japan	Cross-sectional	34 Dementia patients, 94 non-Dementia patients	Terminal restriction fragment length polymorphism (T-RFLP)	Dementia	Identification of Dementia	Multivariable logistic regression analysis	Apparent performance	Models using the most abundant microbial genera could distinguish AD from HC (AUC = 0.94), AD from aMCI (AUC = 0.93) and aMCI from HC (0.89). Adding enterotype to predict dementia improved the sensitivity, specificity and AUC (to AUC = 0.93 from 0.89 and 0.86). Certain enterotypes were independently associated with dementia, with stronger associations than some traditional dementia biomarkers.

Table 1. continued

Authors	Year	Location	Type of Study	Sample size	Sequencing platform	Disease of Focus	Predictive Goal of Model	Type of model	Validation	Results of model
Sheng C, Yang K, et al.	2022	China	Cross-sectional	34 A $\beta$ -negative cognitively normal (CN-) and 32 A $\beta$ -positive cognitively normal (CN+) patients	16S rRNA gene sequencing of the V3-V4 region	Alzheimer's Disease	Predict amyloid PET status (A $\beta$ + vs. A $\beta$ -)	Multivariable logistic regression	Apparent performance	A combined model of plasma A $\beta$ markers, gut taxa, and cognitive tests discriminated CN A $\beta$ + from CN A $\beta$ - individuals with AUC = 0.87 (Sensitivity = 88%, Specificity = 74%). Gut taxa alone outperformed plasma A $\beta$ markers.
Verhaar B, Hendriksen H, et al.	2022	Netherlands	Cross-sectional	33 Alzheimer's Disease (AD) patients, 21 patients with Mild Cognitive Impairment (MCI), 116 patients with Subjective Cognitive Decline (SCD)	16S rRNA gene sequencing of the V3-V4 region	Alzheimer's Disease	Predicting CSF amyloid and p-tau status, and other AD biomarkers	Gradient-boosted tree models	Nested cross-validation	Gut microbiota composition predicted amyloid (AUC = 0.64) and p-tau (0.63) status with poor discrimination and could not predict MRI visual scores.
Wang L, Yan J, et al.	2024	China	Longitudinal cohort	87 patients with Mild Cognitive Impairment (MCI) who completed a two-year follow-up: 44 cases with rapid progression, 43 controls with non-progression.	16S rRNA gene sequencing of the V3-V4 region	Mild Cognitive Impairment (MCI), Alzheimer's Disease	Predict rapid progression of MCI	Random forest analysis	Cross-validation	Microbiome data alone predicted rapid MCI progression with 86% accuracy (AUC = 1.00), increasing to 97% accuracy when combined with demographic and haematological data.
Xi J, Ding D, et al.	2021	China	Cross-sectional	21 Alzheimer's Disease (AD) patients and 44 cognitively normal controls (NC)	16S rRNA gene sequencing of the V3-V4 region	Alzheimer's Disease	Discriminate AD from Healthy Controls	Binary logistic regression	Apparent performance	Combining two gut bacterial genera and four metabolites accurately discriminated AD from NC (AUC = 0.96).

**Table 2.** Summary of Strengths, Limitations, and Recommendations for Future Research for studies on Alzheimer's Disease and related disorders.

Authors	Year	Strengths and Limitations	Recommendations/Areas for Future Research
Ferreiro A, Choi J, et al.	2023	Strengths: novel approach, extensive data collection Limitations: gap between neuroimaging, serum and CSF assessments, and stool analysis, missingness in some biomarker data (particularly PET tau), cross sectional	<ul style="list-style-type: none"> <li>- Synchronous biomarker assessment and stool sampling</li> <li>- Long-term longitudinal studies</li> <li>- Apply broader multiomics (metatranscriptomics, metabolomics)</li> <li>- Validate in larger preclinical AD cohorts and assess causality</li> <li>- Investigate applicability to symptomatic AD and progression</li> <li>- Explore early microbiome features as therapeutic targets</li> </ul>
Haran J, Bhattarai S, et al.	2019	Strengths: Use of metagenomic sequencing for detailed microbial analysis at the species level, integration of clinical parameters, and machine learning for predictive modelling. Limitations: Study population is small and limited to nursing home elders	<ul style="list-style-type: none"> <li>- Validate in larger, more diverse groups</li> <li>- Explore gut microbiome therapies that affect P-glycoprotein</li> <li>- Identify microbes affecting P-glycoprotein</li> <li>- Examine role of butyrate-producers</li> <li>- Study the impact of the diet</li> </ul>
Laske C, Müller S, et al.	2024	Strengths: Longitudinal design, combination of taxonomic and functional gut microbiome data, ensemble learning approach, novel gut microbiome algorithms with stable predictive power over time Limitations: limited sample size, follow-up measurements not performed every year, no CSF analysis	<ul style="list-style-type: none"> <li>- Replicate findings in a larger longitudinal study</li> </ul>
Laske C, Müller S, et al.	2022	Strengths: Validation in an independent cohort, first study to use both taxonomic and functional data of shotgun metagenomics in a training cohort and independent validation cohort, combination of clinical data to enhance diagnostic accuracy. Limitations: Cross-sectional design, CSF data not available for healthy controls, potential influence of antidepressant and acetylcholinesterase inhibitor use on results, no measurement of metabolites in gut samples.	<ul style="list-style-type: none"> <li>- Conduct well-powered longitudinal studies to assess causality</li> <li>- Replicate findings in independent cohorts with healthy controls and CSF data</li> <li>- Investigate the microbiome as a therapeutic target in AD</li> </ul>
Li B, He Y, et al.	2019	Strengths: recruited participants with similar diet habits Limitations: Lack of biomarker tests for MCI patients, need for larger longitudinal studies to validate findings	<ul style="list-style-type: none"> <li>- Validate gut microbiota biomarkers in prospective studies</li> <li>- Evaluate circulating inflammatory markers and pathogenic metabolites</li> <li>- Detailed investigation of microbiota function in neurodegeneration</li> <li>- Conduct clinical trials on probiotics and dietary interventions in AD and MCI</li> </ul>
Li Z, Zhou J, et al.	2022	Strengths: Comprehensive analysis of alpha diversity across multiple neurological conditions; use of multiple alpha diversity indices Limitations: Lack of demographic data and basic characteristics of the disease (e.g. age, sex, BMI, diagnostic criteria), potential impact of diet and medications not fully addressed.	<ul style="list-style-type: none"> <li>- Conduct larger cohort studies accounting for confounders like diet and medications</li> <li>- Investigate links between gut microbiota changes and other biomarkers</li> </ul>
Ling Z, Zhu M, et al.	2021	Limitations: Used 16S rRNA gene sequencing instead of metagenomic sequencing (limited to species level), cross-sectional study design	<ul style="list-style-type: none"> <li>- Conduct longitudinal studies across AD stages</li> <li>- Validate findings in larger samples</li> <li>- Use culturomics and animal models to explore causality between AD and gut dysbiosis</li> </ul>
Liu P, Li W, et al.	2019	Strengths: Novel insights Limitations: cross sectional design, small sample size, AD diagnosed with revised NINCDS-ADRDA criteria	<ul style="list-style-type: none"> <li>- Include larger, ethnically diverse cohorts</li> <li>- Use longitudinal designs to assess causality</li> <li>- Use metabolomic and metagenomic analyses to identify neuroactive compounds and microbiota-related pathways linked to AD progression</li> <li>- Explore therapeutic microbiome interventions for AD</li> </ul>
Saji N, Niida S, et al.	2019	Strengths: Large sample size compared to previous studies, comprehensive cognitive and nutritional assessments, use of detailed neuropsychological tests, brain MRI, and SPECT images. Limitations: Cross-sectional study design prevents establishing causal relationships, relatively small number of patients may risk statistical underpowering, potential selection bias due to single hospital-based cohort, and the T-RFLP method could not identify specific genera or species of 'other' bacteria.	<ul style="list-style-type: none"> <li>- Assess gut microbe-derived metabolites</li> <li>- Include detailed dietary analysis</li> <li>- Investigate dementia subtypes</li> <li>- Consider effects of anti-dementia medications</li> </ul>

Table 2. continued

Authors	Year	Strengths and Limitations	Recommendations/Areas for Future Research
Sheng C, Yang K, et al.	2022	Strengths: Combines plasma A $\beta$ and gut microbiota as a non-invasive, cost-effective diagnostic tool for early AD screening Limitations: Relatively small sample size, single-centre study, lack of amyloid-PET data for all CI patients, diagnosis of MCI and AD based on clinical practice, use of 16S rDNA amplicon sequencing with limited resolution	<ul style="list-style-type: none"> <li>- Conduct larger, multicentre, well-designed studies with standardised methods</li> <li>- Include CI patients with amyloid-PET data</li> <li>- Use metagenomic sequencing for improved taxonomic resolution</li> </ul>
Verhaar B, Hendriksen H, et al.	2022	Strengths: Inclusion of several AD biomarkers (CSF and MRI data), inclusion of patients at various stages of the Alzheimer's disease continuum, standardized protocol for faecal sample collection, robust machine learning models with nested cross-validation Limitations: Cross-sectional design, time lags between biomarker measurements and faecal sampling, some cofounders not adjusted for including diet, metagenomic sequencing needed to assess microbial function including production of SCFAs	<ul style="list-style-type: none"> <li>- Examine associations between SCFA levels in faeces and plasma to brain inflammation markers</li> <li>- Use metagenomics to map microbial pathways</li> <li>- Assess causality between microbiota and AD</li> <li>- Explore SCFA-based therapeutic targets</li> </ul>
Wang L, Yan J, et al.	2023	Strengths: Analyses a wide range of features Limitations: Small sample size, lack of cut-off values for specific features, potential selection bias due to voluntary participation, study was unable to perform before and after comparisons for all patients for the 121 features analysed	<ul style="list-style-type: none"> <li>- Validation with larger sample sizes and multicentre studies</li> </ul>
Xi J, Ding D, et al.	2021	Limitations: Preliminary study with small sample size, diagnosis of AD was based on symptoms without disease severity information, could not establish causal relationships	<ul style="list-style-type: none"> <li>- Validate and refine faecal marker panel in large, diverse, longitudinal cohorts</li> <li>- Assess causality via cross-validation, functional, and animal studies</li> <li>- Compare analytical methods for identifying key taxa</li> <li>- Investigate AD-relevant strains</li> </ul>

chain amino acids, and peptidoglycans [42]. Given the complexity and bidirectionality of this relationship, it is not surprising that current evidence supports an association between gut microbiome changes and neuropsychiatric conditions in the elderly but does not establish causality. A possible way to determine causality is with long-term prospective longitudinal studies capable of tracking microbiome changes decades earlier than the onset of neuropsychiatric symptoms, so that a temporal relationship between microbiome changes and development of neuropsychiatric alterations can be established.

Gut microbiome profiling has potential in precision medicine by stratifying patients with neuropsychiatric manifestations, which are often challenging and overlapping, into specific biotypes or biologically coherent subgroups [43]. At present, these neuropsychiatric conditions exhibit considerable pathological and clinical heterogeneity, and there is no established biological framework that fully explains or unifies their diverse presentations [43]. Therefore, microbiome profiling could be particularly valuable for patients with ambiguous or vague symptoms, enabling more precise diagnosis and targeted interventions early on. Supporting this, two studies found that the microbiome could predict responsiveness to treatments such as levodopa [34] and antidepressants [40], and several others were able to identify patients at risk of disease progression [26, 27, 33, 39]. Additionally, two studies attempted to predict CSF [22] and PET [21] biomarker status in Alzheimer's disease patients, suggesting microbiome-based models could potentially offer a cheaper, less invasive alternative in the future.

However, some microbiome features may be shared across conditions, which could limit their diagnostic specificity. For example, reduced butyrate-producing bacteria is a transdiagnostic feature seen in Alzheimer's disease [44], Parkinson's disease [45], and psychiatric disorders [6]. This overlap in microbial signatures may make it more challenging for models to differentiate between

conditions, particularly when clinical presentations intersect, such as depression occurring independently or in the context of Parkinson's or Alzheimer's disease. Most studies focused on distinguishing patients from healthy controls, with no studies directly comparing psychiatric and neurodegenerative conditions. To improve clinical applicability, future models should aim to distinguish between overlapping conditions rather than solely contrasting patients with healthy controls, as this would better reflect real-world diagnostic challenges.

16S rRNA gene sequencing was the most common method for microbiome profiling, followed by metagenomic sequencing. While 16S rRNA gene sequencing generally identifies bacteria down to the genus level, metagenomic sequencing can achieve species or even strain-level resolution and provide functional information [46]. Multiple studies highlighted the need for metagenomic sequencing to further understand the microbiome's role in these conditions. Nonetheless, 16S rRNA gene sequencing is useful due to its simplicity and cost-effectiveness compared to metagenomics, making it more practical for clinical use. However, different 16S rRNA primers may lead to inconsistent results due to variations in binding affinity and resolution of variable regions. A standardized tool could help create large consistent datasets for better comparison and analysis, as recommended in one study [47]. Two papers used real-time PCR [32, 34] and found it demonstrated high sensitivity and specificity similar to metagenomic sequencing. Real-time PCR offers a rapid, cost-effective, and highly specific method for quantifying known microbial DNA [48], making it ideal for clinical applications and a valuable focus for future research. Furthermore, the widespread use of machine learning in data processing and model construction across most studies underscores its emerging significance in advancing diagnostic frameworks. Many papers also recommended that broader multiomics approaches, such as metatranscriptomics, metabolomics and metaproteomics, be incorporated in future

**Table 3.** Key characteristics of predictive studies focusing on Parkinson's Disease and related conditions.

Authors	Year	Location	Type of Study	Sample size	Sequencing platform	Disease of Focus	Predictive Goal of Model	Type of model	Validation	Results of model
Bedarf J, Hildebrand F, et al.	2017	Germany	Case-control	31 PD patients, 28 controls	Metagenomic shotgun sequencing	Parkinson's Disease	To discriminate PD patients from controls	Logistic regression classifier	Cross-validation using leave-one-out schedule	Bacterial taxa could discriminate PD from control with AUC = 0.84.
Du J, Huang P, et al.	2019	China	Case-control	40 MSA patients: 23 MSA-P (Parkinsonism predominant) and 17 MSA-C (Cerebellar ataxia predominant), 40 healthy controls	16S rRNA gene sequencing of V3-V4 region	Multiple System Atrophy (MSA)	Predicting MSA and differentiating MSA subtypes (Parkinsonism predominant vs Cerebellar ataxia predominant MSA)	Logistic Regression Analysis	Apparent performance	Combined faecal and blood genera predicted MSA (AUC = 0.85) and differentiated subtypes (AUC = 0.90).
Lecomte A, Duru I C, et al.	2023	Finland	Case-control	68 PD patients, 68 Healthy Controls (HC)	Shotgun metagenomic sequencing	Parkinson's Disease	To discriminate between PD patients and HCs	Random Forest Analysis	Cross-validation (1000 random splits into train and test groups)	Highest performing model using phage abundances discriminated PD from HC with AUC = 0.97.
Li Z, Zhou J, et al.	2022	China	Meta-analysis	2758 subjects (1469 patients with various neurological diseases and 1289 controls)	16S rRNA gene sequencing	Alzheimer's Disease, Parkinson's Disease	Predict AD and PD patients from HCs	Statistical analysis models	Apparent performance	Alpha diversity could predict AD (Shannon index AUC = 0.77), but it was a poor predictor for PD (0.63).
Lubomski M, Xiangnan X, et al.	2022	Australia	Cross-sectional	103 PD patients, 81 Healthy Controls	16S rRNA gene sequencing of the V3-V4 region	Parkinson's Disease	To discriminate Parkinson's disease from healthy controls	Random Forest and Support Vector Machine (SVM)	Leave-one-out cross-validation	Genus-level microbiota data predicted PD with AUC = 0.71, improving to 0.74 with carbohydrate data. Other macronutrients did not improve performance.
Nie S, Wang J, et al.	2022	China	Meta-analysis	2505 samples total: 1495 PD, 1010 healthy control	16S rRNA gene sequencing (2269 samples) Shotgun metagenomic sequencing (236 samples)	Parkinson's Disease	Discriminate PD patients from healthy controls	3 machine learning methods: Logistic regression (LR) support vector machines (SVM) and random forests (RF)	Tenfold cross-validation	The optimal models used RF to predict PD using 11 genera (AUC = 0.87) or six genes related to inflammation (0.89).
Nishiwaki H, Ueyama J, et al.	2022	Japan	Cross-sectional	28 Dementia with Lewy Body (DLB) 224 Parkinson's Disease (PD) 26 Idiopathic rapid eye movement sleep behaviour disorder (IRBD) 147 Healthy Controls (HC)	16S rRNA gene sequencing of the V3-V4 region	Dementia with Lewy Body	Differentiate between DLB, PD, and controls	Random forest analysis	Nested cross-validation, Leave-one-out cross-validation for recursive feature elimination	Relative genera abundance could differentiate DLB from HCs (AUC = 0.82) and PD without cognitive decline (0.76), but not PD with cognitive decline (0.60).
Nishiwaki H, Ito M, et al.	2022	Japan	Longitudinal cohort	165 Parkinson patients at year 0 and year 2 Hoehn and Yahr Stage 1 = 24 Stage 2 = 85 Stage 3 = 56	16S rRNA gene sequencing of the V3-V4 regions	Parkinson's Disease	Predict the progression of PD in two years i.e. whether patients deteriorated or remained stable	Random forest analysis	Nested cross-validation, Leave-one-out cross-validation for recursive feature elimination	The microbiota-based model predicted early-stage Parkinson's disease progression (HY stage 1 AUC = 0.80), while clinical feature-based models performed better for advanced stages. Validation showed a maximum AUC of 0.87 for microbiota-based models and 0.64 for clinical feature-based models.
Pietrucci D, Teofani A, et al.	2020	Italy	Case-control	472 PD patients, 374 HCs	16S rRNA gene sequencing of the V3-V4 regions	Parkinson's Disease	Discriminate between PD patients and Healthy Controls	Three machine learning models: Random Forest (RF), Neural Network (NN), and Support Vector Machine (SVM)	Stratified cross-validation with K-fold = 5	The optimal model used RF with 22 bacterial families to predict PD, achieving AUC = 0.80 and 71% accuracy.

Table 3. continued

Authors	Year	Location	Type of Study	Sample size	Sequencing platform	Disease of Focus	Predictive Goal of Model	Type of model	Validation	Results of model
Qian Y, Yang X, et al.	2020	China	Case-control	Case-control cohort: 40 Idiopathic PD patients, 40 Healthy Spouses (HS) Validation cohort: 78 Independent Idiopathic PD patients, 75 healthy control (HC), 40 patients MSA patients, 25 AD patients	Shotgun metagenomic sequencing, validation: real-time PCR	Parkinson's Disease	To discriminate PD from HCs and PD from AD and MSA.	Support Vector Machine classifier	External validation (independent validation cohort with real-time PCR analysis)	A set of 25 gut microbial gene markers accurately differentiated PD from HCs (AUC = 0.91, validation cohort using real-time PCR) and also distinguished PD from MSA (AUC = 0.83) and AD (AUC = 0.88). Real-time PCR showed high sensitivity and specificity comparable to metagenomic sequencing, and performance was unaffected by disease severity or PD medications.
Scheperjans F, Aho V, et al.	2015	Finland	Case-control	72 PD patients and 72 controls.	16S rRNA gene sequencing of the V1-V3 regions	Parkinson's Disease	Discriminate PD patients from controls	Logistic regression classifier	Apparent performance	Using four bacterial families and constipation severity PD was identified with AUC = 0.83, 67% sensitivity, and 90% specificity.
Wang S, Li N, et al.	2019	China	Case-control	31 early-stage PD patients, 28 Healthy Controls	Shotgun metagenomic sequencing	Parkinson's Disease	Discriminate PD from healthy controls	Random forest classifier	Leave-one-out cross-validation method	The model could distinguish PD from HC using biosynthetic gene clusters (AUC = 0.91).
Zhang P, Huang P, et al.	2022	China	Cross-sectional	67 de novo PD patients, 54 Essential Tremor (ET) Patients, 54 Normal Controls (NC)	16S rRNA gene sequencing	Parkinson's Disease and Essential Tremor (ET)	Distinguish ET from PD	Statistical analysis models	Apparent performance	Relative and absolute abundance of four genera differentiated ET from PD with AUC = 0.76.
Zhang Y, He X, et al.	2022	China	Cross-sectional	Primary cohort: 101 PD patients (51 moderate responders, 50 good responders) External validation cohort: 43 PD patients	Quantitative real-time PCR	Parkinson's Disease	Predict levodopa responsiveness	Logistic regression analysis	10-fold cross-validation in the primary cohort, external validation cohort	TyrDC gene abundance could predict levodopa responsiveness in the primary cohort (AUC = 0.85) and external validation (AUC = 0.95).
Zuo S, Wang H, et al.	2023	China	Meta-analysis and validation study	Meta-analysis: 997 PD patients, 889 Healthy Controls (HC) Validation cohort: 39 PD patients, 39 HCs (spouses)	Meta-analysis: 16S rRNA gene sequencing Validation cohort: Shotgun metagenomic sequencing	Parkinson's Disease	Predict PD from healthy controls	Statistical analysis model	Meta-analysis and validation cohort with metagenomic sequencing	Higher abundance of a bacterial family predicted PD with AUC = 0.63, increasing to 0.71 at the species level.

**Table 4.** Summary Strengths, Limitations, and Recommendations for Future Research for studies on Parkinson's Disease and related conditions.

Authors	Year	Strengths and Limitations	Recommendations for Future Research
Bedarf J, Hildebrand F, et al.	2017	Strengths: Shotgun metagenomic sequencing provided detailed resolution of microbial differences at the species level (found altered representation of several taxa which had not been reported previously and might be limited to detection via metagenomics), Inclusion of only L-DOPA-naïve patients minimized confounding effects of medication Limitations: Small sample size, male participants only	<ul style="list-style-type: none"> <li>- Study SCFA gene expression and metabolomics</li> <li>- Explore viral involvement in PD</li> <li>- Assess impact of Parkinsonian medications in larger studies</li> <li>- Investigate gut barrier and immune function in PD patients</li> <li>- Integrate functional microbiome data to identify PD</li> </ul>
Du J, Huang P, et al.	2019	Strengths: Recruitment of healthy spouses as controls to minimize environmental and dietary differences. Limitations: cross-sectional design, small sample size, potential confounding factors not entirely eliminated, findings may not generalise to different geographical and ethnic populations	<ul style="list-style-type: none"> <li>- Validate current findings</li> <li>- Conduct longitudinal research on microbiota's role in MSA development</li> </ul>
Lecomte A, Duru I C, et al.	2023	Strengths: Comprehensive analysis of mobile genetic elements in the gut microbiota	
Li Z, Zhou J, et al.	2022	Strengths: Comprehensive analysis of alpha diversity across multiple neurological conditions; use of multiple alpha diversity indices Limitations: Lack of demographic data and basic characteristics of the disease (e.g. age, sex, BMI, diagnostic criteria), potential impact of diet and medications not fully addressed	<ul style="list-style-type: none"> <li>- Larger cohort studies accounting for confounders like diet and medications</li> <li>- Investigate links between microbiota changes and other biomarkers</li> </ul>
Lubomski M, Xiangnan X, et al.	2022	Strengths: Incorporation of diet to develop predictive models Limitations: Cross-sectional design, does not address confounders such as comorbidities and non-PD medication effects, PD and HC groups were non-optimally matched for age and sex due to spousal recruitment, data self-reported, potential selection bias as population was drawn from specialist PD clinics, patients from a single metropolitan area	<ul style="list-style-type: none"> <li>- Larger, more diverse cohorts with clinical and nutritional data</li> <li>- Standardise study designs to enable meta-analyses</li> <li>- Clarify whether elevated microbiota are compensatory or pathological in PD</li> <li>- Longitudinal studies/meta-analyses to explore causality, therapies, and improve early PD prediction models</li> </ul>
Nie S, Wang J, et al.	2022	Strengths: Largest meta-analysis to date on the gut microbiome in PD, combined 16S rRNA gene and shotgun metagenomic data, included samples from 7 different countries Limitations: Potential confounding factors such as diet, region, gender and sampling method not controlled	<ul style="list-style-type: none"> <li>- Inflammation may be a future therapeutic target for PD</li> </ul>
Nishiwaki H, Ueyama J, et al.	2022	Strengths: First report on gut microbiota in DLB, robust validation methods Limitations: Limited sample size of DLB patients, causality between gut microbiota changes and DLB not established, the way in which the PD group was recognised and assessed was not stated in the methods	<ul style="list-style-type: none"> <li>- Longitudinal analysis and larger sample size of DLB patients needed</li> </ul>
Nishiwaki H, Ito M, et al.	2022	Strengths: Robust validation methods Limitations: Lack of shared features between different stages might limit the generalizability of the findings, absence of MDS-UPDRS III Scores when patients' medication had worn off	
Pietrucci D, Teofani A, et al.	2020	Strengths: Integration of multiple datasets from multiple countries, use of state-of-the-art machine learning algorithms. Limitations: lack of standardization between included datasets	<ul style="list-style-type: none"> <li>- Increase sample size to train algorithm</li> <li>- Develop standardised data processing methods</li> <li>- Create a shared data network across laboratories for reliable PD diagnostics</li> </ul>
Qian Y, Yang X, et al.	2020	Strengths: First study to establish a gut microbial gene catalogue associated with Parkinson's disease, use of both metagenomic sequencing and real-time PCR validation, external validation cohort, spouses used to minimise influence of diet Limitations: Limited to a Chinese Han population	<ul style="list-style-type: none"> <li>- Validate gene markers in larger and more diverse cohorts using longitudinal studies</li> <li>- Include constipated control groups</li> </ul>
Scheperjans F, Aho V, et al.	2015	Strength: first study to compare the composition of the whole faecal microbiome between PD patients and controls Limitations: lack of dietary data for participants, case-control design limits the ability to determine casual relationships between the microbiome and PD, patients from limited geographical area	<ul style="list-style-type: none"> <li>- Assess protective vs. pathological roles of microbiota abundant in PD</li> <li>- Investigate temporal and causal links between microbiome changes and PD</li> <li>- Examine functional metabolic and immunological mechanisms involved in PD</li> </ul>

**Table 4.** continued

Authors	Year	Strengths and Limitations	Recommendations for Future Research
Wang S, Li N, et al.	2019	Strengths: Alternative method to analyse microbiota of PD patients Limitations: Relied on only one public data set, did not analyse meta-transcriptomic reads to check the expression levels of these (Biosynthetic Gene Clusters (BCGs))	- Further experimental validation of identified BGCs - Assess BGC expression using meta-transcriptomic data - Explore links between radical SAM and ageing-related diseases
Zhang P, Huang P, et al.	2022	Strengths: use of both relative and absolute abundance data, inclusion of de novo PD patients to eliminate medication effects Limitations: Cross-sectional nature, potential dietary impacts on microbiota, limited sample size	- Conduct large-scale, multi-population studies - Include dietary assessments - Use metagenomic sequencing and metabolite analysis for functional insights
Zhang Y, He X, et al.	2022	Strengths: Comprehensive analysis using cross-validation and external validation Limitations: Limited to Chinese Han population	- Investigate microbial genes and taxa involved in levodopa metabolism - Conduct multicentre studies with diverse populations - Explore personalised strategies to enhance levodopa bioavailability by modulating microbial decarboxylation pathways, such as downregulating <i>tyrDC</i> gene abundance
Zuo S, Wang H, et al.	2023	Strengths: Comprehensive meta-analysis with a large sample size, validation using a separate cohort with metagenomic sequencing Limitations: Potential statistical bias due to the hospital-based sample population, lack of transcriptomic and proteomic data, included studies all used 16S rRNA gene sequencing which may have variable results due to different primers, only meta-analysis data were used without raw data re-analysis	- Incorporate transcriptomic and proteomic analyses - Explore mechanisms linking elevated microbiota to PD pathogenesis - Conduct meta-analyses addressing current study limitations.

studies. Although this review did not include studies that solely used metabolites in predictive models, we came across some promising studies during the review process [49–51]. This area may be valuable for future scoping reviews to explore.

While these studies show promise, with most achieving an AUC considered good to excellent [18], several limitations need addressing. Many studies had small, non-diverse sample sizes, limiting the generalisability of their findings. Most studies were conducted in one location, but the gut microbiome may differ significantly across countries due to dietary and geographical factors [52]. While studies conducted in a single location are useful to avoid geographical confounders, multicentre studies with controlled variables can better explore whether microbiome changes are disease-related and produce findings with broader applicability. Two meta-analyses [47, 53] in this study used samples from multiple countries; however, primary studies with larger and more diverse cohorts are still needed. Similarly, diet influences the microbiome [54], and studies frequently noted they could be improved by including dietary assessments of participants in their analysis. Some studies attempted to control for diet by using patient's spouses as the healthy controls. Further, most studies were cross-sectional, limiting their ability to investigate the cause-effect relationship between gut dysbiosis and disease. Longitudinal studies are crucial to establish causality and track microbiome changes over time. Furthermore, significant methodological variation across studies, including differences in the incorporation of additional biomarkers and clinical inputs, limits comparability and hinders the ability to draw consistent conclusions for clinical application.

#### **Strengths and limitations of this review and implications for further research**

This scoping review adhered to the established JBI protocol and contributes valuable data to a novel area of research. To our knowledge, it is the first scoping review to map studies that use microbiome profiling-based predictive models for neuropsychiatric

conditions. However, the English-only focus may have excluded relevant studies in other languages, especially given the dominance of Chinese papers in this area. Additionally, due to the novelty of this field, some relevant studies might have been published during the review process. Another limitation is the exclusion of studies focused on relevant conditions but not elderly patients, as their findings might still be applicable to the elderly. There is also the possibility of publication bias, as studies showing predictive success may be more likely to be published, and this review only included published studies. Furthermore, there was considerable design heterogeneity across the selected studies, including variations in diagnostic standards and inputs to the models, which limits our ability to compare their results. Future reviews could focus on individual conditions to provide a more detailed comparison of the specific microbiota used in the models and their predictive importance. Moreover, this scoping review provides a framework for a future meta-analysis to formally determine the quality of these models and provide a quantitative summary of their performance. These findings underscore the potential of this research area and the need for further investigation.

#### **CONCLUSION**

There is a considerable amount of research on diagnostic and prognostic models for neuropsychiatric conditions in the elderly using microbiome profiling, showing promising results. To advance this field, a deeper understanding in the effect of gut microbiome on the metabolism of neurotransmitters and neuromodulators can provide the rationale for developing novel therapeutics interventions and precise diagnosis of neuropsychiatric conditions. Future research should prioritize longitudinal studies and expand profiling methods to incorporate metabolomics and other techniques. Once these results are validated in larger, more diverse cohorts, efforts can focus on translating these findings into clinical practice.

**Table 5.** Key characteristics of predictive studies focusing on geriatric depression and schizophrenia.

Authors	Year	Location	Type of Study	Sample size	Sequencing platform	Disease of Focus	Predictive Goal of Model	Type of model	Validation	Results of model
Chen Y, Le D, et al.	2024	China	Cross-sectional	29 patients with Late-Life Depression (LLD), 33 Healthy Controls (HCs)	16S rRNA gene sequencing of the V4 region	Late-life depression (LLD)	To differentiate LLD patients from healthy controls	Logistic regression analysis	Apparent performance	Combining gut microbiota and serum inflammatory cytokines could accurately differentiate LLD patients (AUC = 0.96). The combined model performed better than microbial (AUC = 0.75) or inflammatory (0.89) factors alone.
Kolobaric A, Andreescu C, et al.	2024	South Korea	Longitudinal cohort	268 total patients at baseline. Cognitive Dx: 17 SCD (Subjective Cognitive Decline), 189 MCI, 40 AD, 22 other dementia. Psychiatric Dx: 62 none, 124 Major Depression, 82 Minor Depression. 70 total patients at 2-year follow up. Cognitive Dx: 4 SCD, 55 MCI, 7 AD, 4 other dementia. Psychiatric Dx: 16 none, 25 with Major Dep, 29 Minor Dep.	16S rRNA gene sequencing of V3-V4 region	Depression, dementia	Predict current and future (2-years) cognitive function and depressive symptoms	Elastic net regression analysis	Cross-validation	Microbiota, clinical, and demographic data predicted current and 2-year cognitive and depressive outcomes, with out-of-bag correlation coefficients of 0.67 (future MMSE) and 0.56 (future SGDS-K).
Lee S, Dong T, et al.	2022	USA	Longitudinal cohort; secondary analysis of a parent randomized placebo-controlled trial	12 patients with Major Depressive Disorder at baseline: 4 on Levomilacipran (LVM), 8 on placebo. 5 remitters, 7 non-remitters.	16S RNA gene sequencing of the V4 region	Depression	Predict remission from depression following treatment	Random forest analysis	5-fold cross-validation	Pre-treatment microbiota predicted remission, with nine genera achieving an AUC of 0.86. Significant genus-level changes from baseline to post-treatment were seen in remitters but not in non-remitters.
Ling Z, Jin G, et al.	2022	China	Cross-sectional	90 hospitalised Schizophrenia patients, 71 Healthy Controls	16S rRNA gene sequencing of the V3-V4 region	Schizophrenia	Predict schizophrenia	Logistic regression analysis	Apparent performance	Gut microbiota distinguished hospitalised schizophrenia patients from healthy controls (AUC = 0.96).

**Table 6.** Summary of Strengths, Limitations, and Recommendations for Future Research for studies on geriatric depression and schizophrenia.

Authors	Year	Strengths and Limitations	Recommendations for Future Research
Chen Y, Le D, et al.	2024	Limitations: small sample size, no standardized diet among patients, cross-sectional study	- Larger longitudinal studies
Kolobaric A, Andreescu C, et al.	2024	Strengths: Large sample size, transdiagnostic approach, use of both cross-sectional and longitudinal data Limitations: Non-probabilistic sampling, predominantly female sample, limited generalizability to non-Korean populations, 16S rRNA sequencing limitations, potential need for longer follow-up to observe significant mood and cognition changes	- Longer-term studies using shotgun metagenomic sequencing - Develop predictive models to personalise treatment
Lee S, Dong T, et al.	2022	Strengths: first study to demonstrate that faecal microbiota could be a potential predictor of treatment response in geriatric depression Limitations: small sample size, high dropout rates	- Conduct larger studies to confirm findings and identify additional taxa - Compare microbiota of elderly patients with depression vs healthy controls - Routinely include faecal microbiome analysis in antidepressant trials - Explore using microbiome data to predict and personalise antidepressant treatment - Investigate microbial taxa as mediators or adjunct therapies for depression
Ling Z, Jin G, et al.	2022	Strengths: High coverage of bacterial identification, well-controlled participants, novel exploration of structural and functional dysbiosis of faecal microbiota in elderly SZ patients, identification of potential biomarkers for non-invasive diagnosis Limitations: Single-centre study, small sample size, limited resolution of bacterial species identification due to 16S rRNA gene V3-V4 regions. Potential confounding due to differences in hospitalisation status between schizophrenia cases and controls; control status not reported	- Metagenomic studies - Multicentre studies with larger cohorts - Investigate biological roles of key bacteria - Clinical studies on microbiota interventions

## REFERENCES

- Xie W, Zhong B, Liang L, Cai YS. Editorial: epidemiology and clinical researches on neuropsychiatric disorders in aging. *Front Psychiatry*. 2023;14:1108474.
- Taslim S, Shadmani S, Saleem AR, Kumar A, Brahma F, Blank N, et al. Neuropsychiatric disorders: bridging the gap between neurology and psychiatry. *Cureus*. 2024;16:e51655.
- Shusharina N, Yukhnenko D, Botman S, Sapunov V, Savinov V, Kamyshov G, et al. Modern methods of diagnostics and treatment of neurodegenerative diseases and depression. *Diagnostics*. 2023;13:573.
- Gauthier SG. Alzheimer's disease: the benefits of early treatment. *Eur J Neurol*. 2005;12(Suppl 3):11–6.
- Hugon P, Dufour JC, Colson P, Fournier PE, Sallah K, Raoult D. A comprehensive repertoire of prokaryotic species identified in human beings. *Lancet Infect Dis*. 2015;15:1211–9.
- Nikolova VL, Smith MRB, Hall LJ, Cleare AJ, Stone JM, Young AH. Perturbations in gut microbiota composition in psychiatric disorders: a review and meta-analysis. *JAMA Psychiatry*. 2021;78:1343–54.
- Cammann D, Lu Y, Cummings MJ, Zhang ML, Cue JM, Do J, et al. Genetic correlations between alzheimer's disease and gut microbiome genera. *Sci Rep*. 2023;13:5258.
- Chen G, Zhou X, Zhu Y, Shi W, Kong L. Gut microbiome characteristics in subjective cognitive decline, mild cognitive impairment and alzheimer's disease: a systematic review and meta-analysis. *Eur J Neurol*. 2023;30:3568–80.
- Knudsen K, Szwebs M, Hansen AK, Borghammer P. Gastric emptying in parkinson's disease - a mini-review. *Parkinsonism Relat Disord*. 2018;55:18–25.
- Savica R, Carlin JM, Grossardt BR, Bower JH, Ahlskog JE, Maraganore DM, et al. Medical records documentation of constipation preceding parkinson disease: a case-control study. *Neurology*. 2009;73:1752–8.
- Svensson E, Horváth-Puhó E, Thomsen RW, Djurhuus JC, Pedersen L, Borghammer P, et al. Vagotomy and subsequent risk of parkinson's disease. *Ann Neurol*. 2015;78:522–9.
- Kumari S, Taliyan R, Dubey SK. Comprehensive review on potential signaling pathways involving the transfer of  $\alpha$ -synuclein from the gut to the brain that leads to parkinson's disease. *ACS Chem Neurosci*. 2023;14:590–602.
- Borghammer P, Van Den Berge N, van LaarT. Brain-first versus gut-first parkinson's disease: a hypothesis. *J Parkinson's Dis*. 2019;9(s2):S281–S95.
- McGuinness AJ, Davis JA, Dawson SL, Loughman A, Collier F, O'Hely M, et al. A systematic review of gut microbiota composition in observational studies of major depressive disorder, bipolar disorder and schizophrenia. *Mol Psychiatry*. 2022;27:1920–35.
- Peters MD, Godfrey C, McInerney P, Munn Z, Tricco AC, Khalil H Scoping Reviews JBI. 2024. <https://synthesismanual.jbi.global>. (Accessed date 30 May 2024).
- Center for Open Science. Open Science Framework 2024. <https://osf.io>. (Accessed date 9 August 2024).
- Veritas Health Innovation. Covidence Systematic Review Software 2024. [www.covidence.org](http://www.covidence.org). (Accessed date 29 May 2024).
- Carter JV, Pan J, Rai SN, Galandiuk S. ROC-ing along: evaluation and interpretation of receiver operating characteristic curves. *Surgery*. 2016;159:1638–45.
- Xi J, Ding D, Zhu H, Wang R, Su F, Wu W, et al. Disturbed microbial ecology in alzheimer's disease: evidence from the gut microbiota and fecal metabolome. *BMC Microbiol*. 2021;21:226.
- Li Z, Zhou J, Liang H, Ye L, Lan L, Lu F, et al. Differences in alpha diversity of gut microbiota in neurological diseases. *Front Neurosci*. 2022;16:879318.
- Sheng C, Yang K, He B, Du W, Cai Y, Han Y. Combination of gut microbiota and plasma amyloid-beta as a potential index for identifying preclinical alzheimer's disease: a cross-sectional analysis from the SILCODE study. *Alzheimer's Res Ther*. 2022;14:35.
- Verhaar BJH, Hendriksen HMA, de Leeuw FA, Doorduijn AS, van Leeuwenstijn M, Teunissen CE, et al. Gut microbiota composition is related to AD pathology. *Front Immunol*. 2022;12:794519.
- Liu P, Wu L, Peng G, Han Y, Tang R, Ge J, et al. Altered microbiomes distinguish alzheimer's disease from amnesic mild cognitive impairment and health in a chinese cohort. *Brain Behav Immun*. 2019;80:633–43.
- Ferreiro AL, Choi J, Ryou J, Newcomer EP, Thompson R, Bollinger RM, et al. Gut microbiome composition may be an indicator of preclinical alzheimer's disease. *Sci Transl Med*. 2023;15:eabo2984.
- Li B, He Y, Ma J, Huang P, Du J, Cao L, et al. Mild cognitive impairment has similar alterations as Alzheimer's disease in gut microbiota. *Alzheimer's Dement : J Alzheimer's Assoc*. 2019;15:1357–66.
- Laske C, Müller S, Munk MHJ, Honold I, Willmann M, Peter S, et al. Prognostic value of gut microbiome for conversion from mild cognitive impairment to alzheimer's disease dementia within 4 years: results from the alzbiom study. *Int J Mol Sci*. 2024;25:1906.
- Wang L, Yan J, Liu H, Zhao X, Song H, Yang J. Predicting the rapid progression of mild cognitive impairment by intestinal flora and blood indicators through machine learning method. *Neurodegener Dis*. 2023;23:43–52.
- Duru IC, Lecomte A, Laine P, Shishido TK, Suppala J, Paulin L, et al. Comparison of phage and plasmid populations in the gut microbiota between Parkinson's disease patients and controls. *Scientific Reports (Nature Publisher Group)*. 2025;15:13723.

29. Wang S, Li N, Zou H, Wu M. Gut microbiome-based secondary metabolite biosynthetic gene clusters detection in parkinson's disease. *Neurosci Lett*. 2019;696:93–8.
30. Scheperjans F, Aho V, Pereira PAB, Koskinen K, Paulin L, Pekkonen E, et al. Gut microbiota are related to parkinson's disease and clinical phenotype. *Mov Disord*. 2015;30:350–8.
31. Lubomski M, Xu X, Holmes AJ, Muller S, Yang JY, Davis RL, et al. Nutritional intake and gut microbiome composition predict parkinson's disease. *Front Aging Neurosci*. 2022;14:881872.
32. Qian Y, Yang X, Xu S, Huang P, Li B, Du J, et al. Gut metagenomics-derived genes as potential biomarkers of parkinson's disease. *Brain: a J Neurol*. 2020;143: 2474–89.
33. Nishiwaki H, Ito M, Hamaguchi T, Maeda T, Kashihara K, Tsuboi Y, et al. Short chain fatty acids-producing and mucin-degrading intestinal bacteria predict the progression of early parkinson's disease. *Npj Parkinsons Dis*. 2022;8:65.
34. Zhang Y, He X, Mo C, Liu X, Li J, Yan Z, et al. Association between microbial tyrosine decarboxylase gene and levodopa responsiveness in patients with parkinson disease. *Neurology*. 2022;99:e2443–e53.
35. Du J, Huang P, Qian Y, Yang X, Cui S, Lin Y, et al. Fecal and blood microbial 16S rRNA gene alterations in chinese patients with multiple system atrophy and its subtypes. *J Parkinsons Dis Print*. 2019;9:711–21.
36. Nishiwaki H, Ueyama J, Kashihara K, Ito M, Hamaguchi T, Maeda T, et al. Gut microbiota in dementia with lewy bodies. *npj Parkinson's Dis*. 2022;8:169.
37. Zhang P, Huang P, Du J, He Y, Liu J, He G, et al. Specific gut microbiota alterations in essential tremor and its difference from parkinson's disease. *Npj Parkinsons Dis*. 2022;8:98.
38. Chen Y, Le D, Xu J, Jin P, Zhang Y, Liao Z. Gut microbiota dysbiosis and inflammation dysfunction in late-life depression: an observational cross-sectional analysis. *Neuropsychiatric Dis Treat*. 2024;20:399–414.
39. Kolobaric A, Andreescu C, Jasarevic E, Hong CH, Roh HW, Cheong JY. et al. Gut microbiome predicts cognitive function and depressive symptoms in late life. *Mol Psychiatry*. 2024;29:3064–75.
40. Lee SM, Dong TS, Krause-Sorio B, Siddarth P, Milillo MM, Lagishetty V, et al. The intestinal microbiota as a predictor for antidepressant treatment outcome in geriatric depression: a prospective pilot study. *Int Psychogeriatr*. 2022;34:33–45.
41. Ling Z, Jin G, Yan X, Cheng Y, Shao L, Song Q, et al. Fecal dysbiosis and immune dysfunction in chinese elderly patients with schizophrenia: an observational study. *Front Cell Infect Microbiol*. 2022;12:886872.
42. Cryan JF, O'Riordan KJ, Cowan CSM, Sandhu KV, Bastiaanssen TFS, Boehme M, et al. The microbiota-gut-brain axis. *Physiol Rev*. 2019;99:1877–2013.
43. McGorry PD, Hickie IB, Kotov R, Schmaal L, Wood SJ, Allan SM, et al. New diagnosis in psychiatry: beyond heuristics. *Psychol Med*. 2025;55:e26.
44. Wu S, Liu X, Jiang R, Yan X, Ling Z. Roles and mechanisms of gut microbiota in patients with alzheimer's disease. *Front Aging Neurosci*. 2021;ume 13:2021.
45. Elford JD, Becht N, Garssen J, Kraneveld AD, Perez-Pardo P. Buty and the beast: the complex role of butyrate in parkinson's disease. *Front Pharmacol*. 2024;ume 15:2024.
46. Alfonsi C, Pietro F, Papa F, Gabrielli F. Decoding microbial networks: an insight into 16S rRNA and whole genome sequencing approaches in metagenomic studies. *J Biomed Res Environ Sci*. 2023;4:1443–6.
47. Pietrucci D, Teofani A, Unida V, Cerroni R, Biocca S, Stefani A, et al. Can gut microbiota be a good predictor for parkinson's disease? a machine learning approach. *Brain Sci*. 2020;10:19.
48. Kubista M, Andrade JM, Bengtsson M, Forootan A, Jonák J, Lind K, et al. The real-time polymerase chain reaction. *Mol Asp Med*. 2006;27:95–125.
49. Wu L, Han Y, Zheng Z, Peng G, Liu P, Yue S, et al. Altered gut microbial metabolites in amnesic mild cognitive impairment and alzheimer's disease: signals in host-microbe interplay. *Nutrients*. 2021;13:228.
50. Lu L, Qin L, Zhao X, Liu Z, Qiu X, Yang S, et al. Metabolites of intestinal flora can be used as diagnostic and progressive markers for mild cognitive impairment. *Front Cell Infect Microbiol*. 2024;14:1351523.
51. Han Y, Quan X, Chuang Y, Liang Q, Li Y, Yuan Z, et al. A multi-omics analysis for the prediction of neurocognitive disorders risk among the elderly in macao. *Clin Transl Med*. 2022;12:e909.
52. Gupta VK, Paul S, Dutta C. Geography, ethnicity or subsistence-specific variations in human microbiome composition and diversity. *Front Microbiol*. 2017;8:1162.
53. Nie S, Wang J, Deng Y, Ye Z, Ge Y. Inflammatory microbes and genes as potential biomarkers of parkinson's disease. *Npj Biofilms Microbiomes*. 2022;8:101.
54. Zhang P. Influence of foods and nutrition on the gut microbiome and implications for intestinal health. *Int J Mol Sci*. 2022;23:9588.

## ACKNOWLEDGEMENTS

Special thanks to Jessica Green and Emma Todd from the Food and Mood Centre at Deakin University —Jessica for her initial advice on the topic and Emma for her comments on the manuscript.

## AUTHOR CONTRIBUTIONS

ET was involved in the design, execution of searches and writing of the manuscript. CL and RS contributed with editing and critical review of the manuscript. The double screening for abstracts and full-text articles was performed collectively by ET, CL and RS. Data extraction from included studies was carried out by ET, with a subset of the data undergoing double extraction by RS and subsequent review of data by CL to ensure accuracy and reliability.

## COMPETING INTERESTS

The authors declare no competing interests.

## ADDITIONAL INFORMATION

**Supplementary information** The online version contains supplementary material available at <https://doi.org/10.1038/s41398-025-03685-w>.

**Correspondence** and requests for materials should be addressed to Cristian E. Leyton.

**Reprints and permission information** is available at <http://www.nature.com/reprints>

**Publisher's note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.



**Open Access** This article is licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License, which permits any non-commercial use, sharing, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if you modified the licensed material. You do not have permission under this licence to share adapted material derived from this article or parts of it. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit <http://creativecommons.org/licenses/by-nc-nd/4.0/>.

© The Author(s) 2025