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META REVIEW

The Gut Microbiome Composition of Individuals with Alzheimer Disease and Related Dementia: Implications for Sub-Saharan Africa: A Systematic Review

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ABSTRACT

Background: Alzheimer's disease (AD) and Alzheimer's disease related dementias (ADRD) are emerging public health concerns in aging populations. Although evidence suggests that gut microbiome dysbiosis may be associated with AD, little is known about gut microbiome composition in sub-Saharan Africa, where adults aged 65+ years comprise approximately 2.7% of the population. This systematic review aimed to identify relevant studies on gut microbiota profiles in patients with AD and related cognitive conditions and to identify implications and research priorities for this region.

Methods: This systematic review was registered with PROSPERO (CRD42022354219). A systematic search of PubMed, Embase, and Scopus identified 344 records. After removal of duplicates and other ineligible records, 74 records underwent title and abstract screening, of which 22 were excluded. Fifty-two full-text reports were sought for retrieval; nine could not be retrieved, leaving 43 reports assessed for eligibility. Of these, 20 were excluded, and among the remaining 23 articles, four reviews, one opinion article, and one animal study were excluded. Seventeen original human studies met the eligibility criteria and were included in the final review.

Results: No eligible studies from sub-Saharan Africa were identified. The included studies, conducted in Asia, Europe, and North America, consistently reported differences in gut microbiome composition between individuals with AD or related cognitive conditions and cognitively healthy controls. Frequently reported alterations included increased relative abundance of *Proteobacteria, Verrucomicrobia*, and *Actinobacteria* with reduction in taxa such as *Bacteroides* reported in some studies. However, the specific microbial signatures varied across study populations, diagnostic categories and microbiome profiling methods.

Conclusion: Current evidence suggests that gut microbiome composition differs between individuals with AD and cognitively healthy controls, although reported microbial signatures remain heterogeneous. The absence of eligible studies from sub-Saharan Africa represents a major evidence gap. Region-specific studies are needed to determine whether gut microbiome patterns reported elsewhere are applicable to African populations and to inform future prevention, diagnostic and therapeutic research.

BACKGROUND

Globally, individuals aged ≥65 years comprise approximately 11% of the total population, and this proportion is expected to increase substantially in the coming decades.[1] In sub-Saharan Africa, older persons represent approximately 5% of the population, equivalent to about 43 million people, with further growth projected by 2030[2]. In Uganda, older adults account for approximately 2.7% of the population, and life expectancy has increased from approximately five decades to more than six decades within a relatively short period. Within this aging population, Alzheimer's Disease (AD) and Alzheimer's Disease-Related Dementias (ADRD) are emerging public health concerns because they contribute to cognitive decline, functional impairment, disability, caregiver burden, and increased demand for diagnostic and supportive health services[3]. In Uganda, these challenges are compounded by limited access to specialist diagnostic services and the under-recognition of dementia. A population-based study conducted in rural Uganda reported a dementia prevalence of 20% and identified increasing age, lower educational attainment, and poor kitchen ventilation as major associated factors.[4] These findings suggest that dementia is already a significant public health problem among older Ugandan adults, although AD-specific mechanisms and biomarkers remain under-studied.

The aetiology of AD is complex and multifactorial, involving genetic, environmental, metabolic, inflammatory, and lifestyle-related factors.[5] Studies suggest that gut microbiota, a diverse community of microorganisms found in the gastrointestinal tract, may play a role in the pathophysiology and development of AD/ADRD[6]. Investigations into the potential role of the gut microbiome in AD onset and progression have been driven by observed differences between the gut microbiomes of individuals with AD and cognitively healthy individuals.[7]

Studies conducted in Asia, Europe, and North America have reported differences in gut microbiome composition across the AD continuum, although findings are not fully consistent across regions.[8,9] Studies from Asian populations, particularly China, Taiwan, South Korea, Thailand, and Turkey, have commonly reported alterations involving the phyla *Proteobacteria*, *Actinobacteria*, *Verrucomicrobia*, *Firmicutes*, and *Bacteroidetes*, as well as families such as *Ruminococcaceae*, *Lachnospiraceae*, *Enterobacteriaceae*, and genera including *Bacteroides*, *Akkermansia*, *Lactobacillus*, *Bifidobacterium*, *Blautia*, *Escherichia-Shigella*, and Faecalibacterium.[8,10-13] Similarly, studies from Europe and North America have identified differences in microbial composition and short-chain-fatty-acid-producing taxa among individuals with AD and those with preclinical disease.[14-16] However, variations in study populations, diagnostic definitions, sequencing approaches, bioinformatic pipelines, and analytical methods have contributed to heterogeneity in reported findings. Collectively, these studies suggest that gut microbiome alterations may be associated with AD and related cognitive states, while highlighting the need to determine whether similar or distinct microbial patterns occur in African populations.

Several factors unique to sub-Saharan Africa may influence gut microbiome composition and limit the direct generalizability of findings from studies conducted in Europe, North America, and Asia. These include dietary patterns characterised by high-fibre traditional diets and fermented foods, sanitation and water exposure, infectious disease burden, antibiotic use, urbanisation, socioeconomic conditions, and host genetic diversity[17-21]. These factors may shape gut microbial diversity, inflammatory pathways, and the production of microbiome-derived metabolites, including short-chain fatty acids that influence the microbiota-gut–brain axis. Consequently, the scarcity of studies from sub-Saharan Africa represents an important evidence gap, particularly as the burden of AD and ADRD continues to increase across aging African populations.

Patients with AD have been reported to exhibit reduced abundance of potentially beneficial bacteria, including *Bifidobacterium* and *Faecalibacterium*, together with increased abundance of potentially pro-inflammatory bacteria, such as *Escherichia coli*.[22] These alterations, commonly referred to as gut microbial dysbiosis, may influence the microbiota–gut–brain axis, a bidirectional communication pathway linking the gastrointestinal tract and the central nervous system. The microbiota–gut–brain axis has therefore become an important area of investigation in neurodegenerative diseases.[23] Dysbiosis has been associated with altered gut microbial diversity, disruption of microbial metabolites, impaired intestinal barrier function and increased production of pro-inflammatory cytokines.

Growing evidence further links gut microbiota to inflammatory cytokines in AD. Alterations in gut microbial composition may promote immune activation and increase the production of inflammatory mediators, thereby activating immune cells in the brain and contributing to chronic neuroinflammation and neuronal injury[24]. Previous studies have shown that the gut microbiome can influence the production and release of inflammatory cytokines such as interleukin-1 beta, interleukin-6, and tumour necrosis factor-alpha in individuals with AD.[22,24-26] In addition, microbiome-derived metabolites may also affect brain function, microglial activation, neuroinflammation, blood–brain barrier permeability, amyloid-beta metabolism, and neurogenesis.[27-29] Together, these findings support the hypothesis that the gut microbiome may influence AD pathogenesis through interconnected immune, metabolic, and neuroinflammatory pathways.

Despite increasing interest in the gut microbiome–brain axis, the relationship between gut microbiome composition and AD/ADRD in African populations remains poorly characterised. Understanding gut microbiome patterns in African populations may provide region-specific insights into microbial signatures, inflammatory pathways, and environmental exposures that influence AD/ADRD risk and progression.

The specific problem addressed by this review is the lack of evidence regarding gut microbiome composition in AD and related dementia conditions among sub-Saharan African populations, including within the East African Community. Although studies from Asia, Europe, and North America suggest that gut microbiome dysbiosis is associated with AD and cognitive impairment, it remains unclear whether these findings are applicable to African populations. This uncertainty is important because dietary practices, fermented food consumption, infectious disease burden, sanitation and water exposure, antibiotic use, socioeconomic conditions, rural–urban residence, and host genetic diversity may shape gut microbiome composition differently in sub-Saharan Africa. Without regional evidence, it is difficult to determine whether microbial patterns reported elsewhere are relevant for disease prevention, diagnosis, or future microbiome-targeted interventions in African settings.

This systematic review was conducted in response to the increasing burden of AD and ADRD in aging African populations, the expanding international evidence linking gut microbiome dysbiosis to cognitive impairment, and the absence of synthesised evidence from sub-Saharan Africa. The review aimed to synthesize current evidence on gut microbiome composition in individuals with AD, mild cognitive impairment, preclinical AD, and related dementia conditions; summarize reported microbial alterations across studies; and identify evidence gaps and research priorities relevant to sub-Saharan Africa.

METHODS

Search Strategy

A systematic literature search was conducted in three electronic databases: PubMed, Embase, and Scopus, to

identify relevant studies published between January 1, 2013, and August 30, 2023. The search strategy combined controlled vocabulary and free text terms related to AD and the gut microbiome. Search terms included "Dementia," "Alzheimer's Disease," "Alzheimer Dementia," "Alzheimer Syndrome," "Alzheimer*," "Cognitive Impairment," "Gut microbiome*," "Gastrointestinal Microbiome," "Intestinal Microbiome," "Microbiome, intestinal," and "Microbiome, Gastrointestinal." The search strategy was adapted as appropriate for each database.

Records retrieved from the databases were imported into Endnote, where duplicate citations were identified and removed. Titles and abstracts were screened for relevance, followed by full-text assessment of potentially eligible studies. Reviews were excluded from the systematic analysis because they did not provide original data, however, they were considered in the Discussion where they contributed to understanding the possible role of gut microbiota in modulating cognitive function, AD physiopathology and underlying mechanisms. Only original human studies reporting gut microbiome composition were included in the final review.

Eligibility Criteria

Inclusion Criteria

Studies were included if they met the following criteria: (i) Original human studies reporting gut microbiome composition in individuals with AD, mild cognitive impairment (MCI), preclinical AD, or related dementia conditions; (ii) Included an appropriate comparison group, such as cognitively healthy controls, individuals with MCI, preclinical AD, or other cognitive categories along the AD continuum; (iii) Used gut microbiome profiling methods, including 16S rRNA gene sequencing, shotgun metagenomics sequencing, or metagenomic sequencing; (iv) Reported microbial taxonomic and/or functional differences between diagnostic groups; (v) Were full-text articles published in English between January 1, 2013, and August 30, 2023.

No geographical restrictions were applied during the search, screening, or eligibility assessment.

Exclusion Criteria

Studies were excluded if they were review articles, systematic reviews, meta-analyses, opinion pieces, editorials, commentaries, conference abstracts without full text publications, animal studies, non-English publications, or studies that did not contain original human gut microbiome data. Studies were also excluded if they did not include participants with AD, MCI, preclinical AD, or related dementia conditions, or if they did not assess gut microbiome composition.

Study Selection

All records identified through PubMed, Embase, and Scopus were imported into EndNote for duplicate removal. Study selection was performed in two stages. First, two reviewers independently screened titles and abstracts to identify potential eligible studies. Records were excluded at this stage if they clearly did not investigate AD, MCI, preclinical AD, related dementia conditions, or gut microbiome composition.

Second, full-text articles of potentially eligible studies were subsequently retrieved and independently assessed by the same two reviewers according to the prespecified inclusion and exclusion criteria. Disagreements were resolved through discussion, and unresolved discrepancies were referred to a third reviewer. The study selection process was documented using a Preferred Reporting Items for Systematic Reviews and meta-analyses (PRISMA) 2020 flow diagram.

Data Extraction

Data were extracted independently by two reviewers using a standardised, pre-piloted data extraction form. Extracted variables included the first author, year of publication, country of study, study design, sample size, study population, diagnostic category, comparison group, gut microbiome sample type, microbiome profiling method, sequencing approach, key microbial taxa reported as increased or reduced, taxonomic level of reported findings, and main study conclusions.

Diagnostic categories included AD, MCI, preclinical AD, cognitively unimpaired participants, cognitively normal participants, healthy controls, and other related cognitive states where reported. Microbiome findings were extracted according to the reported taxonomic level, including phylum, class, order, family, genus, and species.

Extracted data were entered into a structured data extraction sheet and cross-checked for completeness and consistency. Any discrepancies were resolved through discussion, with unresolved disagreements referred to a third reviewer. Extracted data were summarized narratively according to study characteristics, diagnostic comparisons, microbiome profiling methods, and reported taxonomic findings.

Quality Assessment

The methodological quality and risk of bias of the included studies were assessed independently by two reviewers using the Newcastle–Ottawa Scale (NOS) for observational studies. The assessment considered three main domains: selection of study participants, comparability of study groups, and ascertainment of exposure or outcome. For this review, quality assessment focused on whether diagnostic groups were clearly defined, whether control groups were appropriate, whether important confounders such as age and sex were considered, whether gut microbiome sampling and sequencing methods were adequately described, and whether microbial outcomes were reported transparently.

Two reviewers independently assessed the quality of each included study. Any disagreements were resolved through discussion, and unresolved discrepancies were referred to a third reviewer. Based on the overall NOS assessment, studies were categorised as having low, moderate, or high risk of bias.

Data Synthesis

A narrative synthesis was undertaken because of substantial heterogeneity across the included studies in terms of study populations, diagnostic criteria, sample sizes, microbiome profiling methods, sequencing platforms, bioinformatics pipelines, and reported taxonomic outcomes. Findings were summarized according to diagnostic comparisons, including AD versus cognitively healthy controls and

MCI versus cognitively healthy controls where applicable. Microbial alterations were synthesized by taxonomic level, including phylum, class, order, family, and genus. Because of methodological and clinical heterogeneity, quantitative meta-analysis was not considered appropriate. Instead, the review focused on identifying recurring patterns of gut microbiome alteration across studies and highlighting evidence gaps relevant to sub-Saharan Africa.

Ethical Considerations

This systematic review analysed data from previously published studies and did not involve direct human participation, collection of new data, or access to identifiable personal information. Consequently, ethical approval was not required. The review protocol was prospectively registered with the International Prospective Register of Systematic Reviews (PROSPERO; registration number CRD42022354219).

RESULTS

Literature Search

The study selection process is summarised in Figure 1. A total of 344 records were identified through searches of PubMed, Embase, and Scopus. After removing 270 duplicate records, 74 records remained for title and abstract screening. After screening, 22 records were excluded, and 52 reports were sought for full-text retrieval. Of these, 9 reports could not be retrieved, leaving 43 full-text articles for eligibility assessment. Of these, 20 were excluded because they did not meet the eligibility criteria. Among the remaining articles, 4 were review articles, one was an opinion article, and one was an animal study. Therefore, 17 studies were included in the final systematic review.

Characteristics of Included Studies

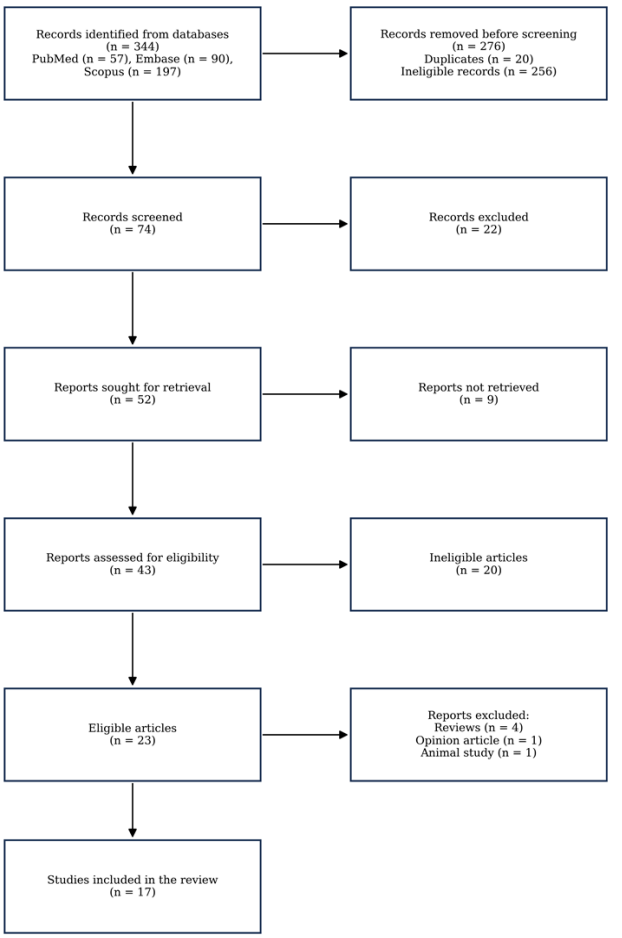
The characteristics of the included studies are presented in Table 1. Although no geographical restrictions were applied during the search, screening, or eligibility assessment, no eligible studies conducted in sub-Saharan Africa were identified. Consequently, all included studies originated from China, Taiwan, the USA, South Korea, Kazakhstan, Germany, Thailand, and Turkey. This geographical distribution demonstrates growing global interest in the relationship between gut microbiota and cognitive disorders, while also highlighting the absence of eligible evidence from sub-Saharan Africa.

Sample sizes ranged from 50 to 302 participants. Most studies used case-control designs, allowing comparison between individuals with AD, MCI, preclinical AD, or related cognitive conditions with cognitively healthy controls.

Gut microbiome composition was characterised using a variety of profiling methods, including 16S ribosomal RNA (16S rRNA) gene sequencing, metagenomic sequencing, and shotgun metagenomic sequencing. These methods differ in taxonomic resolution and functional characterisation, potentially contributing to variation in reported findings across studies.

The included studies reported gut microbiome differences across a range of cognitive categories, including AD, MCI, preclinical AD, and cognitively healthy controls. Reported microbial alterations involved several taxonomic levels, including phylum, class, order, family, genus, and species. However, some studies, including those by Ferreiro et al., Li et al., Ling et al., Sheng et al., Xi et al., Yıldırım et al., Zhou et al., Zhu et al., and Zhuang et al., reported microbial alterations in AD, MCI, or preclinical AD groups but did not consistently provide equivalent detail on taxa enriched or reduced among control groups. This inconsistency limited direct comparison across studies.

FIGURE 1: PRISMA Flow Diagram for Study Selection



Findings by Microbiome Profiling Method

Most included studies used 16S rRNA gene sequencing to characterise gut microbiome composition. Across these studies, individuals with AD, MCI, or preclinical AD showed differences in gut microbial composition compared with cognitively healthy controls. Commonly reported findings included increased relative abundance of taxa within Proteobacteria, Actinobacteria, Verrucomicrobia, Enterobacteriaceae, Erysipelotrichales, and Veillonellaceae, as well as genera such as *Escherichia-Shigella*, *Bacteroides*, *Akkermansia*, *Lactobacillus*, *Bifidobacterium*, and *Blautia*. Several studies also reported reduced abundance of Firmicutes, Bacteroidetes, Ruminococcaceae, Lachnospiraceae, Clostridia, and short-chain fatty acid-producing taxa producing genera

TABLE 1: Characteristics of Included Studies on Gut Microbiome Composition in Alzheimer's Disease and Related Cognitive Conditions

No.	Author, Year	Study design	Sample Size, Study Population	Methods	Country
1	Chen et al 2022 (L. Chen et al., 2022)	case control	40 controls 43 mild AD 89 moderate AD	16S rRNA	China
2	Fan et al 2023(Fan et al., 2023)	case control	31 cases 65 controls	16S rRNA	Taiwan
3	Ferreiro et al 2023(Ferreiro et al., 2023)	case control	69 controls 30 preclinical AD	metagenomic sequencing	USA
4	Jung et al 2022(Jung et al., 2022)	case control	18 Aβ+ CN 60 Aβ− CN	16S rRNA	South Korea
5	Kaiyrlykyzy et al 2022 (Kaiyrlykyzy et al., 2022)	case control	41 cases 43 controls	16S rRNA	Kazakhstan
6	Laske et al 2022(Laske et al., 2022)		75 AD cases 100 controls	shotgun metagenomics	Germany
7	Li et al 2019(B. Li et al., 2019)	case control	30 cases 30 MCI 30 normal	16S rRNA	China
8	Ling et al 2020(Ling et al., 2020)	case control	100 AD cases 71 controls	16S rRNA	China
9	Liu et al 2019(P. Liu et al., 2019)	case control	33 AD cases 32 aMCI 32 HC	16S rRNA	China
10	Marizzoni et al 2023 (Marizzoni et al., 2023)	case control	37 AD (CI-NAD) 13 (CU)	16S rRNA	USA
11	Sheng et al 2022(Sheng et al., 2022)	case control	4(CN-), 32 (CN+) 22 (CI) (11 MCI & 11 AD)	16S rRNA	China
12	Wanapaisan et al 2022 (Wanapaisan et al., 2022)	case control	(Normal; n = 20, MCI; n = 12, AD; n = 20)	16S rRNA	Thailand
13	Xi et al 2021(Xi et al., 2021)	case control	21 AD 44 controls	16S rRNA	China
14	Yıldırım et al 2022(Yıldırım et al., 2022)	case control	27 MCI, 47 AD, & 51 controls	16S rRNA	Turkey
15	Zhou et al 2021(Zhou, Wang, Quan, Zhao, & Jia, 2021)	case control	60 AD (30 with NPS & 30 without NPS) and 32 (HC) 16S	rRNA	China
16	Zhu et al 2022(Zhu et al., 2022)	case control	94 (NC), 125 MCI, and 83 AD	16S rRNA	China
17	Zhuang et al 2018 (Z. Q. Zhuang et al., 2018)	case control	43 AD cases 43 controls	16S rRNA	China

Note: AD, Alzheimer's disease; MCI, mild cognitive impairment; aMCI, amnestic mild cognitive impairment; Aβ, amyloid-beta; CN, cognitively normal; CN+, amyloid-beta-positive cognitively normal; CN−, amyloid-beta-negative cognitively normal; CI, cognitively impaired; CI-NAD, cognitively impaired non-Alzheimer's disease; CU, cognitively unimpaired; HC, healthy controls; NC, normal controls; NPS, neuropsychiatric symptoms; 16S rRNA, 16S ribosomal ribonucleic acid

such as *Faecalibacterium*. However, the direction and magnitude of these alterations varied across studies.

One study used metagenomic sequencing and reported that gut microbiome composition may differ in preclinical AD, with alterations involving genera such as *Formicigenerans*, *Oscillibacter*, *Faecalibacterium prausnitzii*, *Coprococcus catus,* and *Anaerostipes hadrus*. This approach provided greater resolution at species and functional levels compared with 16S rRNA sequencing.

One study used shotgun metagenomic sequencing and reported differences in gut microbial signatures between AD cases and cognitively healthy controls. Taxa enriched among AD cases included: *Moritella*, *Parabacteroides*, *Basfia*, *Arsenophonus*, *Acidothermus*, *Aureimonas*, Candidatus *Arthromitus,* and *Asaia,* whereas control groups showed enrichment of taxa such as *Aliivibrio*, *Propionibacterium*,

Orrella, *Veillonella*, *Mucinivorans*, *Paenarthrobacter*, *Plesiomonas*, *Roseovarius*, *Lactococcus*, and *Sulfuricella*. Overall, differences in sequencing approaches influenced the level of taxonomic and functional detail reported across studies, contributing to heterogeneity in findings.

Gut Microbiome Alterations in Alzheimer's Disease Compared with Controls

Table 2 summarizes gut microbiome alterations reported among individuals with AD compared with cognitively healthy controls. Across the included studies, reported differences involved multiple taxonomic levels, including phylum, class, order, family, genus, and species. Several studies reported increased abundance of taxa such as *Proteobacteria*, *Actinobacteria*, *Verrucomicrobia*, *Enterobacteriaceae*, *Escherichia-Shigella*, *Bacteroides*, *Akkermansia*, *Lactobacillus*, *Bifidobacterium*, and *Blautia* in AD groups.

Conversely, reduced abundance of *Firmicutes*, *Bacteroidetes*, *Ruminococcaceae*, *Lachnospiraceae*, *Clostridia*, and other short-chain-fatty-acid producing bacterial groups was reported in several studies. Nevertheless, the specific microbial alterations varied across study populations, sequencing methods and analytical approaches.

Gut Microbiome Alterations in Mild Cognitive Impairment and Preclinical Alzheimer's Disease

Table 3 summarises gut microbiome alterations reported among individuals with MCI or preclinical AD compared with cognitively healthy controls. These studies reported differences in several taxa, including *Proteobacteria*, *Verrucomicrobia*, *Actinobacteria*, *Negativicutes*, *Flavobacteriales*, *Gemellaceae*, *Saccharimonadaceae*, *Veillonellaceae*, *Erysipelotrichales*, and *Saccharimonadales*. Some findings overlapped with those reported in AD, suggesting that gut microbiome alterations may occur across the cognitive impairment continuum.

Control groups were more frequently characterised by taxa such as *Ruminococcus*, *Butyricimonas*, *Oxalobacter*, *Clostridium sensu stricto 1*, *Fusicatenibacter*, *Lachnospiraceae*, *Agathobacter*, *and Faecalibacterium*. However, substantial heterogeneity remained across study populations, diagnostic definitions, microbiome profiling methods, and reporting approaches.

Quality Assessment

The quality assessment showed variability in methodological quality across the included studies. Most studies clearly described diagnostic criteria and gut microbiome profiling methods. However, several studies had limitations related to small sample size, incomplete reporting of control-group characteristics, limited adjustment for potential confounders, and heterogeneity in sequencing methods and bioinformatics approaches. Overall, most studies were classified as having low-to-moderate or moderate risk of bias according to the Newcastle-Ottawa Scale. These methodological differences were considered during interpretation of the findings and supported the decision to perform a narrative synthesis rather than a quantitative meta-analysis (Table 4).

TABLE 4: Summary of Quality Assessment and Risk of Bias of Included Studies

No.	Study	Study design	Overall risk of bias	Main concerns
1	Chen et al., 2022	Case-control	Moderate	Potential residual confounding; group comparability
2	Fan et al., 2023	Case-control	Moderate	Limited generalizability; confounder adjustment
3	Ferreiro et al., 2023	Case-control/ preclinical AD	Low-to-moderate	Preclinical AD definition differs from clinical AD
4	Jung et al., 2022	Case-control/ preclinical AD	Moderate	Small subgroup sizes
5	Kaiyrlykyzy et al., 2022	Case-control	Moderate	Sample size and population-specific generalizability
6	Laske et al., 2022	Case-control	Low-to-moderate	Participant heterogeneity
7	Li et al., 2019	Case-control	Moderate	Modest sample size; potential confounding
8	Ling et al., 2020	Case-control	Moderate	Sequencing/reporting heterogeneity
9	Liu et al., 2019	Case-control	Low-to-moderate	Residual confounding; generalizability
10	Marizzoni et al., 2023	Case-control	Moderate	Small comparison groups; clinical heterogeneity
11	Sheng et al., 2022	Cross-sectional/ case-control	Moderate	Small subgroup numbers; preclinical classification
12	Wanapaisan et al., 2022	Case-control	Moderate	Small sample size
13	Xi et al., 2021	Case-control	Moderate	Modest sample size; confounder adjustment
14	Yıldırım et al., 2022	Case-control	Low-to-moderate	Population-specific generalizability
15	Zhou et al., 2021	Case-control	Moderate	Subgroup heterogeneity
16	Zhu et al., 2022	Case-control	Low-to-moderate	Diagnostic-group heterogeneity
17	Zhuang et al., 2018	Case-control	Moderate	Modest sample size; limited confounder adjustment

AD, Alzheimer's disease; MCI, mild cognitive impairment; NOS, Newcastle–Ottawa Scale.

TABLE 2: Gut Microbiome Alterations in Alzheimer's Disease Compared with Controls

No.	Study	Country	Microbiome Method	Comparison	Reported taxonomic level	Increased in AD / cognitive impairment	Reduced in AD / cognitive impairment
1	Chen et al., 2022	China	16S rRNA sequencing	AD vs cognitively healthy controls	Phylum	Proteobacteria; Verrucomicrobia; Actinobacteria	Firmicutes; Bacteroidetes
2	Kaiyrlykyzy et al., 2022	Kazakhstan	16S rRNA sequencing	AD vs controls	Mixed: phylum, class, lineage, genus	Acidobacteriota; Latescibacterota; Verrucomicrobiota; Synergistota; Planctomycetota; Zixibacteria; Blastocatellia; Synergistia; Vicinamibacteria; Pla4; Phycishaerae; Akkermansia; Niastella; Oxalobacter; Prevotella; Flavobacterium	Clostridia; Bacteroidia; Gammaproteobacteria; Actinobacteria; Bifidobacterium; uncultured Clostridia bacterium; Castellaniella; Erysipelotrichaceae; Roseburia; Tuzzerella; Lactobacillaceae-related genera
3	Laske et al., 2022	Germany	Shotgun metagenomics	AD vs controls	Genus	Moritella; Parabacteroides; Basfia; Arsenophonus; Acidothermus; Aureimonas; Candidatus Arthromitus; Asaia	Not reported
4	Li et al., 2019	China	16S rRNA sequencing	AD vs controls	Genus	Lactobacillus; Akkermansia; Dorea; Bifidobacterium; Streptococcus; Acinetobacter; Blautia	Parabacteroides; Alistipes; Bacteroides; Alloprevotella; Haemophilus; Paraprevotella; Succinivibrio; Sutterella; Prevotella; Barnesiella; Butyricimonas
5	Ling et al., 2020	China	16S rRNA sequencing	AD vs controls	Phylum	Actinobacteria; Verrucomicrobia	Firmicutes
6	Liu et al., 2019	China	16S rRNA sequencing	AD vs aMCI/ controls	Mixed: phylum, class, order, family, genus	Proteobacteria; Bacteroidetes; Enterobacteriales; Enterobacteriaceae; Gammaproteobacteria	Firmicutes; Ruminococcaceae; Blautia; Clostridiaceae
7	Sheng et al., 2022	China	16S rRNA sequencing	Cognitive impairment/ AD continuum vs controls	Phylum/class	Bacteroidetes	Firmicutes; Deltaproteobacteria
8	Wanapaisan et al., 2022	Thailand	16S rRNA sequencing	AD vs controls	Genus/family	Escherichia-Shigella; Bacteroides; Holdemanella; Romboutsia; Megamonas	Not reported
9	Xi et al., 2021	China	16S rRNA sequencing	AD vs controls	Genus	Faecalibacterium; Pseudomonas	Not reported

Continue

TABLE 2: Continued

No.	Study	Country	Microbiome Method	Comparison	Reported taxonomic level	Increased in AD / cognitive impairment	Reduced in AD / cognitive impairment
10	Yıldırım et al., 2022	Turkey	16S rRNA sequencing	AD continuum vs controls	Mixed: phylum, genus, family	Proteobacteria; Prevotella; Bacteroides; Ruminococcaceae	Not reported
11	Zhou et al., 2021	China	16S rRNA sequencing	AD vs controls	Genus	Bifidobacterium; Sphingomonas; Lactobacillus; Blautia	Odoribacter; Anaerobacterium; Papillibacter
12	Zhu et al., 2022	China	16S rRNA sequencing	AD vs controls	Mixed: family, order, phylum, class	Erysipelatoclostridiaceae; Erysipelotrichales; Patescibacteria; Saccharimonadales; Saccharimonadia	Not reported
13	Zhuang et al., 2018	China	16S rRNA sequencing	AD vs controls	Family/class	Ruminococcaceae	Negativicutes; Lachnospiraceae

Note: AD, Alzheimer's disease; HC, healthy controls; 16S rRNA, 16S ribosomal ribonucleic acid.

TABLE 3: Gut Microbiome Alterations in Mild Cognitive Impairment or Preclinical Alzheimer's Disease Compared with Controls

No.	Study	Country	Microbiome Method	Comparison	Reported taxonomic level	Increased/found in MCI or preclinical AD	Increased/ found in controls
1	Chen et al., 2022	China	16S rRNA sequencing	MCI vs controls	Phylum	Proteobacteria; Verrucomicrobia; Actinobacteria	Proteobacteria Verrucomicrobia, & Actinobacteria
2	Fan et al., 2023	Taiwan	16S rRNA sequencing	MCI vs controls	Mixed: order, family, genus	Negativicutes; Flavobacteriales; Gemellaceae; Saccharimonadaceae; Phocea; Gemella; Anaeroglobus; Cloacibacillus; Lactococcus; Flavonifractor; Lactiplantibacillus; Cetobacterium; Eubacterium fissicatena	Oxalobacteraceae; Ruminococcus; Butyricimonas; Oxalobacter
3	Ferreiro et al., 2023	USA	Metagenomic sequencing	Preclinical AD vs controls	Genus/species	Formicigenerans; Oscillibacter sp.; Faecalibacterium prausnitzii; Coprococcus catus; Anaerostipes hadrus	Not reported

Continue

TABLE 3: Continued

No.	Study	Country	Microbiome Method	Comparison	Reported taxonomic level	Increased/found in MCI or preclinical AD	Increased/ found in controls
4	Jung et al., 2022	South Korea	16S rRNA sequencing	Aβ+ cognitively normal vs Aβ− cognitively normal	Genus/family	Not reported	Controls showed slight Megamonas, Serratia, Leptotrichia, and Clostridium
5	Liu et al., 2019	China	16S rRNA sequencing	aMCI vs controls	Family	Veillonellaceae	Not reported
6	Marizzoni et al., 2023	USA	16S rRNA sequencing	Cognitively unimpaired/ control comparison	Class/genus/ family	Not reported	Clostridia; Eubacterium; Collinsella
7	Wanapaisan et al., 2022	Thailand	16S rRNA sequencing	MCI/AD vs normal controls	Genus/family	Not reported for MCI in extracted table	Clostridium sensu stricto 1; Fusicatenibacter; Lachnospiraceae; Agathobacter; Faecalibacterium
8	Zhu et al., 2022	China	16S rRNA sequencing	MCI vs controls	Mixed: family, order, phylum, class	Erysipelatoclostridiaceae; Erysipelotrichales; Patescibacteria; Saccharimonadales; Saccharimonadia	Not reported

Note: AD, Alzheimer's disease; MCI, mild cognitive impairment; CU, cognitively unimpaired; CN, cognitively normal; Aβ, amyloid-beta; 16S rRNA, 16S ribosomal ribonucleic acid.

DISCUSSION

The stability and composition of the gut microbiome are crucial to human health, and alterations in its composition may contribute to neurological conditions such as AD. Research suggests that AD may be associated with gut microbiome dysbiosis, characterised by an imbalance in the composition and function of the gut microbial community.[30] Across the studies included in this review, differences in gut microbiome composition between individuals with AD and cognitively healthy controls were consistently reported, although the specific microbial taxa identified varied between studies. Chen et al. reported a notable increase in the abundance of *Proteobacteria*, *Verrucomicrobia*, and *Actinobacteria* among individuals with AD compared with cognitively healthy controls.[31] These findings indicate a distinct microbial profile in individuals with AD and suggest that alterations in the gut microbiome composition may be associated with disease development or progression.

Furthermore, other studies have identified differences in bacterial classes and lineages between cases and controls. Kaiyrlykyzy et al. reported differences in *Acidobacteria*, *Latescibacterota*, *Verrucomicrobiota*, and *Synergistota*.[32] These findings suggest that AD may be associated with dysbiosis of multiple bacterial classes and lineages, indicating broader disruption of the gut microbiome. Moreover, specific genera such as *Formicigenerans*, *Oscillibacter sp.*, *Faecalibacterium prausnitzii*, *Coprococcus catus*, *and Anaerostipes hadrus*, were more prevalent in cases than in controls.[14] These genera may play a role in the pathogenesis of AD or serve as potential biomarkers for the condition. The differences in the gut microbiome composition between patients with AD and controls suggest dysregulation of the microbial community in individuals with the disease. This dysregulation may have implications in the pathogenesis and progression of AD. Furthermore, the association between gut microbiome changes and AD has been supported by studies that have correlated these changes with specific pathological biomarkers. Overall, these findings highlight the potential role of the gut microbiome in AD and suggest that targeting the gut microbiota could be a promising avenue for future therapeutic interventions and diagnostic approaches for AD.

In summary, the reviewed studies indicate that individuals with AD have distinct gut microbial profiles compared with healthy individuals. These differences include an increase in specific bacterial taxa, such as *Proteobacteria*, *Verrucomicrobia*, and *Actinobacteria*, and a decrease in others, such as *Bacteroides*. This dysbiosis in gut microbiome composition may be associated with the development or progression of AD.

There is a significant lack of research on the role of the gut microbiome in AD in sub-Saharan Africa, which has important implications for understanding and addressing neurodegenerative disorders. Without research studies on the gut microbiome in AD that have been conducted specifically in sub-Saharan Africa, there is a dearth of information about the potential role of gut microbial imbalances in the emergence and progression of this disease within the local population. This lack of understanding hinders the development of region-specific interventions for diagnosis, prevention, and treatment.

One of the most important findings of this review is the absence of eligible studies from sub-Saharan Africa despite the absence of geographic restrictions during the literature search. This represents a major evidence gap in the current literature. Although dementia and AD-related research has been conducted in Uganda and other African settings, studies integrating cognitive diagnosis with gut microbiome profiling remain lacking. Consequently, it is currently unknown whether the gut microbiome patterns reported elsewhere are applicable to sub-Saharan African populations.

The absence of eligible studies from sub-Saharan Africa does not diminish the importance of the current evidence, rather it highlights the need for region-specific research. Gut microbiome composition is influenced by various factors, including diet, lifestyle, host genetics, infectious diseases, antibiotic use, and environmental exposures. Because these factors differ substantially between African and non-African populations, gut microbiome composition and its potential role in AD may also differ. Without research specific to the sub-Saharan African populations, it is challenging to determine the relevance and impact of gut microbial alterations on AD within this context, potentially leading to missed opportunities for targeted interventions and therapeutics. Furthermore, studying the gut microbiome in sub-Saharan Africa may provide novel insights and potential biomarkers specific to the population, which could aid development of locally relevant diagnostic and preventive strategies.

Research Priorities for Sub-Saharan Africa

The absence of eligible studies from sub-Saharan Africa highlights the need for regionally grounded research on the gut microbiome–brain axis in AD and related dementias. First, population-based studies are needed to describe gut microbiome composition among older adults with AD, MCI, and cognitively healthy controls in African settings. Such studies should comprehensively assess dietary patterns, medication use, antibiotic exposure, comorbidities, sanitation, socioeconomic factors, and rural–urban residence, as these factors may substantially influence gut microbial diversity and function.

Second, longitudinal studies are needed to determine whether gut microbiome alterations precede cognitive decline, occur during disease progression, or reflect shared environmental and lifestyle exposures. Integrating microbial profiling with cognitive assessments, clinical diagnosis, inflammatory biomarkers, and metabolite measurements may provide greater insights into the biological pathways linking gut microbial dysbiosis to neuroinflammation and cognitive impairment.

Third, future studies should validate microbial, inflammatory, and metabolite biomarkers in African populations rather than assuming direct transferability of findings from other regions. Finally, intervention studies examining diet, fermented foods, probiotics, antibiotics, or other microbiome-modifying exposures are needed to determine whether modulation of the gut microbiome can contribute to the prevention or supportive management of AD and related dementias in sub-Saharan Africa.

Limitations

This review has several limitations. First, publication bias cannot be excluded because studies reporting significant gut microbiome differences may have been more likely to be published than studies reporting null results. Second, the review was limited to English-language publications, which may have excluded relevant studies published in other languages. Third, substantial heterogeneity in study design, participant characteristics, diagnostic criteria, sequencing methods, bioinformatics pipelines, reported taxonomic levels, and outcome measures precluded a quantitative meta-analysis; therefore, findings were summarised narratively.

Fourth, heterogeneity in microbiome profiling methods may have affected comparability across studies. Most studies used 16S rRNA sequencing, while others used metagenomic or shotgun metagenomic sequencing. These approaches differ in taxonomic resolution, ability to detect functional pathways, and sensitivity to differences in sample processing and analytic methods. Finally, the absence of eligible studies from sub-Saharan Africa limits the direct applicability of the findings to African populations where diet, environment, infectious exposures, antibiotic use, socioeconomic conditions, and genetic diversity may influence gut microbiome composition differently.

CONCLUSION

This systematic review found that individuals with AD and related cognitive conditions often show differences in gut microbiome composition compared with cognitively healthy controls. Reported alterations involved multiple bacterial taxa such as Proteobacteria, Verrucomicrobia, Actinobacteria, Bacteroidetes, Firmicutes, and several bacterial genera, although considerable heterogeneity existed across study populations, diagnostic groups, sequencing methods, and analytic approaches.

Despite growing global interest in the microbiota-gut–brain axis, no eligible studies from sub-Saharan Africa were identified. This represents an important evidence gap because gut microbiome composition is influenced by region-specific dietary, environmental, infectious, socioeconomic, and genetic factors. Consequently, findings from studies conducted in Asia, Europe, and North America may not be directly generalisable to African populations.

Future research in sub-Saharan Africa should prioritise population-based studies characterising gut microbiome profiles among older adults with AD, MCI, and cognitively healthy controls; longitudinal studies to determine whether microbiome changes precede or follow cognitive decline; validation of microbial, inflammatory, and metabolite biomarkers in African populations; and intervention studies examining microbiome-targeted approaches, including dietary modification, fermented foods, antibiotics, probiotics, and other microbiome-modifying strategies. Such studies will help determine the relevance of the gut microbiome to AD in African settings and support the development of context-specific prevention, diagnostic, and therapeutic strategies.

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