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Review

Fecal Microbiota Transplantation in Alzheimer's Disease: A Scoping Review of Human, Registry, and Preclinical Evidence

Jiayi Xu[1#], Zhiwen Cao[2,3#], Yansong Liu[2,3*], Aibo Gao[2,3*], Yanyan Kong[1*]

[1]Department of Nuclear Medicine & PET Center, Huashan Hospital, Fudan University, Shanghai, China. [2]Department of Endocrine and Metabolic Diseases, Shanghai Institute of Endocrine and Metabolic Diseases, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China. [3]Shanghai National Clinical Research Center for Metabolic Diseases, Key Laboratory for Endocrine and Metabolic Diseases of the National Health Commission of the PR China, Shanghai National Center for Translational Medicine, Shanghai, China.

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ABSTRACT: Fecal microbiota transplantation (FMT) is being explored as a microbiota-directed intervention for Alzheimer's disease (AD), with evidence drawn mainly from preclinical studies. This scoping review mapped published human reports, registered trials and animal microbiota-transfer studies to inform FMT research in AD. Five human reports, eight unique registered trials and 34 animal studies were included. Four human reports concerned FMT administered for *Clostridioides difficile* infection (CDI). The remaining report was an uncontrolled five-patient pilot comprising two patients with AD, two with mild cognitive impairment (MCI) and one with frontotemporal dementia (FTD). It described maintained cognition in AD and FTD and improvement or maintenance in MCI. The published human studies were nonrandomized. Among the eight registered trials, two required AD biomarker confirmation and two specified donor-referenced engraftment outcomes. Among 30 animal studies assessing cognition, 24 reported positive findings and six mixed findings. Restriction to genetic/transgenic AD models reduced the positive proportion from 24/30 (80.0%) to 17/23 (73.9%). Cognition-specific randomization and blinding were reported in 16/30 (53.3%) and 4/30 (13.3%) studies, respectively. The evidence supports early-phase investigation, with attention to donor and product characterization, appropriate comparators, and separate measurement of engraftment, microbial function, systemic responses and AD outcomes. Safety data remain insufficient for patients with AD, particularly outside the CDI setting. FMT should remain investigational for AD.

Keywords: Alzheimer's disease, fecal microbiota transplantation, gut-brain axis, gut microbiota, scoping review

INTRODUCTION

Alzheimer's disease (AD) is the most common neurodegenerative dementia, and its core pathology comprises amyloid-beta (Aβ) deposition, tau pathology and neurodegeneration [1, 2], often operationalized through the amyloid/tau/neurodegeneration (AT(N)) biological framework. Beyond these core lesions, AD is accompanied by synaptic dysfunction, neuro-inflammation, cerebrovascular and blood-brain barrier injury, metabolic disturbance and peripheral immune abnormalities [1]. Recent anti-amyloid immunotherapies, such as lecanemab and donanemab, can slow clinical decline in selected patients with early symptomatic AD [3, 4]. Their use depends on biomarker confirmation, careful eligibility screening and active safety monitoring [3-5]. Alongside amyloid-directed treatment, the involvement of immune, metabolic and barrier

***Correspondence should be addressed to:** Dr. Yanyan Kong (Email: ykong11@fudan.edu.cn), Department of Nuclear Medicine & PET Center, Huashan Hospital, Fudan University, Shanghai, China. Dr. Aibo Gao (Email: aibogao@shsmu.edu.cn) and Dr. Yansong Liu (Email: 392082868@qq.com), Department of Endocrine and Metabolic Diseases, Shanghai Institute of Endocrine and Metabolic Diseases, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China. #These authors contributed equally to this work.

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dysfunction in AD has prompted investigation of other therapeutic approaches. FMT is being explored for its potential to modify these processes through changes in the gut microbiota [6, 7].

The gut microbiota communicates bidirectionally with the central nervous system through microbial metabolites, intestinal barrier integrity, peripheral immune activation, neuroendocrine signaling and the vagus nerve [8, 9]. Differences in gut microbial composition have been observed between patients with AD and cognitively normal older adults [10]. Animal FMT studies suggest that microbiota transfer can influence Aβ pathology, neuroinflammation, barrier function and behavioral phenotypes [11, 12]. Although FMT and microbiota-based therapeutics have been most clinically developed in recurrent *Clostridioides difficile* infection (CDI) [13-15], their relevance to AD remains far less defined. This is the rationale for considering FMT in AD, but it is also the source of its complexity. Unlike a single-strain probiotic or a defined metabolite intervention, FMT transfers a complex mixture of microorganisms and other stool-derived constituents. The same feature that makes it mechanistically broad—its potential to reshape community ecology, metabolite production, barrier integrity, and immune signaling—also makes causal attribution, engraftment verification, product standardization, and clinical reproducibility difficult [6, 15, 16].

Previous reviews have addressed microbiota-related mechanisms and therapeutic approaches in AD [17], including reviews specifically focused on FMT [6, 7]. The literature spans CDI-context human exposure reports, a small non-CDI cognition-targeted pilot, registered trial plans and animal transfer experiments. These sources address different clinical and mechanistic questions and require separate interpretation.

We therefore mapped published human observations, registered trial designs and animal transfer experiments separately. The objectives were to describe the populations and comparisons studied, summarize cognitive and biological findings, and identify the measurements and design features needed for clinical translation. AD-specific findings were distinguished from evidence in broader dementia or cognitive-impairment populations.

MATERIALS AND METHODS

Because the eligible literature comprised heterogeneous source types rather than comparable efficacy trials, we used a scoping-review approach and synthesized the findings descriptively [18]. The review followed the five-stage framework of Arksey and O'Malley [19], the Joanna Briggs Institute (JBI) guidance for scoping reviews [20, 21], and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) guideline [22] (Supplementary information, Appendix 1). The protocol was registered prospectively on the Open Science Framework (https://doi.org/10.17605/OSF.IO/GH7YS). The published-human eligibility criteria were narrowed after registration, and the registry eligibility criteria were specified more explicitly, to distinguish AD-linked longitudinal clinical observations from broader cognitive-disorder trial plans. The final eligibility criteria are provided in Supplementary information, Appendix 3. Because the objective was to map evidence types and design implications rather than to estimate a pooled treatment effect, no meta-analysis was undertaken.

Identifying the research question

The review question was: what published human, registered-trial, and animal evidence exists for FMT in AD or AD-relevant cognitive impairment, and what inferences can each source type support?

Identifying relevant sources

We searched bibliographic databases and public trial registries from inception to September 29, 2026. Published human reports were searched in PubMed, Embase via Ovid, Web of Science, and the Cochrane Central Register of Controlled Trials. Animal studies were searched in PubMed, Embase via Ovid, Web of Science, and Scopus. Registered trials were searched in ClinicalTrials.gov, the Chinese Clinical Trial Registry (ChiCTR), and the World Health Organization International Clinical Trials Registry Platform (WHO ICTRP). Human and animal literature searches used English-language terms; Chinese-language terms were used only in trial-registry searches. CNKI, WanFang and SinoMed were not searched. Full search strategies are provided in Supplementary information, Appendix 2.

Inclusion and exclusion criteria

Eligible published human reports explicitly identified FMT recipients with a reported clinical diagnosis of AD and provided standardized cognitive or dementia-related functional assessments before and after FMT. Mixed diagnostic cohorts were eligible when AD participation was documented. The actual indication for FMT was recorded separately; CDI-directed administration did not itself preclude inclusion. Findings in other diagnostic groups and aggregate findings from mixed cohorts were retained at the reported level as contextual evidence and

were not attributed to the AD subgroup. Reports without explicitly identified AD recipients or qualifying longitudinal assessments were excluded. Eligible registry records described trials designed to evaluate FMT or whole-microbiota transfer as an investigational intervention for AD, dementia or cognitive impairment, including studies with safety, feasibility, engraftment or mechanistic objectives. Studies enrolling participants with and without AD were eligible when designed to inform FMT development for AD. Broader dementia or cognitive-impairment registrations provided contextual evidence and were not treated as AD-specific trials. Trials recruiting patients because they already required FMT for another clinical indication were excluded irrespective of whether cognitive outcomes were planned. Animal studies used genetic/transgenic AD models or other AD-relevant models and tested FMT or whole-microbiota transfer with cognitive, pathological or mechanistic outcomes. Reviews, editorials, conference abstracts without full data, probiotic- or prebiotic-only interventions, unrelated animal models, and recolonization studies designed primarily to restore pathology after microbial depletion were excluded. Detailed eligibility criteria and model definitions are provided in Supplementary information, Appendix 3.

Bibliographic records were imported into Rayyan for deduplication and screening. Two reviewers screened titles, abstracts and potentially eligible full texts; disagreements were resolved by consensus. Registry records were checked against their primary entries. Two WHO ICTRP mirrors were identified by matching registry identifiers and counted with their primary registrations. Publications were linked to registry identifiers when the relationship was reported. Registered plans, actual enrollment, current status and published results were charted as distinct fields.

Data charting

Two reviewers charted data using a predefined form, resolving discrepancies by consensus. Human-study items included design, diagnostic basis, actual FMT indication, reported sample, comparator, concomitant treatment, product, recipient preparation, route, dose, schedule, follow-up, and cognitive, biological and safety observations. Comparisons and measurement times were recorded explicitly. Registry extraction distinguished planned procedures and endpoints from actual enrollment and public results. Donor variables included age, sex, genotype, health or disease status, medication and antibiotic exposure, diet, metabolic status, donor number and pooling. Animal extraction additionally recorded recipient model, sex, transfer context, experimental units and the comparison eligible for therapeutic synthesis. Study-level extraction data are provided in Supplementary Information, Tables S1–S6; coding rules are specified in Appendix 4.

Collating, summarizing and reporting the data

Sources were synthesized separately as human reports, registered trials and animal studies. Animal transfer designs were classified as direct animal-donor transfer, transfer from intervention-conditioned animal donors, or human-donor transfer into animals. Recipient models were classified independently as genetic/transgenic AD models or other AD-relevant models. We summarized cognition both by transfer design and after restriction to genetic/transgenic models.

Each animal study contributed once to a given outcome domain within its eligible therapeutic comparisons. Reported directions were classified as Positive, Mixed, No statistically significant difference, Negative or Unclear. Mixed indicates significant favorable and adverse findings, or favorable and explicitly nonsignificant findings across distinct eligible comparisons, cognitive tasks or experimental conditions. Within a biological outcome domain, nonsignificant individual markers or regional measures did not alone determine a mixed classification. Nonsignificance required an explicit statistical statement; missing statistics did not qualify. Outcome interpretation was based primarily on explicit statements in the Results text for the eligible FMT comparisons. Descriptive wording alone was not treated as evidence of statistical significance, and omnibus tests were not substituted for pairwise FMT comparisons. Not assessed denoted an unmeasured outcome, NR an unreported result or detail, and Unclear unresolved assessment, comparison or direction. Outcomes with unclear direction remained in the assessed denominator; uncertain assessment did not. Coverage and positive proportions were descriptive, without effect-size pooling or quality weighting.

A structured methodological reporting inventory recorded donor screening, random allocation, blinding, cage or batch control, post-FMT timing, tolerability, and allocation and analysis units (Supplementary Table 4). Overall and cognition-specific randomization and blinding were recorded separately. Yes required explicit reporting within the stated experimental scope; NR did not establish that a procedure was absent. We did not calculate a quality score or conduct a formal risk-of-bias assessment. These reporting features informed interpretation of the findings.

RESULTS

Study selection

The evidence map comprised five published human reports, eight unique registered trials and 34 animal studies. Bibliographic selection is shown in Figure 1. The registry search yielded ten hits: three ClinicalTrials.gov records, five ChiCTR records and two WHO ICTRP mirrors of NCT07332260 and ChiCTR2100045955. Removal of these mirrors left eight trials. The Chen et al. pilot publication was linked to ChiCTR2100043548 and was not counted as an additional registered trial [23].

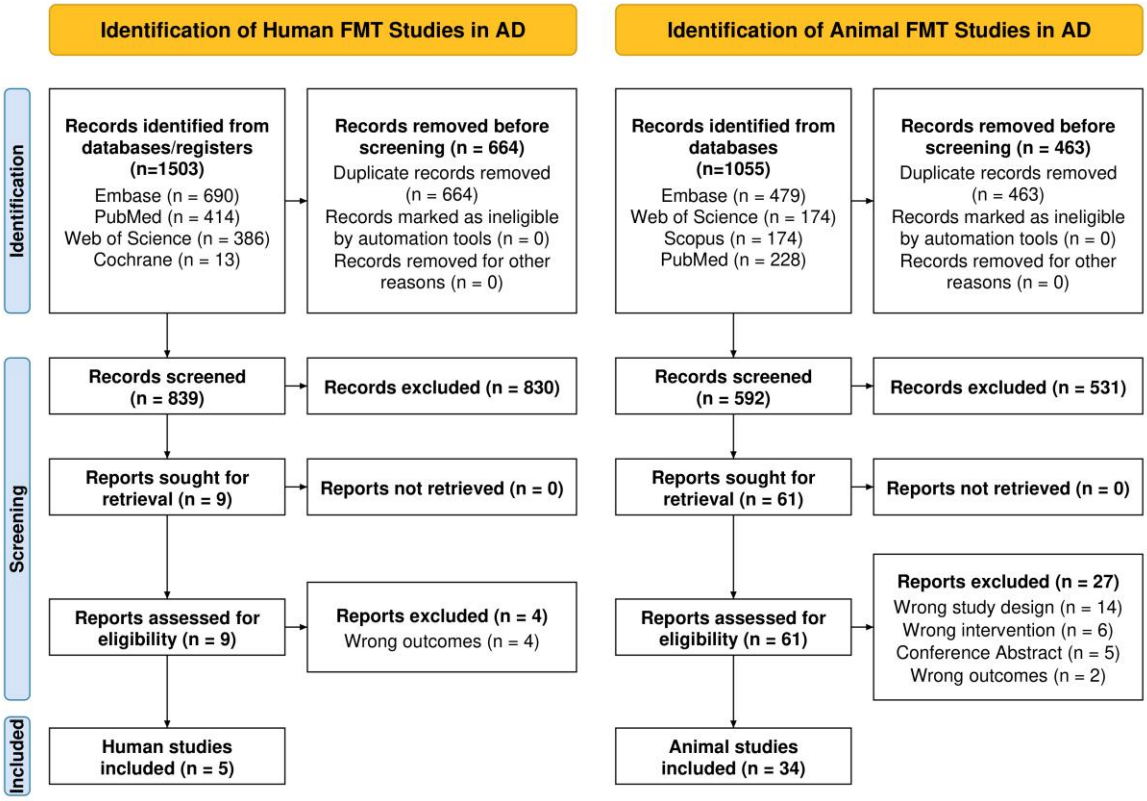


Figure 1. PRISMA-ScR flow diagram. Parallel selection of human and animal FMT studies from database inception to September 29, 2026. Five human reports and 34 animal studies were included. Registered trials were identified and deduplicated separately. FMT, fecal microbiota transplantation; PRISMA-ScR, Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews

Published human evidence

Five human reports were included (Table 1; Supplementary Table 1) [23-27]. Four described patients receiving FMT for recurrent, severe or relapsed CDI: two case reports, one prospective matched observational study and one uncontrolled case series. The matched study included ten FMT recipients with dementia, including documented AD and vascular dementia, and ten antibiotic-treated controls (Park et al., 2022) [26]. The Kim et al. case series analyzed five of 14 patients after six were lost to follow-up and three had unsuitable fecal samples [27]. The fifth report was a cognition-directed, single-arm pilot in five patients: two with AD, two with MCI and one with frontotemporal dementia (FTD; Chen et al., 2023) [23].

The CDI reports described improvements on serial cognitive assessments, including Mini-Mental State Examination (MMSE) scores of 20 at baseline and 29 at six months in Hazan's case [24], and median scores of 11 and 17 at baseline and three months in Kim et al. (2024) [27]. In Park et al. (2022), median MMSE increased from 10 to 16 and Clinical Dementia Rating–Sum of Boxes (CDR-SB) decreased from 10 to 5.5 at one month in FMT recipients [26]. These tests compared follow-up with baseline; they did not estimate the between-group treatment effect. In the non-CDI pilot, the reported improvements or maintenance in MCI and maintenance in

AD/FTD were described separately, without an AD-specific inferential estimate [23].

All five reports were nonrandomized, and none assessed an AD-specific biomarker response. Cognitive changes during CDI treatment occurred alongside gastrointestinal recovery and other treatment changes. Follow-up ranged from one to six months, with serial assessments and repeat FMT differing between reports. Transient gastrointestinal symptoms were reported in some studies; adverse-event ascertainment was incomplete in others. These samples were insufficient to estimate common or rare harms in patients with AD.

Table 1. Published human FMT studies involving AD or related cognitive impairment.

Study/design/n	Population/FMT indication	FMT regimen	Cognitive/functional findings	Safety/interpretation
Hazan, 2020 [24]; case report; n = 1.	Clinical AD; recurrent CDI. Aβ/tau confirmation: NR.	Single 300-mL infusion; route NR in primary report.	MMSE 20 → 26 (2 months) → 29 (6 months); uncontrolled observation.	AE assessment and results: NR. CDI recovery, antibiotics and AD medication limit attribution.
Park et al., 2021 [25]; case report; n = 1.	Clinical AD; severe refractory CDI, recurrent at 3 months.	Colonoscopy; 60 g per FMT × 2, about 3 months apart.	MMSE 15 → 20; CDR 1 → 0.5 by about 3 months; both stable 1 week after FMT2.	Nausea after FMT1; no side effects reported after FMT2. Uncontrolled; CDI/antibiotic confounding.
Park et al., 2022 [26]; prospective matched observational cohort; 10 FMT vs 10 antibiotic-only controls.	Dementia (AD and vascular dementia documented); severe/recurrent CDI.	Colonoscopy; 60 g/300 mL; one FMT (n = 9), two (n = 1).	At 1 month: FMT median MMSE 10 → 16 and CDR-SB 10 → 5.5 (within-group P = 0.005 each). Controls: MMSE 14 → 10 and CDR-SB 10 → 8 (both within-group changes NS).	No SAEs reported; minor AEs reported.
Kim et al., 2024 [27]; uncontrolled longitudinal case series; n = 5 analyzed.	Clinical AD; relapsed/severe CDI. Aβ/tau confirmation: NR.	Colonoscopy; 60 g/300 mL.	Medians at baseline → 1 → 3 months: MMSE 11 → 16 → 17; MoCA 12 → 17 → 21; CDR-SB 10 → 5.5 → 5.5. Friedman tests significant; CDR-SB changes from 1 to 3 months NS.	No SAEs reported; transient nausea and abdominal pain reported. Attrition and CDI/antibiotic confounding.
Chen et al., 2023 [23]; open-label single-arm pilot; n = 5; ChiCTR2100043548.	Clinical diagnoses: 2 AD, 2 MCI, 1 FTD; cognitive impairment (non-CDI).	40 oral capsules/dose (1 g fecal mixture/capsule), every 2 weeks × 3.	At 6 months: MCI scores improved/maintained; the 2 AD patients and the FTD patient were described as maintaining cognition. No AD-specific inferential effect estimate.	No AEs or SAEs reported. Registered 12-month primary-endpoint results: NR in this pilot report.

Five reports; four concern CDI-directed FMT. Observations refer to the stated comparisons and follow-up. Recipient and donor details are provided in Supplementary Table 1.

AD, Alzheimer's disease; AE/SAE, adverse/serious adverse event; Aβ, amyloid-β; CDI, *Clostridioides difficile* infection; CDR, Clinical Dementia Rating; CDR-SB, Clinical Dementia Rating–Sum of Boxes; FMT, fecal microbiota transplantation; FTD, frontotemporal dementia; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; NR, not reported; NS, no statistically significant difference.

Registered trials

Eight unique trials were registered in Norway, the United States and China (Table 2; Table S2). Five targeted AD, one allowed participants with or without AD (NCT03998423), and two targeted broader cognitive-impairment or dementia populations (ChiCTR2200065110 and ChiCTR2100043548). Two trials required molecular evidence of AD: Core 1 biomarker positivity in NCT07332260 and amyloid positron emission tomography (PET) positivity in ChiCTR2200055932. Two were randomized placebo-controlled studies (ChiCTR2200055932 and ChiCTR 2300078857). NCT03998423 randomized participants among FMT dosing regimens without a non-FMT control. The remaining studies were single-arm or nonrandomized controlled designs or did not report randomization.

Five records specified oral capsules, including one that also permitted nasoduodenal suspension; one specified colonoscopic infusion, one gastroscopic or colonoscopic infusion, and one did not report the route.

Six of eight records listed a microbiota-related endpoint, but only two specified donor-referenced engraftments (NCT07332260 and NCT03998423). These donor-referenced measures did not explicitly specify longitudinal donor-strain tracking. Primary outcomes included safety and feasibility, microbiota measures, and cognitive or functional scales, with different measurement schedules. NCT06920212 listed both cognitive/functional scales and microbiota composition as primary outcomes.

The records listed four trials as recruiting, one as active but not recruiting, one as not yet recruiting, one as terminated and one without a reported status. NCT03998423 enrolled five participants and was terminated because of potential severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) transmission through FMT despite screening; its public record did not identify an observed trial-associated infection. ChiCTR2100043548 was linked to the five-patient, six-month Chen et al. pilot, whereas the registration planned 30 participants and a 12-month Alzheimer's Disease Assessment Scale-Cognitive Subscale (ADAS-Cog) endpoint [23]. The pilot was not a completed report of that registered endpoint. No other public trial results were identified.

Table 2. Registered FMT trials targeting AD or cognition.

Registry/country	Population	Phase/design/ comparator	Planned/actual n	Primary endpoints/timing	Status
NCT07332260 (Norway)	AD; Core 1 biomarker positive	Phase 1; single-arm; open-label.	10/NR	Safety, engraftment: 3 months; feasibility: 3 months/1 year	Recruiting
ChiCTR2200055932 (China)	Mild AD; amyloid PET positive	NA; randomized; placebo; five roles masked.	160 / NR	ADAS-Cog 13: weeks 0-72	Recruiting
NCT03998423 (USA)	With or without clinical AD	Phase 1; randomized FMT schedules; open-label.	30 / 5	Safety, feasibility, engraftment: up to 1 year	Terminated
NCT06920212 (China)	Clinical/imaging AD	NA; single-arm; open-label.	30 / NR	Cognition/function and microbiota: baseline, months 1, 2, 3, 6	Active, not recruiting
ChiCTR2100045955 (China)	Clinical AD; men	NA; FMT + basic therapy vs basic therapy; allocation/ masking NR.	60 / NR	CDR: timing NR	Recruiting
ChiCTR2300078857 (China)	Clinical AD	NA; randomized; placebo; double-blind.	20 / NR	CDR: baseline, days 7, 30, 90, 180	Not yet recruiting
ChiCTR2200065110 (China)	Broad cognitive impairment	NA; nonrandomized; FMT + usual care vs donepezil.	60 / NR	ADAS-Cog, MoCA: timing NR	Recruiting
ChiCTR2100043548 (China)	Dementia	NA; single-arm; masking NR.	30 / NR	ADAS-Cog: 12 months	NR

Entries describe plans. No public results were identified except the Chen et al. (2023) pilot linked to ChiCTR2100043548 (5 patients, 6 months); full 12-month results remain NR. NCT03998423 stopped to minimize potential SARS-CoV-2 transmission despite screening. Further trial details are provided in Supplementary Table 2.

AD, Alzheimer's disease; ADAS-Cog (13), Alzheimer's Disease Assessment Scale-Cognitive Subscale (13-item); CDR, Clinical Dementia Rating; ChiCTR, Chinese Clinical Trial Registry; FMT, fecal microbiota transplantation; MoCA, Montreal Cognitive Assessment; NA, not applicable; NR, not reported; PET, positron emission tomography; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Preclinical animal evidence

The 34 animal studies comprised T1 (direct animal-donor transfer; n = 12) [11, 12, 28-37], T2 (transfer from intervention-conditioned animal donors; n = 18) [38-55] and T3 (human-donor transfer into animal recipients; n = 4) [56-59]. T1 studies examined age, phenotype or disease-related donor contrasts; T2 studies tested transfer after an upstream dietary, exercise, drug or natural-product intervention; and T3 studies examined cross-species transfer from human donors. Genetic/transgenic AD models accounted for 26 studies. Other models comprised senescence-accelerated mouse prone 8 (SAMP8; n = 1), Aβ injection (n = 4), combined D-galactose and Aβ injection (n = 1), AlCl3/D-galactose (n = 1) and scopolamine-induced impairment (n = 1). Twenty-two studies used only male recipients, five only female recipients, five both sexes, and two did not report recipient sex. Two of the five studies using both sexes

explicitly reported a 1:1 balance. Oral gavage or intragastric administration was reported in 31 studies, and three did not report the route (Supplementary Table 3). Within eligible therapeutic comparisons, cognition was assessed in 30 studies: 24 were classified as Positive and six as Mixed; none was classified as Negative, No statistically significant difference or Unclear (Table 3; Supplementary Table 6). Adverse findings in disease-donor or normal-recipient reference experiments were mapped separately in Supplementary Table 3. Positive cognitive findings predominated among published studies, although the proportion fell from 24/30 (80.0%) overall to 17/23 (73.9%) when restricted to genetic/transgenic AD models. All six Mixed studies were in the genetic/transgenic stratum. The other-model stratum contained seven assessed studies, all classified as Positive. Across transfer designs, positive proportions were 7/10 for T1, 16/17 for T2 and 1/3 for T3.

Endpoint coverage varied. Favorable directions were reported in 20/23 studies assessing Aβ pathology, 11/13 assessing tau pathology, 10/12 assessing neuronal, synaptic or neurotrophic outcomes, 21/24 assessing brain inflammation or glial markers, and 9/9 assessing barrier-related outcomes. The remaining assessed studies had mixed, nonsignificant or unclear findings. Recipient microbiota were profiled in 21 studies, metabolites measured in 12, and lipopolysaccharide measured in six. Comparisons, compartments, endpoint coverage and directions are detailed in Supplementary Table 3; microbial and metabolite findings are presented in Supplementary Table 5.

Random allocation and blinding within any reported FMT experimental scope were recorded in 21/34 and 7/34 studies. Within the cognitive experiments, the corresponding counts were 16/30 and 4/30. Donor screening and cage or batch control were each explicitly reported in one study, with assay-specific qualifications retained. Seven of 34 studies described assessment timing after FMT cessation, and six of 34 reported tolerability-related observations or basic monitoring, including body-weight tracking (Supplementary Table 4). Such reporting did not necessarily constitute systematic adverse-event assessment.

Table 3. Cognitive findings by animal transfer design and recipient model.

Evidence stratum	Studies, n	Cognition assessed, n	Cognitive direction, n Positive / Mixed / NS / Negative / Unclear	Positive / assessed, n (%)
T1: direct animal-donor transfer	12	10	7 / 3 / 0 / 0 / 0	7/10 (70.0%)
T2: intervention-conditioned animal donors	18	17	16 / 1 / 0 / 0 / 0	16/17 (94.1%)
T3: human donors	4	3	1 / 2 / 0 / 0 / 0	1/3 (33.3%)
All studies	34	30	24 / 6 / 0 / 0 / 0	24/30 (80.0%)
Genetic/transgenic AD models	26	23	17 / 6 / 0 / 0 / 0	17/23 (73.9%)
Other AD-relevant models	8	7	7 / 0 / 0 / 0 / 0	7/7 (100.0%)

Transfer tiers and model categories classify the same 34 studies and are not additive.
Each study contributes once within its eligible therapeutic comparisons. Positive indicates significant favorable findings without an adverse or Mixed pattern. Direction definitions and coding rules are provided in Supplementary Information, Appendix 4. Assessed-but-Unclear studies remain in the denominator; four studies did not assess cognition.
Positive proportions describe reported direction, not effect size or evidence strength. Cognition-specific randomization and blinding were reported in 16/30 and 4/30 assessed studies, respectively (Supplementary Table 4). Domain coverage: Supplementary Table 3.
AD, Alzheimer's disease; NS, no statistically significant difference.

DISCUSSION

The central translational question is whether modifying the gut microbiota can produce reproducible biological and clinical responses in a defined AD population. The human observations and animal experiments provide a rationale for early-phase studies of feasibility, product delivery, biological responses and safety. FMT should not be used to treat AD outside rigorously controlled clinical trials.

Interpretation of clinical and preclinical evidence

The indication for FMT is central to interpreting the human findings. Relief of severe or recurrent CDI can change nutrition, hydration, systemic illness and medication exposure, all of which may influence cognitive testing. Serial score improvements in this setting cannot isolate an AD treatment effect. Diagnostic composition also matters: observations in MCI or FTD should not be attributed to an AD subgroup, and stable scores in an uncontrolled AD cohort cannot show whether

decline was slowed [23]. These distinctions favor trials with a clearly defined AD population, stable background treatment and a concurrent comparator.

The precautionary termination of NCT03998423 highlights the need for trial procedures that can adapt to emerging infection risks. Protocols should define how screening is updated, material is quarantined, donor batches are traced to recipients and dosing is paused when the risk assessment changes. Such safeguards are relevant to trial continuity as well as participant safety.

Animal transfer designs address complementary questions. T1 studies test donor-community effects under defined recipient conditions. T2 studies test whether intervention-associated phenotypes can be transferred; residual compounds and other fecal constituents may contribute alongside living organisms. T3 studies incorporate human donor variation, with engraftment and microbial function influenced by host filtering, recipient-species biology and diet [60, 61]. Positive cognitive findings were most frequent in T2 studies (16/17), which test intervention-associated transfer rather than the efficacy of a standardized healthy-donor FMT product. These descriptive proportions do not provide a head-to-head comparison of transfer strategies.

The lower consistency of favorable findings after restriction to genetic/transgenic models emphasizes the importance of recipient-model selection. Acute Aβ exposure, pharmacological impairment and accelerated senescence capture selected features rather than the full course of AD, so their findings should not carry the same disease-specific interpretation. Model restriction is a descriptive sensitivity analysis; it does not resolve selective publication or incomplete reporting. The low frequency of cognitive blinding further limits confidence in the apparent consistency.

Donor, recipient and product considerations

Donor phenotype varied substantially across studies. Human reports included an 85-year-old spouse donor [24] as well as young adult donors [25], while animal studies contrasted donor age, genotype, disease status or intervention exposure. Donor replication also differed: Chevalier et al. used one human donor per phenotype [56], Zou et al. one donor overall [58], and Soriano et al. pooled cecal material from three donors of each sex [32]. When recipients share the same donor or pool, increasing recipient numbers do not increase independent donor-level replication. Similarly, sections or image fields from one animal are subsamples, and shared cages can introduce dependence (Table S4).

Recipient antibiotic pretreatment was reported in 27/34 studies, including the supplementary therapeutic FMT experiment in Kim et al. (2020) [12]. Among these studies, antibiotic exposure was matched in the eligible comparator in 18, unmatched in five and unclear in four. Antibiotics can alter microbial ecology, immune signaling, metabolism and behavior before FMT is given [62, 63]. Matched pretreatment supports interpretation of donor contrasts. Marizzoni et al. (2025) compared FMT alone with microbiota transfer therapy (MTT), which combined FMT with antibiotics, a laxative and a proton-pump inhibitor. In recipients of human-donor microbiota, the combined regimen reduced Aβ40-positive plaque counts relative to FMT alone [59]. This comparison estimates the combined preparation effect; the contribution of antibiotics requires separate testing. Clinical protocols should justify pretreatment and account for its tolerability and biological effects.

Safety requires particular attention in older adults with AD. Frailty, swallowing impairment and polypharmacy may alter tolerance of preparation and delivery; relevant risks include aspiration and complications of endoscopy or sedation [15]; delirium should also be considered in prospective safety monitoring. Drug-microbiome interactions may be bidirectional: medications can alter microbial composition [64], while microbial metabolism can change drug exposure [65]. Concomitant medications and treatment changes should therefore be recorded alongside cognitive and safety assessments. Prospective monitoring should capture infection, gastrointestinal symptoms, delirium, falls, hospitalizations and treatment changes, with surveillance extending beyond dosing.

As a biological product, FMT requires controls for pathogen transmission, potential transfer of antimicrobial-resistance genes and manufacturing consistency. Donor screening and product testing should accompany standardized collection, processing, storage and release criteria, with batch-to-recipient traceability [15]. Reported transmission of multidrug-resistant organisms in the wider FMT literature illustrates the need for these controls [66]. Defined microbial consortia or live biotherapeutic products could improve control of composition and manufacturing [67], although their efficacy and safety in AD and their comparability with conventional FMT require direct study.

Measurements and design priorities for early trials

Early studies should specify the clinical stage and biological definition of AD, characterize the donor product, and use a comparator that addresses procedural burden and background treatment. Apolipoprotein E (APOE) genotype may inform stratification or exploratory analyses of effect modification. Safety, feasibility and evidence of product delivery are appropriate initial objectives; an AD efficacy claim

requires a suitable controlled design and a prespecified clinical outcome.

Early trials should distinguish four measurement domains: engraftment, microbial function, systemic biological responses, and downstream central nervous system or clinical outcomes (Fig. 2). Engraftment concerns the acquisition and persistence of donor-associated strains in serial recipient samples [16]. Microbial function can be assessed through expression [68], activity or metabolite measurements, whereas gene content and inferred pathways describe functional potential. Systemic responses may provide evidence of target engagement when their relationship to a prespecified target or pathway is established. Downstream outcomes comprise central nervous system and AD biomarkers, cognition and daily function. Reference donor-product samples and serial recipient samples should be collected before treatment, during or at the end of dosing, and after treatment to assess persistence. Metabolite and host-response measurements should use prespecified compartments and time points, with prespecified longitudinal analyses examining relationships across domains. An appropriately controlled comparison with follow-up suited to the efficacy question is needed to determine whether biological responses are accompanied by cognitive or functional benefit. Undetected donor strains should be interpreted alongside exposure, sampling and assay sensitivity.

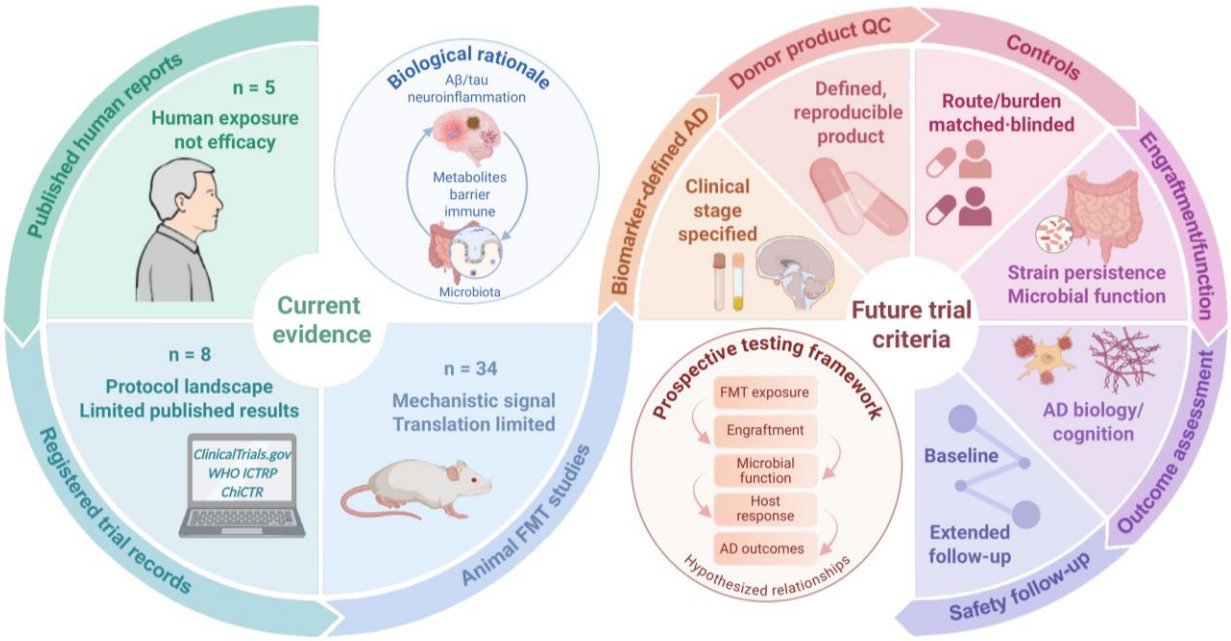


Figure 2. A testable framework for FMT research in AD. The framework relates five published human reports, eight unique registered trials and 34 animal studies to six trial-design domains: AD definition and clinical stage, donor and product characterization, comparators, engraftment and microbial function, AD-relevant outcomes, and safety follow-up. The central sequence organizes prospective assessment after FMT exposure. Donor-strain engraftment, microbial functional change, systemic host responses, and AD biomarker and clinical outcomes are distinct measurement domains. Systemic responses are interpreted as target engagement only when linked to a prespecified biological target or pathway. Arrows in the central sequence denote hypothesized relationships for prospective testing, not an established causal pathway. AD, Alzheimer's disease; FMT, fecal microbiota transplantation; QC, quality control; Aβ, amyloid-beta; ChiCTR, Chinese Clinical Trial Registry; WHO ICTRP, World Health Organization International Clinical Trials Registry Platform. Created with BioRender.com.

Two complementary monitoring measures could be prioritized in early trials. Serial donor-associated strain detection would address a gap in the included evidence by directly assessing transfer and persistence, supported by strain-tracking methods in the wider FMT literature [16]. Compartment-specific butyrate measurement could serve as an exploratory metabolic-response measure, supported by repeated, although inconsistent, recipient findings in the animal studies. Recipient butyrate increases were reported in seven studies, but compartments and comparisons differed; Soriano et al. reported no significant treatment-related change in serum butyrate proportions [32], Zhou et al. (2022) reported no significant fecal butyrate change [52], and Tang et al. reported no significant fecal butyrate change [45] (Supplementary Table 5). Fecal, serum and plasma

measurements should therefore be specified separately. The extracted taxonomic findings did not identify a genus with sufficiently consistent direction across comparisons to serve as a universal marker. Donor-strain persistence and butyrate are candidates for validation, not established surrogates for AD benefit.

Relation to previous reviews

Recent reviews have addressed FMT in AD, including microbial mechanisms, preclinical findings and therapeutic prospects [6, 7]. Broader reviews have also examined gut–brain signaling and microbial metabolism in AD [17]. The contribution of the present review is the joint interpretation of published human observations, registered plans and animal transfer experiments using distinct units of evidence. It separates CDI-directed exposure from cognition-directed intervention, AD-specific populations from broader impairment, and registered endpoints from public results. Within animal studies, transfer design and recipient model are classified independently, and favorable findings are considered alongside mixed results and reporting of randomization, blinding and replication. These distinctions connect the existing evidence to specific clinical measurements and comparator choices.

Strengths and limitations

The review integrates clinical exposure reports, trial registrations and experimental transfer studies while retaining the question addressed by each source. Study-level comparisons, donor features, outcome directions and methodological reporting are available in the supplementary tables, allowing the summary counts to be traced to individual reports.

The human and animal literature searches used English-language terms and did not include CNKI, WanFang or SinoMed, so relevant Chinese-language publications may have been missed. The human bibliographic and trial-registry searches were centered on AD and MCI terminology, so reports or trials indexed only under broader dementia or cognitive-impairment terms may have been missed. The published animal literature may also favor positive findings, and a study-level direction does not reflect effect size, precision or the number of endpoints tested. The structured methodological reporting inventory is not a formal risk-of-bias assessment. Human samples were small, and registry entries varied in detail and availability of results. Heterogeneity in populations, products, comparisons and measurement schedules precluded a pooled efficacy estimate.

Conclusion

FMT remains investigational for AD. Most human observations arose during CDI treatment, while the non-CDI evidence comes from a small uncontrolled pilot with mixed diagnoses. Positive cognitive findings predominated in animal reports, with less consistency after restriction to genetic/transgenic models and limited reporting of cognitive blinding. Early clinical studies should use a clearly defined population and product, suitable controls, separate measures of microbial and host responses, and safety monitoring appropriate to older adults. These studies should determine whether reproducible biological responses are accompanied by cognitive or functional benefits.

List of abbreviations

AD, Alzheimer's disease; ADAS-Cog, Alzheimer's Disease Assessment Scale-Cognitive Subscale; Aβ, amyloid-β; APOE, apolipoprotein E; AT(N), amyloid/tau/neurodegeneration; CDR, Clinical Dementia Rating; CDR-SB, Clinical Dementia Rating–Sum of Boxes; CDI, *Clostridioides difficile* infection; ChiCTR, Chinese Clinical Trial Registry; FMT, fecal microbiota transplantation; FTD, frontotemporal dementia; ICTRP, International Clinical Trials Registry Platform; JBI, Joanna Briggs Institute; MCI, mild cognitive impairment; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; MTT, microbiota transfer therapy; NR, not reported; OSF, Open Science Framework; PRISMA-ScR, Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews; T1/T2/T3, direct animal-donor transfer/transfer from intervention-conditioned animal donors/human-donor transfer into animal recipients; WHO ICTRP, World Health Organization International Clinical Trials Registry Platform.

Availability of data and materials

All data generated or analyzed during this study are included in this article and the Supplementary Information. The review protocol is available through the Open Science Framework (DOI: 10.17605/OSF.IO/GH7YS).

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

J.Y.X.: Conceptualization, Methodology, Data curation, Formal analysis, Visualization, Writing - original draft, Writing - review and editing, Project administration. Z.W.C.: Methodology, Data curation, Formal analysis, Validation, Writing - review and editing. Y.S.L.: Conceptualization, Validation, Supervision, Writing - review and editing. A.B.G.: Methodology, Validation, Funding acquisition, Supervision, Writing - review and editing. Y.Y.K.: Conceptualization, Supervision, Project administration, Funding acquisition, Writing - review and editing. J.Y.X. and Z.W.C. performed study selection and data charting, and disagreements were resolved by consensus. All authors read, revised, and approved the final manuscript.

Supplementary Materials

The Supplementary data can be found online at: www.aginganddisease.org/EN/10.14336/AD.2026.0883.

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