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NARRATIVE REVIEW

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The effects of the interplay between vitamins, antibiotics, and gut microbiota on the pathogenesis and progression of dementia: A systematic review and meta-analysis

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Abstract

Background: Given that there is already evidence of a neural network that connects the brain and gut and that the gut microbiota actively modulates gut health, it is crucial to know which foods, supplements, and medications to use or avoid when treating any disease that causes dementia or cognitive impairment. Previous research has examined the relationships between vitamins, antibiotics, and gut microbiota and the correlations between these factors and dementia. The question arises of how these three factors interact together and if evidence suggests one element is more important than the others in the pathogenesis and development of dementia.

Methods: The Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) standards were followed when conducting this review. The papers' publication dates varied from (2012–2022). Cochrane/EMBASE, PEDro, and PubMed/Medline databases were searched. The precise terms "gut microbiota," vitamins," antibiotics," and "dementia" were included in the search method, along with the conjunctions "OR" and "AND."

Results: Gut dysbiosis has a significant impact on cognition, brain function, and the development and progression of dementia. The two most popular probiotics used in studies linked to cognition benefits were Lactobacillus and Bifidobacterium. Numerous scales were used to evaluate cognition, but the mini-mental state examination was the most popular, and the most prevalent impairment was Alzheimer's disease. The supplements with the most significant impact on gut microbiota were vitamin B-12 and folic acid.

Conclusion: This systematic review concluded that vitamins, gut microbiota and antibiotics have a close association with the development of dementia. More research is required to establish causality and elucidate the underlying mechanisms because there is still little evidence connecting the interactions of vitamins, medications, and microbiota with dementia. The complexity of interactions between genetics, lifestyle factors, and comorbidities, as well as the heterogeneity of dementia, may make it more challenging to interpret the findings.

KEYWORDS
antibiotics, dementia, gut microbiota, vitamins

1 | INTRODUCTION

1.1 | Dementia etiology and management

A considerable deterioration in cognitive capacities affects social and professional functioning in dementia. 5.8 million Americans have dementia-related Alzheimer's disease (AD).[1] Many neuropathologies, including Alzheimer's and cerebrovascular pathology, cause dementia. A thorough assessment of the patient's medical history, cognitive impairment, and everyday activities is needed to diagnose dementia. These findings should be confirmed by a close friend or family member. A clinician will also complete a thorough mental status examination to identify issues in memory, language, attention, and visuospatial cognition, which includes spatial orientation, executive function, and mood.[2] Short cognitive impairment screening tests can help start and organize the examination.

Neuropsychological examination can detect dementia if the review is unclear.[3] The physical exam helps determine dementia's etiology. Concentrated neurologic problems may suggest a stroke.[3] Neuroimaging can detect malignancies, infarcts, and localized atrophy that a physical exam may miss.[3] Genetic or CSF testing may be investigated for atypical dementia cases beginning beyond 65 years of age, fast symptom progression, and cognitive impairment in many domains but not episodic memory. Nonpharmacologic therapies including reading, exercise, and family reunions may help patients. Pharmacologic treatments can improve some symptoms.

1.2 | The gut microbiota

The "gut microbiota."—a varied variety of bacteria, archaea, and eukarya—live in the gastrointestinal system and benefit the host. Thousands of years have shaped this interaction.[4–7] The number of bacteria in the gastrointestinal system is estimated to surpass 1014, 100 times the human genome and 10 times the number of cells.[8,9] Human gastrointestinal tracts are large interfaces between the body, environmental stimuli, and antigens, covering 250–400 square meters. In a lifetime, 60 tons of food and environmental bacteria travel through the digestive tract, threatening gut health. The ratio of human to bacterial cells is currently 1:1.[10–14] The microbiota protects the host from infections, forms the intestinal epithelium, gathers energy, and maintains gut integrity. Dysbiosis, or microbial imbalance, can disrupt these systems and contribute to intestinal and extra-intestinal disorders.[15]

1.3 | Role of gut microbiota in causing dementia

The gut-brain axis interacts during the condition, allowing gut microorganisms to affect behavior, neurological development, and cognition.[8] These pathogenic alterations disturb gut microorganisms, producing dementia. Dysbiosis can infiltrate the gut and intestines at any age.[8] Small intestine bacterial overgrowth dominates the gastrointestinal system. Gut dysbiosis causes extra-intestinal (allergies, metabolic syndrome, asthma, obesity, and cardiovascular disease) and intestinal (coeliac disease, IBS, and IBD) problems.[9] Gut dysbiosis can cause neurological degeneration, depression, anxiety, dementia, sleep disturbance, pain, stroke, stress, and autism owing to inflammation and age-related dysbiosis.[10] Microbial colonies in cells discharge plenty of waste. Due to settlement growth and waste removal, bodily processes become overworked and affect brain function, causing dementia and other neurological abnormalities.[12] Due to beta diversity and taxonomic composition, gut dysbiosis is associated to dementia. Serum diamine oxidase (DAO) and systemic inflammation increase intestinal permeability, enhancing the 14-level differentiation cluster. The damaged proteins combine to create neuroinflammation, which microglia cells mediate to induce dementia.[13]

1.4 | Neurotransmitters of gut microbiota leading to dementia

Gut microbiota generates acetylcholine, GABA, serotonin, and dopamine, intestinal toxins, vitamins, and altered nerve signals, especially the vagus nerve.[16] Gut dysbiosis affects protein synthesis signals, interfering with dementia metabolism.[11] As gut microbiota disrupts inflammatory pathways and metabolic functions, it changes

microflora composition, producing dementia.[17] The serotonin hypothesis also suggests that circulatory platelets store and pick up intestinal serotonin, which is produced by enterochromaffin intestinal cells and maintains the permeability of brain, intestine, and other organ membranes.[18] Serotonin in the colon may regulate hormones, such as regulatory signals mediated by platelets and reflecting intestinal circumstances. Thus illustrating how gut dysbiosis causes psychiatric and neurodevelopmental problems.[19]

1.5 | Role of nutrients and medications on gut microbiota

Gut bacteria produce acetylcholine, GABA, serotonin, dopamine, intestinal toxins, vitamins, and altered nerve signals, notably the vagus nerve.[16] Gut dysbiosis disrupts protein production signals and dementia metabolism.[11] When gut microbiota alters inflammatory pathways and metabolic functioning, it modifies microflora composition, causing dementia.[17] Circulatory platelets store and take up intestinal serotonin, which enterochromaffin intestinal cells create and maintain brain, gut, and organ membrane permeability.[18] Platelets' regulatory signals and intestinal conditions may be regulated by colon serotonin. Thus showing gut dysbiosis induces psychological and neurodevelopmental issues.[19]

A decade ago, most adult human gut microbiota data was acquired using time-consuming and difficult culture-based approaches.[9] We now understand gut microbiota better due to culture-independent approaches like high-throughput and low-cost sequencing.[18] Gut microbiota research frequently focuses on the bacterial 16 S ribosomal RNA (rRNA) gene, which is ubiquitous in all bacteria and archaea and includes nine variable portions that allow species differentiation.[19] Former approaches read the whole 16 S rRNA gene. An early study using this strategy found that 76% of the rRNA sequences from a sample of adult male feces belonged to unknown and uncharacterized species, highlighting the limitations of culturing.[20] 16 S rRNA sequencing has recently focused on shorter gene subregions to analyze them more closely, but shorter read lengths can cause errors. Shotgun whole-genome metagenomics improves microbiota composition and diversity estimates.[21] Human Microbiome Project and MetaHit data provide all human-associated microbes. Seventy-two human-isolated species were divided into 12 phyla.[22] The species was 93.5% Bacteroidetes, Firmicutes, Actinobacteria, and Proteobacteria. One of the 12 phyla, Verrucomicrobia, isolated intestinal species Akkermansia muciniphila.[23] The gastrointestinal system and mouth cavity house 386 anaerobic human species.[21]

Gut microbiomes create short-chain fatty acids to develop microglia. These bacteria are crucial for dementia therapy and diagnosis.[24] Age-related gut microbiota loss increases infections and decreases beneficial taxa. Increasing age increases inflammatory cells, which depend on mucosa inflammation, bacterial translocation, and gut permeability.[25]

1.6 | Rationale and objectives

Since it is already established that there exists a neural network between the brain and the gut, and the fact that gut microbiota actively controls the state the gut is in, it is essential to know in the management of any disease resulting in dementia or cognitive impairment, which food, supplement, medication should or should not be used. Previous studies have looked at the individual links between vitamins and dementia or antibiotics and dementia, or gut microbiota and dementia; however, how do all three factors interact with each other, and what evidence is available showing that one aspect deserves more attention than the others. This systematic review aims to find studies that show the associations between those mentioned above, or if little to none are available, attempt to deduce a connection through cross-study analysis. In addition, this review intends to fill in the literature gap present regarding the etiology of dementia and the factors mentioned.

2 | METHODS

2.1 | Search strategy

For this review, the authors adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The review encompassed a decade of research, from 2012 to 2022, and included all relevant studies published during that period. To identify relevant studies, the authors searched multiple databases, including Cochrane reviews, PEDro, and PubMed/Medline, using a combination of specific terms such as “gut microbiota,” “vitamins,” “antibiotics,” and “dementia,” using the conjunctions “OR” and “AND.” The search was conducted using MESH terms or by searching within the titles and abstracts of publications, as outlined in Table 1.

We looked at the search results in two steps. First, we read the titles and abstracts and purged any irrelevant research

TABLE 1 Search strategy used to find relevant articles.

Search No	Search Terms
#1	Gut Microbiota [Title/Abstract]
#2	Vitamins [Title/Abstract]
#3	Vitamins [MeSH Term]
#4	Antibiotics [Title/Abstract]
#5	Antibiotics [MeSH Term]
#6	Dementia [Title/Abstract]
#7	#1 AND #2 OR #3
#8	#1 AND #4 OR #5
#9	#1 AND #6
#10	#6 AND #7
#11	#6 AND #8

[exclusion criteria shown below]. Abstracts that appeared unrelated to our topic were marked for a more thorough review in the future. The whole texts of all marked and matched articles were then retrieved and rechecked for eligibility. The needed outcomes were then examined in all eligible studies, and those that had them were added to the final synthesis. The search results that conform to PRISMA standards are summarized in the flowchart depicted in Figure 1.

2.2 | Eligibility criteria

2.2.1 | Inclusion criteria

The studies were selected based on the following inclusion criteria:

1. Randomized control trials or observational studies looking at changes in gut microbiota and the effects on dementia OR cognitive function.
2. Randomized control trials or observational studies looking at how vitamins, antibiotics, and probiotics influence gut microbiota.

2.2.2 | Exclusion criteria

The studies were excluded based on the following inclusion criteria:

1. Studies not including dementia OR cognitive impairment within the sample population.
2. Studies not taking into account the changes in gut microbiota.
3. Studies not in English or involving animal populations.

2.3 | Data collection

Microsoft Edge's Zoterro plugin was used to find the articles in the databases. The titles and abstracts were then imported into the Zotero desktop program for review. After gathering the data, tables were created directly in LibreOffice. The recent research on the relationship between antibiotics, vitamins, gut flora, and dementia symptoms is summarized well in this systematic review through the examination of the collected papers and their findings (Tables 2 and 3).

2.4 | Data items

1. Author
2. Country
3. Sample size
4. Gender ratio
5. Age [mean]

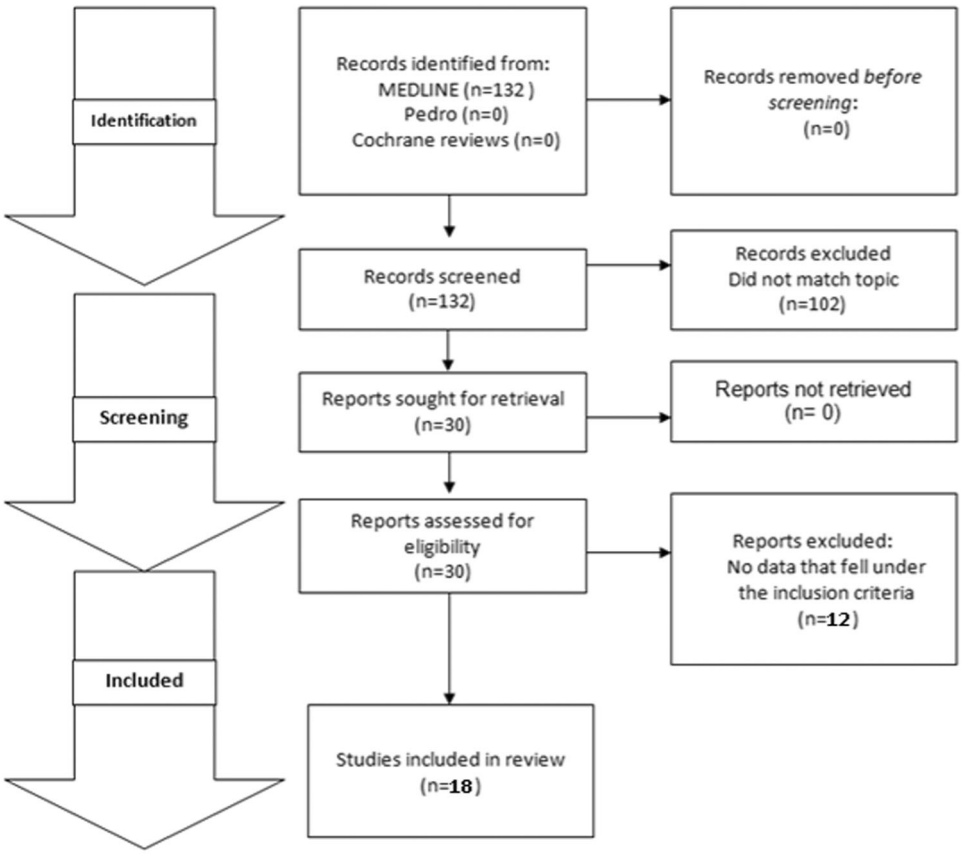

FIGURE 1 PRISMA Flowchart showing search strategy. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analysis.

TABLE 2 Synthesis of data from the included studies in this review [Changes in Gut microbiota affecting dementia].

Study no	Country	Sample size	Gender ratio [M/F]	Mean age	State of dementia	Intervention	Control	Outcomes	Significance
Sakurai et al.[4]	Japan	39 versus 39	18/21 versus 18/21	76.8 versus 76.9		*Lactiplantibacillusplantarum* [OLL2712]	Placebo	Visual memory, Verbal memory, Composite Memory	The intervention improved visual memory $p = 0.044$
Tamtaji et al.[5]	Iran	27 versus 26 versus 26	-	76.2 versus 78.8 versus 78.5	Alzheimer's Disease	Probiotics containing Lactobacillus acidophilus, Bifidobacterium bifidum, and Bifidobacterium longum combined with selenium	Placebo	Mini-Mental State Examination [MMSE] score, hs-CRP, TAC, GSH, markers of insulin metabolism triglyceridesVLDL, LDL, HDL, cholesterol	MMSE hs-CRP, insulin HOMA-IR all improved after probiotic + selenium [$p < 0.001$]
						OR Selenium alone			
Agahi et al.[6]	Iran	25 versus 23	7/18 versus 10/13	79.70 versus 80.57	Alzheimer's Disease	Lactobacillus fermentum, Lactobacillus plantarum, and Bifidobacterium lactis OR Lactobacillus acidophilus, Bifidobacterium bifidum, and Bifidobacterium longum	Placebo	TYM TAC GSH MDA NO TNF-α IL-10 IL-6 8-OHdG	Only IL-6 was improved after intervention [$p < 0.001$]
Akbari et al.[7]	Iran	30 versus 30	6/24 versus 6/24	77.67	Alzheimer's Disease	Lactobacillus acidophilus, Lactobacillus casei, Bifidobacterium bifidum, and Lactobacillus fermentum	Placebo	MMSE score, hs-CRP, TAC, GSH, MDA markers of insulin metabolism triglyceridesVLDL, LDL, HDL, cholesterol	MMSE, MDA, hs-CRP improved after the intervention [$p < 0.001$]
Sanborn et al.[8]	USA	127	-	64.3	Healthy, physically active adults	*Lactobacillus rhamnosus* GG	Placebo	Cognitive performance	No significant changes in cognitive performance from baseline to follow up
Hwang et al.[9]	Korea	50 versus 50	20/30 versus 14/36	68.5	Mild cognitive impairment	*Lactobacillus plantarum* C29-fermented soybean [DW2009]	Placebo	Composite score of cognitive functions related to memory and attention	The intervention group showed greater improvements in the combined cognitive functions [$p = 0.02$]

(Continues)

TABLE 2 (Continued)

Study no	Country	Sample size	Gender ratio [M/F]	Mean age	State of dementia	Intervention	Control	Outcomes	Significance
Kobayashi et al.[10]	Japan	121	30/31 versus 30/30	61.5	Subjects with memory complaints	Bifidobacterium breve A1	Placebo	The Japanese version of the Repeatable Battery for the Assessment of Neuropsychological Status [RBANS] and MMSE	A significant difference between groups in terms of the subscale 'immediate memory' of RBANS and MMSE total score in the subjects with low RBANS total score at baseline
Xiao et al.[11]	Japan	80	19/21 versus 20/20	61.5	Mild cognitive impairment	Bifidobacterium breve A1	Placebo	RBANS	In the probiotic group, RBANS total score improved [$p < 0.0001$]
								The Japanese version of the Mild cognitive impairment Screen [JMCIS]	JMCIS improved in intention to treat [ITT] analysis [$p = 0.052$] and per-protocol PP analysis [$p = 0.036$]

6. Etiology of dementia
7. Intervention
8. Control
9. Outcomes
10. Significance

2.5 | Information sources

1. PubMed/Medline (2012–2022)
2. Cochrane reviews (2012–2022)
3. Pedro (2012–2022)

2.6 | Search terms

The search methodology followed the evidence-based medicine approach of Population, Intervention, Comparison, and Outcome (PICO). The patients considered were those exhibiting symptoms and indications of dementia, without regard to the underlying cause. The intervention was any form of management leading to a change in gut microbiota, for example, antibiotics, probiotics, and vitamins. The comparison was between the interventions, and the outcomes included changes in signs and symptoms of dementia as reflected by scales such as the mini-mental state examination (MMSE). The search procedure conducted on the MEDLINE database utilized a combination of keywords connected by the conjunctions "AND" or "OR," as demonstrated in the search terms (Appendix A).

3 | RESULTS

In this review, we evaluated the effects of the interplay between vitamins, antibiotics, and gut microbiota on the state of dementia. Our search yielded 18 studies (Changes in Gut microbiota affecting dementia, effects of vitamins on gut microbiota) that met our inclusion criteria and were included in the final analysis. The studies varied in their design, population, and outcomes, but all investigated the relationship between one or more of the three factors of interest and the state of dementia. Pre-screening was done first from the total of 132 studies gathered, and all duplicates were eliminated. Then, only the papers that were pertinent to the issue were selected from the titles and abstracts. This equated to 102 research being left out. The 30 studies were then all downloaded from the internet. The data elements from these papers that met the inclusion criteria were then assessed. Only 12 studies failed to fulfill the requirements for inclusion. The references to the publications were also checked for any omitted studies that would have produced the intended results, but they still need to be discovered. In the end, the synthesis only contained 18 studies. After analysing the studies, we found evidence to suggest a complex interplay between vitamins, antibiotics, and gut microbiota that may influence the state of dementia. Specifically, we identified the following key findings.

TABLE 3 Synthesis of data from the included studies in this review [Effects of vitamins on gut microbiota].

Study No	Country	Sample size	Gender ratio [M/F]	Mean age	State of dementia	Intervention [vitamin or antibiotic]	Control	Outcomes	Findings
Aisenet al.[12]	USA	250 versus 138	44.3% M	75.7 versus 77.3	Mild Alzheimer's Disease	Vitamin B-12	Placebo	The cognitive subscale of the Alzheimer Disease Assessment Scale [ADAS-cog]	No beneficial effects of vitamins on cognitive functions
Connelly et al.[13]	UK	23 versus 18	29.31% M	75.65 versus 77.6	Mild Alzheimer's Disease	Vitamin B-12	Placebo, Folic acid	MMSE Instrumental Activities of Daily Living and Social Behavior scores [IADL & SB]	Only improvement in IADL + SB in intervention group [$p = 0.05$]
Jager et al.[14]	UK	266	36% M	77	Mild cognitive impairment	B-12 + Folic acid	Placebo	MMSE HVLT Category fluency CLOX tHcy	Association between vitb12 and MMSE [$p < 0.001$]
Kwok et al.[15]	China	70 versus 70	36.5% M	79.1 versus 77.2	Mild Alzheimer's Disease	Vitamin B-12	Supplementation	Mattis dementia rating scale [MDRS]	Elevated Hcy was associated with a smaller decline in MDRS [$p = 0.003$]
Sun et al.[16]	China	45 versus 44	50.5% M	74.9 versus 74.6	Mild Alzheimer's Disease	Vitamin B-12	Placebo, Multivitamin	Alzheimer's Disease Assessment Scale 11-item Cognition subscale ADL	No beneficial effects of vitamins on cognitive functions
Clark et al.[17]	UK	149	-	75	Mild cognitive impairment	B-12 + Folic acid	Placebo, Aspirin	ADAS-cog MMSE Bristol ADL tHcy	No beneficial effects of vitamins on cognitive functions
Fioravantiet al.[18]	Italy	30	18% M	80	Mild cognitive impairment	B-12 + Folic acid	Placebo	RMT	Memory is positively associated with folic acid but not B12
Hankeyet al.[19]	Australia	481	-	63	Mild cognitive impairment	B-12 + Folic acid + B6	Placebo	MMSE tHcy	No beneficial effects of vitamins on cognitive functions
Sommeret al.[20]	USA	11	-	77	Mild cognitive impairment	Folic acid	Placebo	Boston naming COWAT WMS: logical memory WMS: associate learning Trails A Trails B Finger tapping	No beneficial effects of vitamins on cognitive functions
Ting et al.[21]	Singapore	230	60% M	67	77	Folic acid	Placebo	MMSE DIGSF DIGSB VISMSF VISMSBCATNAA DIGCAN FABTOT tHcy	No beneficial effects of vitamins on cognitive functions

3.1 | Salient findings

1. Gut dysbiosis causes a significant change in cognition and contributes to the development and progression of dementia (Table 2).
2. Lactobacillus and Bifidobacterium were the two most common probiotics used in experiments associated with positive cognition effects (Table 2).
3. Cognition was evaluated with numerous scales, but the most common was MMSE (Table 2).
4. Majority of the sample size had a mean age above 70 (Tables 2 and 3).
5. Alzheimer's was the most commonly tested cognition impairment (Tables 2 and 3).
6. Most probiotic studies were conducted in Japan, while vitamin studies were done in the UK (Tables 2 and 3).
7. Vitamin B-12 and folic acid were the most tested supplements on gut microbiota (Table 3).
8. No randomized control or clinical trials were found on the effects of particular antibiotics on gut dysbiosis and, indirectly, cognition.
9. The link between antibiotics/probiotics, vitamins, and gut microbiota remains ambiguous, but each indirectly and directly affects cognition.
10. Probiotics have a much more significant effect on cognition than vitamins.
11. Due to the nonhomogeneity of the outcomes and findings from each study, it was challenging to obtain a sizeable amount of meta-analytical data.

The findings in Tables 4 and 5 suggest that the interplay between vitamins, antibiotics, and gut microbiota may play an essential role in the development and progression of dementia. Therefore, identifying and addressing vitamin deficiencies, avoiding unnecessary antibiotic use, and maintaining a healthy gut microbiota through diet and other interventions may be essential strategies for preventing and treating dementia. The key findings of included literature suggest that:

1. Vitamin deficiencies, particularly deficiencies in B vitamins, have been associated with an increased risk of cognitive decline and dementia.
2. Alterations in the composition of the gut microbiota, such as reductions in beneficial bacteria and increases in harmful bacteria, have been associated with cognitive impairment and dementia.
3. Antibiotic use has been shown to disrupt the composition of the gut microbiota, which may adversely affect cognitive function and increase the risk of developing dementia.
4. Certain bacteria in the gut microbiota, such as those that produce vitamins and other beneficial compounds, may protect against cognitive decline and dementia.

3.2 | Risk of bias

Overall, all studies reporting the ADAS[12,16] and MMSE[5,7,10,13,14] outcomes had a low risk of bias. No study reported a high risk of bias (Figure 2).

3.3 | Meta-analysis

Two studies[12,16] with 285 participants in the experimental group and 213 participants in the control group reported ADAS outcomes variable in effects of vitamins on gut microbiota. 162/285 participants in the experiments group were females, and 111/213 participants in the control group were females. The mean age of participants was 75.7 ± 8.0 and 74.9 ± 7.1 in experimental groups and 77.3 ± 7.9 and 74.6 ± 7.5 in control groups. (AISEN & SUN REF) There was a high statistically significant difference between groups in ADAS score (MD = -1.20 95% CI = [−1.34 to −1.06]), $p < 0.00001$, $I^2 = 97\%$ (Figure 3). Five studies[5,7,10,13,14] with 250 participants in the experimental group and 247 participants in the control group reported MMSE outcomes variable in effects of vitamins on gut microbiota and change in gut microbiota affecting dementia. There was a statistically significant difference between groups in MMSE score (MD = 0.52 95% CI = [0.11−0.92]), $p = 0.01$, $I^2 = 92\%$ (Figure 4).

4 | DISCUSSION

Dementia is a complex and multifaceted condition that impacts millions of individuals worldwide. The pathogenesis of dementia has been linked to the gut microbiota, and recent studies suggest that the relationship between antibiotics, vitamins, and gut microbiota could potentially have a significant influence on the onset and advancement of dementia.[13] The aim of this study was to investigate the effects of this interplay on the state of dementia. From what was collected in the literature search, although the etiology of dementia is multifactorial, it can be deduced that a potential role for the interplay between vitamins, drugs, and microbiota in the pathogenesis of dementia. Most studies have yet to give a homogenous answer regarding changes in cognition; thus, multiple factors are present that most studies need to consider, leading to interference in the findings.

TABLE 4 Pre and post-treatment values of ADAS outcome variable in effects of vitamins on gut microbiota.

	Treatment group Mean ± SD		Placebo group Mean ± SD	
Studies	Baseline	After intervention	Baseline	After intervention
Aisen et al.[12]	25.6 ± 0.4	23.6 ± 0.7	25.6 ± 0.4	24.8 ± 0.7
Sun et al.[16]	24.63 ± 8.34	20.56 ± 8.44	24.98 ± 7.57	23.28 ± 8.15

TABLE 5 Pre and post-treatment values of MMSE outcome variable.

Studies	Treatment group Mean ± SD		Placebo group Mean ± SD	
	Baseline	After intervention	Baseline	After intervention
Effects of vitamins on gut microbiota				
Jager et al.[14]	27.5 ± 1.9	28.5 ± 1.6	27.6 ± 2.0	27.5 ± 1.9
Connelly et al.[13]	18.4 ± 4.4	19.4 ± 4.3	17.7 ± 4.4	18.2 ± 4.8
Changes in Gut microbiota affecting dementia				
Kobayashi et al.[10]	26.2 ± 2.8	26.5 ± 2.5	26.6 ± 2.6	26.7 ± 2.7
Akbari et al.[7]	28.83 ± 9.05	23.50 ± 10.14	28.16 ± 8.9	28.16 ± 8.92
Tamtaji et al.[5]	29.16 ± 10.22	22.96 ± 10.79	31.28 ± 10.59	29.40 ± 11.62

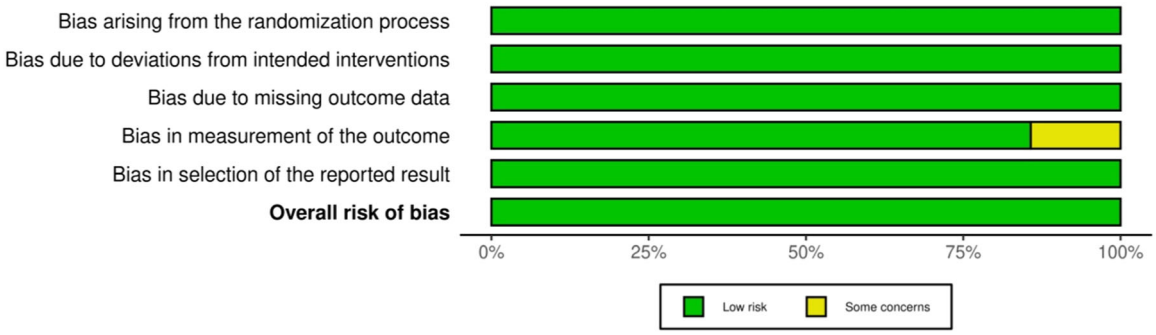

FIGURE 2 Overall risk of bias of ADAS and MMSE outcomes studies. ADAS, Alzheimer Disease Assessment Scale; MMSE, mini-mental state examination.

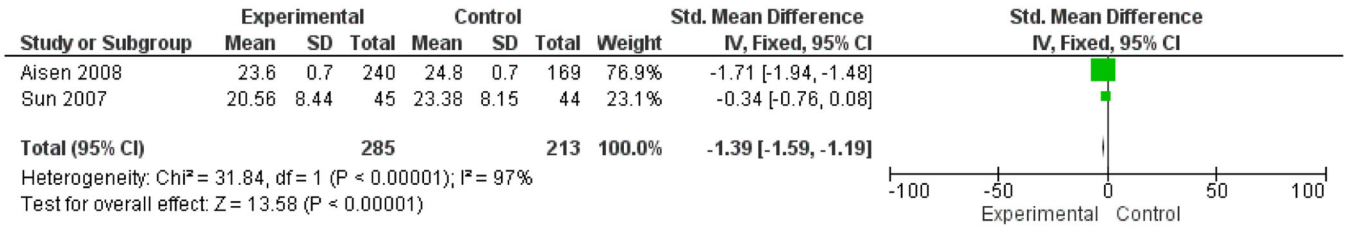

FIGURE 3 Forest Plot of ADAS outcome.

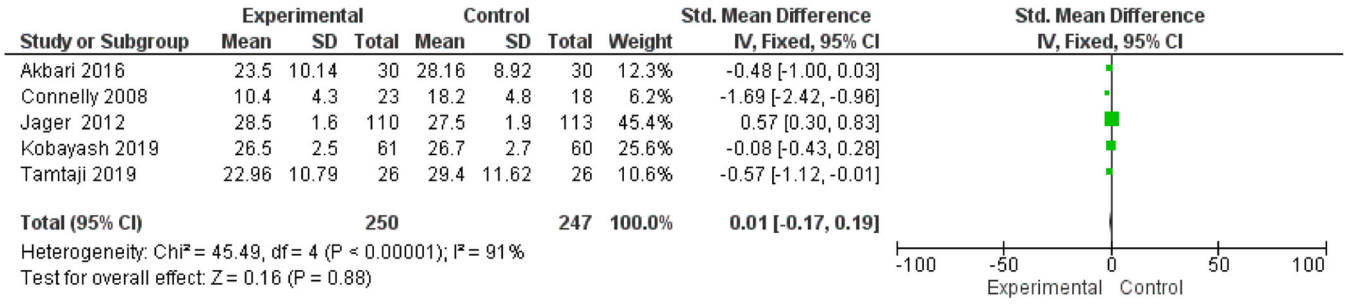

FIGURE 4 Forest Plot of MMSE. MMSE, mini-mental state examination.

4.1 | Dementia

Dementia, the 7th leading cause of disability and death worldwide, has several brain cell damage symptoms.[10] Symptoms include behavior change, cognitive, and memory deficiencies impair target persons' functioning capacities.[12] A study reveals that dementia symptoms may include emotional instability, diminished motivation, and language processing difficulties in addition to memory problems.

However, dementia does not affect consciousness.[14] Dementia is incurable, although treatment can enhance quality of life. Dementia symptoms include judgment, clinical reasoning, communication, attention deficit, memory, and visual perception.[1]

Pre-dementia, early dementia, middle dementia, and late dementia cause functional and cognitive deficits.[1,2] Predementia includes prodromal and preclinical phases. Sensory dysfunction in the preclinical stage causes olfactory loss and appetite loss due to chemosensory receptor cell destruction and blood-brain barrier interference.[26] Prodromal symptoms include behavioral and cognitive deficits, memory loss, and brain word aggregation and pronunciation issues. These changes are seen on the mini-mental state evaluation scale, revealing patients' cognitive abilities.[26] This stage causes trouble with word pronunciation, memory processing, and executive function organization and planning. In frontotemporal dementia, personality changes and planning and organizing difficulties may be the initial symptoms.[27] It's called the intermediate stage of dementia as symptoms worsen. The symptom drop rate ranges from 6 to 17 MMSE scores.[26] Social judgment and problem-solving skills are frequently weakened at this stage of dementia. Most patients at this stage need help with personal duties. The latter stage of dementia necessitates complete patient help. This stage causes facial recognition problems, sleeping disruptions, and aberrant eating.[28]

4.2 | Role of gut dysbiosis on dementia

Gut dysbiosis, an imbalance in the gastrointestinal tract's microbial ecology, can cause health issues.[29] The GIT microbiota has a major role in dementia development. Metabolic illnesses caused by gut dysbiosis develop low-grade systemic inflammation to change important risk variables.[30] The exact association between gut dysbiosis and dementia is unknown, however there is accumulating evidence.[31] Research demonstrates that the gut microbiota helps maintain the blood-brain barrier, which prevents hazardous compounds from reaching the brain.[32] Disrupting the gut microbiota increases gut permeability and inflammation, which may cause neurological illnesses like dementia.[33] Vogt et al. found that intestinal dysbiosis increases inflammatory markers in Alzheimer's patients.[34] The protein beta-amyloid in brain cells during positive results is detected in dementia patients. This protein activates microglia and produces inflammatory cytokines by initiating an immunological response. Brain injury and inflammation result from these inflammatory cytokines. It is thought that gut dysbiosis-induced inflammation may accelerate AD. In another study, Haran et al. found that gut dysbiosis elevated brain amyloid beta in mice. C reactive protein, an inflammatory marker in AD patients, causes neuronal cell inflammation and contributes to disease development.[35]

Studies further show that gut microbiome alterations might create metabolic, hazardous compounds like AD-associated amyloid beta.[36] Gut dysbiosis also alters neurotransmitter synthesis, including dopamine and serotonin, which can affect cognition. In an AD mouse model.

Research is needed to completely understand the link between gut dysbiosis and dementia, however some studies have shown a substantial link.[35,36] A balanced diet and other lifestyle variables may help reduce dementia risk by maintaining a healthy gut microbiota.[37] Cattaneo et al. discovered that Alzheimer's patients have altered gut flora compared to healthy controls.[38] The study found that gut dysbiosis affects brain function, including neurotransmitter levels and blood-brain barrier integrity. These alterations can cause cognitive impairment and neurodegenerative illnesses like AD and Parkinson's. Systemic inflammation from gut dysbiosis can affect brain health. Chronic inflammation may cause cognitive impairment, and gut dysbiosis can raise blood proinflammatory cytokines.

4.3 | Impact of homocysteine on dementia

The body produces homocysteine during methionine synthesis and degradation.[39] High blood homocysteine levels are linked to various health issues, including dementia. The mechanism of homocysteine-induced dementia is complicated.[40] The link between cognitive deterioration and high homocysteine levels has been explained by many mechanisms.[41,42] Neurotoxicity is also associated with homocysteine. Oxidative stress, inflammation, and brain cell loss can result from high homocysteine levels.[43] This injury can affect neural function and cognitive decline. Homocysteine also affects dopamine and serotonin metabolism, which are necessary for cognitive function.[44]

Research shows that high blood homocysteine levels damage brain blood vessels, impair cognition, and raise dementia risk.[41,44,45] Homocysteine also promotes AD-related amyloid plaques and tau tangles. Cognitive performance and dementia risk have been shown to improve with homocysteine-lowering therapies such B vitamin intake.[41,46]

4.4 | Impact of vitamins on dementia

Organic vitamins regulate metabolic processes in living things.[47] Vitamins K and B are created by gut bacteria, whereas others are derived through dairy, meat, vegetables, and fruits.[22] Vitamin deficiencies caused by intestinal malabsorption and insufficient vitamin intake affect memory and hippocampal neuron development.

Vitamin A regulates immunological activities for central nervous system development by encouraging cell differentiation and neuron plasticity.[48] Vitamin A insufficiency induces colon inflammation, hyperplasia, inflammatory cell infiltration, and shorter villi.[48] Vitamin A improves memory and dendritic arborization in young neurons. Oral vitamin A alters gut microbiota, favoring Lactobacillaceae.[48]

Vitamin B insufficiency increases the likelihood of behavioral and cognitive impairments due to neurological and mental diseases.[16,18] Normal brain growth and function depend on vitamin B levels. Thiamine (B1), pyridoxine (B6), biotin (B7), folic acid (B9), and cobalamin (B12) are synthesized by gut bacteria.[21–23] Gut bacteria reconstruct environmental corrinoids. Vitamins, especially the B-complex, are crucial for brain function.[24,25] Cognitive impairment

and dementia are connected to their lack. B vitamins co-factor several metabolic processes, including methylation, which regulates DNA synthesis, repair, and gene expression.[20] This method may affect gut microbiota and cognitive function. Several studies have shown that B-vitamin supplementation may enhance cognitive performance in elderly people, particularly those with moderate cognitive impairment.[21,49] However, the data is conflicting, and some studies need to prove benefit.

The ideal amount, duration, and type of B-vitamin therapy are yet unknown. Some research must address covert drug usage by individuals, which is problematic. A more controlled testing environment may have yielded different results.[21–25]

Some data suggests antibiotics may interact with vitamins, notably B vitamins.[50] The gut microbiota synthesizes B vitamins, particularly B12, which is required for brain function and myelin production. Antibiotic-induced dysbiosis may disrupt gut microbiota B vitamin production, causing vitamin shortages that may impair cognitive function.[51]

Vitamins and bacteria may impair cognitive function when taken alongside central nervous system drugs. Anticholinergics, antidepressants, and antipsychotics can impair cognition, especially in older persons.[24,52] These medicines may impair vitamin B12 production and absorption, which is necessary for myelin formation and neural function. Some drugs can change gut microbiota, causing dysbiosis, inflammation, oxidative stress, and cognitive impairment.[25] Antibiotics are the most probable medications to indirectly affect dementia due to their diverse modes of action.[49]

Vitamin D deficiency may increase oxidative stress and inflammation, which are linked to dementia.[53] Fat-soluble vitamin D is needed for phosphorus, calcium, bone health, and immunological function. Recent research show vitamin D may be involved in dementia pathogenesis. Vitamin D reduces oxidative stress and inflammation in the brain, therefore shortage may enhance it.[54] Vitamin D insufficiency causes cardiovascular, mental, and neurological diseases. Vitamin D insufficiency in mothers causes neurodevelopmental problems in fetuses.[55] Vitamin D deficiency and its receptor diminish butyrate-producing bacteria, boosting Bacteroides and proteobacteria.

Vitamin K2, also known as menaquinone, and K1, commonly known as phylloquinone, are required for brain function.[56] A few brain regions contain both vitamins. Vitamin K2 is more prevalent in large brain regions. Vitamin D insufficiency may cause dementia, however the specific pathophysiology is unknown. However, decreased beta-amyloid clearance, inflammation, oxidative stress, and vascular dysfunction have been suggested. More study is needed to understand vitamin D's function in dementia and create effective prevention and treatment methods.

4.5 | Impact of antibiotics on dementia

Antibiotics change the gut flora, having long-term consequences.[57] The most common broad-spectrum antibiotic is rifaximin, which treats diarrhea and IBS.[58] Antibiotics can diminish the variety and richness of the gut microbiota, increasing pathogenic bacteria and decreasing beneficial bacteria.[59] This dysbiosis can modify microbial metabolites including short-chain fatty acids, which impact gut-brain communication and neuroinflammation.[26] Antibiotics can also cause allergies, inflammatory bowel disease, metabolic problems, and cognitive impairment.[27]

Antibiotics may affect dementia progression. Several suggestions have been offered for how antibiotics may influence the brain and cognitive function[57,58] Antibiotics may disturb the gut flora, which affects brain health and cognition.[57] The gut microbiome creates neurotransmitters and metabolites that affect brain function. Antibiotic-induced gut microbiome disruption may impair cognition and increase dementia risk.[57]

Antibiotics may also collect brain beta-amyloid plaques, which are associated with AD. Some studies show that antibiotics that target bacterial cell walls may promote beta-amyloid plaque formation and accumulation.[59] The information on antibiotics and dementia is sparse and inconsistent.[59] Some antibiotics may raise dementia risk, whereas others have not. While the link between antibiotics and dementia is unclear, research shows they may harm brain health and cognitive performance.[59]

Prolonged antibiotic usage can also impair cognition and increase dementia risk.[57] One study examined antibiotic exposure and dementia risk using a population-based retrospective cohort. The South Korean National Health Insurance Service-Health Screening Cohort [NHIS-HEALS] was used.[60] The results revealed that antibiotic usage for 91 or more days increased the incidence of dementia, AD, and vascular dementia. Antibiotic users of five or more classes had a greater incidence of dementia and AD.

A mouse research demonstrated that long-term antibiotic therapy affected gut microbiome and brain function genes, affecting spatial memory.[61] These data imply that antibiotic-induced dysbiosis may directly affect cognitive function and cause dementia. Most studies in our evaluation found that probiotics, like antibiotics, influence dementia.[43,62] Due to the links between microbiota, stomach, and brain, they may cure dementia, however most experimental studies focus on AD. Probiotics increase Bifidobacterium and Lactobacillus in the gut microbiota. This improves intestinal barrier function, inflammation, and immunity. Probiotics increase the synthesis of microbial metabolites including short-chain fatty acids, which benefit brain function and cognition.[43]

In animal studies, rats administered probiotics (Lactobacillus, Bifidobacterium, and Streptococcus) had lower insulin resistance, cognitive decline, and oxidative stress than controls.[63] Other animal studies show Lactobacillus therapy helps rats with hypertension-induced vascular dementia. Enhanced nitric oxide synthesis lowered blood pressure through vasodilating. Clostridium butyricum enhanced cognitive function, prevented neuronal death, and increased brain-derived neurotrophic factor and proapoptotic proteins in rats.[64] The faeces of persons with frontotemporal lobar degeneration have more Bacteroidetes species and less Firmicutes species.[63,64]

Some data suggests probiotics interact with vitamins and medications.[64,65] Vitamin B12 and vitamin K absorption and

utilization are improved by some probiotic strains. Antibiotics and immunosuppressants may interact with probiotics, altering therapeutic effectiveness or adverse effects. Probiotics, vitamins, and medicines may interact, therefore prescribing or advising them requires consideration.

All investigations revealed that long-term and active probiotic treatment in dementia patients may improve cognitive performance.[65] But take this with a grain of salt. The ideal probiotic dose, duration, and strains for dementia patients are also unknown. Until clear guidelines are established, dementia patients should use probiotics carefully after weighing long-term benefits versus relative contraindications.

According to our analysis, dysbiosis, which is linked to inflammation, oxidative stress, and neurodegeneration, causes cognitive function impairments. Any dysbiosis-causing interaction, whether vitamins, medications, or diet, can affect cognitive performance. Gut bacteria synthesizing B vitamins, vitamin intake, drugs eliminating gut flora, or pharmaceuticals disrupting gut integrity all dynamically alter (positively and negatively) cognitive function.

Our literature review showed a complicated interaction between vitamins, antibiotics, and gut flora that can affect dementia. Vitamin shortages, gut microbiome changes, and antibiotic usage can all cause dementia. Additionally, certain gut microbiome bacteria create brain-healthy vitamins, suggesting a relationship between vitamins and dementia.

5 | CONCLUSION

The evidence linking the interplay between vitamins, drugs, and microbiota to cognitive function and dementia is still limited. Gut dysbiosis is significantly related to the development and progression of various dementias such as Alzheimer's dementia and dementia associated with Parkinson's disease. More research is needed to establish causality and elucidate the underlying mechanisms. Moreover, the optimal interventions, such as B-vitamin supplementation, probiotics, or drugs that target the gut-brain axis, still need to be determined. Furthermore, the heterogeneity of dementia and the complex interactions between genetics, lifestyle factors, and comorbidities may complicate the interpretation of the results. Future research should focus on elucidating the underlying mechanisms, identifying the optimal interventions, and considering the heterogeneity of dementia. Clinicians should remain vigilant for potential drug interactions, monitor their patient's nutritional status, and assume the role of gut microbiota in cognitive function and dementia.

6 | PRACTICAL IMPLICATIONS AND LIMITATIONS

These findings have important implications for the prevention and treatment of dementia. Maintaining a healthy gut microbiota through diet, probiotics, and other interventions may help to prevent the development of dementia or slow its progression. Additionally, identifying and addressing vitamin deficiencies and avoiding unnecessary antibiotic use may also play a role in preventing dementia. Further research is needed to understand better the complex interplay between vitamins, antibiotics, and gut microbiota and their effects on the state of dementia. One of the limitations of this study is that it included some of the studies with a sample size < 50 patients.

7 | RECOMMENDATIONS

The exact detailed mechanisms underlying the interplay between vitamins, drugs, and microbiota in the pathogenesis of dementia, however, remains unclear, and this meta-analysis has not yielded anything that could shed light on this complex interaction otherwise. However, several hypotheses have been proposed. First, vitamin deficiency may impair methylation, leading to epigenetic changes and altered gene expression in the brain. Thus, it is recommended that all deficiencies in such patients are rectified early on. Drugs may alter the gut-brain axis, leading to dysbiosis, inflammation, and oxidative stress. So prolonged use or even high doses should be used with precaution after weighing the benefits against the potential risks. Thirdly, a person's gut microbiota may produce neuroactive metabolites, such as short-chain fatty acids, that can modulate neuronal function and protect against neurodegeneration. This is why diseases affecting them could be counteracted with probiotics; the choice of which has not been elucidated but, according to the collected studies, must be from the genus lactobacillus.

AUTHOR CONTRIBUTIONS

Priyadarshi Prajjwal: Conceptualization; methodology; resources; visualization; writing—original draft. **Pugazhendi Inban**: Conceptualization; data curation; investigation; writing—original draft. **Valleru Pushkar Sai**: Methodology; validation; writing—original draft; writing—review and editing. **Karnati Susannah Shiny**: Visualization; writing—original draft. **Justin Riley Lam**: Supervision; validation; writing—original draft. **Jobby John**: Validation; writing—original draft. **Mukhamed Sulaimanov**: Writing—original draft; writing—review and editing. **Yogesh Tekuru**: Writing—original draft; writing—review and editing. **Muhammad Wasi ul Haq**: Writing—original draft; writing—review and editing. **Mohammed Dheyaa Marsool Marsool**: Writing—original draft; writing—review and editing. **Venu vasanthi Sivarajan**: Writing—review and editing. **Omniat Amir Hussin**: Writing—review and editing.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

TRANSPARENCY STATEMENT

The lead author Omniat Amir Hussin affirms that this manuscript is an honest, accurate, and transparent account of the study being

reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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REFERENCES

1. Hebert CA, Scales K. Dementia friendly initiatives: A state of the science review. *Dementia*. 2019;18(5):1858-1895.
2. Mitchell SL, Black BS, Ersek M, et al. Advanced dementia: state of the art and priorities for the next decade. *Ann Intern Med*. 2012;156(1_Part_1):45-51.
3. Weintraub S. Neuropsychological assessment in dementia diagnosis. *Continuum (Minneapolis, Minn.)*. 2022;28(3):781-799. doi:10.1212/CON.0000000000001135
4. Sakurai K, Toshimitsu T, Okada E, et al. Effects of LactiplantibacillusPlantarum Oll2712 on memory function in older adults with declining memory: a randomized placebo-controlled trial. *Nutrients*. 2022;14(20):4300.
5. Tamtaji OR, Heidari-Soureshjani R, Mirhosseini N, et al. Probiotic and selenium co-supplementation, and the effects on clinical, metabolic and genetic status in Alzheimer's disease: a randomized, double-blind, controlled trial. *Clin Nutr*. 2019;38(6):2569-2575.
6. Agahi A, Hamidi GA, Daneshvar R, et al. Does severity of alzheimer's disease contribute to its responsiveness to modifying gut microbiota? A double blind clinical trial. *Front Neurol*. 2018;9:662.
7. Akbari E, Asemi Z, DaneshvarKakhaki R, et al. Effect of probiotic supplementation on cognitive function and metabolic status in alzheimer's disease: a randomized, Double-Blind and controlled trial. *Front Aging Neurosci*. 2016;8:256.
8. Sanborn V, Aljumaah M, Azcarate-Peril MA, Gunstad J. Examining the cognitive benefits of probiotic supplementation in physically active older adults. *Appl Physiol Nutr Metab*. 2022;47(8):871-882.
9. Hwang YH, Park S, Paik JW, et al. Efficacy and safety of lactobacillus plantarum C29-Fermented soybean (DW2009) in individuals with mild cognitive impairment: A 12-week, multi-center, randomized, double-blind, placebo-controlled clinical trial. *Nutrients*. 2019;11(2):305.
10. Kobayashi Y, Kuhara T, Oki M, Xiao JZ. Effects of bifidobacterium breve A1 on the cognitive function of older adults with memory complaints: a randomised, double-blind, placebo-controlled trial. *Beneficial Microbes*. 2019;10(5):511-520.
11. Xiao J, Katsumata N, Bernier F, et al. Probiotic bifidobacterium breve in improving cognitive functions of older adults with suspected mild cognitive impairment: a randomized, Double-Blind, Placebo-Controlled trial. *J Alzheimer's Dis*. 2020;77(1):139-147.
12. Aisen PS. High-Dose B vitamin supplementation and cognitive decline in alzheimer disease: a randomized controlled trial. *JAMA*. 2008;300(15):1774-1783.
13. Connelly PJ, Prentice NP, Cousland G, Bonham J. A randomised double-blind placebo-controlled trial of folic acid supplementation of cholinesterase inhibitors in Alzheimer's disease. *Int J Geriatr Psychiatry*. 2008;23(2):155-160.
14. De Jager CA, Oulhaj A, Jacoby R, Refsum H, Smith AD. Cognitive and clinical outcomes of homocysteine-lowering B-vitamin treatment in mild cognitive impairment: a randomized controlled trial. *Int J Geriatr Psychiatry*. 2012;27(6):592-600.
15. Kwok T, Lee J, Law CB, et al. A randomisedplacebocontrolled trial of homocysteine lowering to reduce cognitive decline in older demented people. *ClinNutr*. 2011;30(3):297-302.
16. Sun Y, Lu CJ, Chien KL, Chen ST, Chen RC. Efficacy of multivitamin supplementation containing vitamins B6 and B12 and folic acid as adjunctive treatment with a cholinesterase inhibitor in alzheimer's disease: a 26-week, randomized, double-blind, placebo-controlled study in Taiwanese patients. *Clin Ther*. 2007;29(10):2204-2214.
17. Group VTC. Effect of vitamins and aspirin on markers of platelet activation, oxidative stress and homocysteine in people at high risk of dementia. *J Intern Med*. 2003;254(1):67-75.
18. Fioravanti M, Ferrario E, Massaia M, et al. Low folate levels in the cognitive decline of elderly patients and the efficacy of folate as a treatment for improving memory deficits. *Arch GerontolGeriatr*. 1997;26(1):1-13.
19. Hankey GJ, Ford AH, Yi Q, et al. Effect of B vitamins and lowering homocysteine on cognitive impairment in patients with previous stroke or transient ischemic attack. *Stroke*. 2013;44(8):2232-2239.
20. Sommer BR, Hoff AL, Costa M. Folic acid supplementation in dementia: a preliminary report. *J Geriatr Psychiatry Neurol*. 2003;16(3):156-159.
21. Ting SKS, Earnest A, Li H, et al. B vitamins and cognition in subjects with small vessel disease: a substudy of VITATOPS, a randomized, placebo-controlled trial. *J Neurol Sci*. 2017;379:124-126.
22. Danielyan KE. Subcomponents of vitamine B complex regulate the growth and development of human brain derived cells. *Am J Biomed Res*. 2013;1(2):28-34.
23. Ou Z, Deng L, Lu Z, et al. Protective effects of Akkermansia muciniphila on cognitive deficits and amyloid pathology in a mouse model of Alzheimer's disease. *Nutr Diabetes*. 2020;10(1):12. doi:10.1038/s41387-020-0115-8
24. Sun HL, Feng Y, Zhang Q, et al. The Microbiome-Gut-Brain axis and dementia: a bibliometric analysis. *Int J Environ Res Public Health*. 2022;19(24):16549. doi:10.3390/ijerph192416549
25. Zhang DM, Ye JX, Mu JS, Cui XP. Efficacy of vitamin B supplementation on cognition in elderly patients with cognitive-related diseases: a systematic review and meta-analysis. *J Geriatr Psychiatry Neurol*. 2017;30(1):50-59.
26. Bermejo-Pareja F, Contador I, Del Ser T, et al. Predementia constructs: mild cognitive impairment or mild neurocognitive disorder? A narrative review. *Int J Geriatr Psychiatry*. 2021;36(5):743-755. doi:10.1002/gps.5474
27. Prajjwal P, Shashank S, Al-Ezzi SMS, et al. Frontotemporal dementia: addressing the scattered harbingers of genetics and its relationship with glucose metabolism, bipolar disorder, and amyotrophic lateral sclerosis. *Dis Mon*. 2023;69(5):101545. doi:10.1016/j.disamonth.2023.101545
28. Mitchell SL. Advanced dementia. *N Engl J Med*. 2015;372(26):2533-2540. doi:10.1056/NEJMcp1412652
29. (a) Angelucci F, Cechova K, Amlerova J, Hort J. Antibiotics, gut microbiota, and Alzheimer's disease. *J Neuroinflammation*. 2019;16(1):108; (b) Gemikonakli G, Mach J, Hilmer SN. Interactions between the aging gut microbiome and common geriatric giants: polypharmacy, frailty, and dementia. *The journals of gerontology. Series A, Biological sciences and medical sciences*. 2021;76(6):1019-128.
30. Tengeler AC, Kozicz T, Kiliaan AJ. Relationship between diet, the gut microbiota, and brain function. *Nutr Res*. 2018;76(8):603-617.
31. Welcome MO. Current perspectives and mechanisms of relationship between intestinal microbiota dysfunction and dementia: a review. *Dement Geriatr Cogn Dis Extra*. 2018;8(3):360-381.
32. Pellegrini C, Antonioli L, Colucci R, Blandizzi C, Fornai M. Interplay among gut microbiota, intestinal mucosal barrier and enteric neuroimmune system: a common path to neurodegenerative diseases? *Actaneuropathologica*. 2018;136:345-361.

33. Cady N, Peterson SR, Freedman SN, Mangalam AK. Beyond metabolism: the complex interplay between dietary phytoestrogens, gut bacteria, and cells of nervous and immune systems. *Front Neurol*. 2020;11:150.
34. Vogt NM, Kerby RL, Dill-McFarland KA, et al. Gut microbiome alterations in Alzheimer's disease. *Sci Rep*. 2017;7(1):13537.
35. Haran JP, Bhattarai SK, Foley SE, et al. Alzheimer's disease microbiome is associated with dysregulation of the anti-inflammatory P-glycoprotein pathway. *mBio*. 2019;10(3):e00632-19. doi:10.1128/mBio.00632-19
36. Zhu X, Li B, Lou P, et al. The relationship between the gut microbiome and neurodegenerative diseases. *Neurosci Bull*. 2021;Oct 37(10):1510-1522.
37. Ford AH, Almeida OP. Effect of vitamin B supplementation on cognitive function in the elderly: a systematic review and meta-analysis. *Drugs Aging*. 2019;36:419-434.
38. Cattaneo A, Cattane N, Galluzzi S, et al. Association of brain amyloidosis with pro-inflammatory gut bacterial taxa and peripheral inflammation markers in cognitively impaired elderly. *Neurobiol Aging*. 2017;49:60-68. doi:10.1016/j.neurobiolaging.2016.08.019
39. Azzini E, Ruggeri S, Polito A. Homocysteine: its possible emerging role in at-risk population groups. *Int J Mol Sci*. 2020;21(4):1421. doi:10.3390/ijms21041421
40. Smith AD, Refsum H, Bottiglieri T, et al. Homocysteine and dementia: an international consensus statement. *J Alzheimer's Dis*. 2018;62(2):561-570. doi:10.3233/JAD-171042
41. Bhargava S, Bhandari A, Choudhury S. Role of homocysteine in cognitive impairement and alzheimer's disease. *Indian J Clin Biochem*. 2018;33(1):16-20. doi:10.1007/s12291-017-0646-5
42. Luzzi S, Cherubini V, Falsetti L, Viticchi G, Silvestrini M, Toraldo A. Homocysteine, cognitive functions, and degenerative dementias: state of the art. *Biomedicines*. 2022;10(11):2741. doi:10.3390/biomedicines10112741
43. Saji N, Tsuduki T, Murotani K, et al. Relationship between the Japanese-style diet, gut microbiota, and dementia: a cross-sectional study. *Nutrition*. 2022;94:111524.
44. Moretti R, Caruso P. The controversial role of homocysteine in neurology: from labs to clinical practice. *Int J Mol Sci*. 2019;20(1):231. doi:10.3390/ijms20010231
45. Kumar A, Palfrey HA, Pathak R, Kadowitz PJ, Gettys TW, Murthy SN. The metabolism and significance of homocysteine in nutrition and health. *Nutr Metab (Lond)*. 2017;14:78. doi:10.1186/s12986-017-0233-z
46. Pi T, Liu B, Shi J. Abnormal homocysteine metabolism: an insight of alzheimer's disease from DNA methylation. *Behav Neurol*. 2020;2020:8438602. doi:10.1155/2020/8438602
47. McGarel C, Pentieva K, Strain JJ, McNulty H. Emerging roles for folate and related b-vitamins in brain health across the lifecycle. *Proc Nutr Soc*. 2015;74(1):46-55.
48. Nunes ACF, Piuvezam G. Nutritional supplementation of vitamin A and health-related outcomes in patients with multiple sclerosis: a protocol for a systematic review and meta-analysis of randomized clinical trials. *Medicine*. 2019;98(25):e16043. doi:10.1097/MD.0000000000016043
49. Merigliano C, Mascolo E, La Torre M, Saggio I, Vernì F. Protective role of vitamin B6 (PLP) against DNA damage in drosophila models of type 2 diabetes. *Sci Rep*. 2018;8(1):11432. doi:10.1038/s41598-018-29801-z
50. Antibiotics and B-vitamin requirements. *Nutr Res*. 1952;10(4):107-108. doi:10.1111/j.1753-4887.1952.tb01094.x
51. Hossain KS, Amarasena S, Mayengbam S. B vitamins and their roles in gut health. *Microorganisms*. 2022;10(6):1168. doi:10.3390/microorganisms10061168
52. Campbell N, Boustani M, Limbil T, et al. The cognitive impact of anticholinergics: a clinical review. *Clin Interv Aging*. 2009;4:225-233.
53. Ghahremani M, Smith EE, Chen HY, Creese B, Goodarzi Z, Ismail Z. Vitamin D supplementation and incident dementia. *Alzheimers Dement (Amst)*. 2023;15(1):e12404. doi:10.1002/dad2.12404
54. Yamamoto EA, Jørgensen TN. Relationships between vitamin D, gut microbiome, and systemic autoimmunity. *Front Immunol*. 2020;10:3141. doi:10.3389/fimmu.2019.03141
55. Kaushal M, Magon N. Vitamin D in pregnancy: a metabolic outlook. *Indian J Endocrinol Metab*. 2013;17(1):76-82. doi:10.4103/2230-8210.107862
56. Alisi L, Cao R, De Angelis C, et al. The relationships between vitamin K and cognition: a review of current evidence. *Front Neurol*. 2019;10:239. doi:10.3389/fneur.2019.00239
57. Kim M, Park SJ, Choi S, et al. association between antibiotics and dementia risk: a retrospective cohort study. *Front Pharmacol*. 2022;13:888333.
58. Fröhlich EE, Farzi A, Mayerhofer R, et al. Cognitive impairment by antibiotic-induced gut dysbiosis: analysis of gut microbiota-brain communication. *Brain Behav Immun*. 2016;56:140-155.
59. Mosaferi B, Jand Y, Salari AA. Antibiotic-induced gut microbiota depletion from early adolescence exacerbates spatial but not recognition memory impairment in adult male C57BL/6 mice with Alzheimer-like disease. *Brain Res Bull*. 2021;176:8-17.
60. Kim M, Park SJ, Choi S, et al. Association between antibiotics and dementia risk: a retrospective cohort study. *Front Pharmacol*. 2022;13:888333. doi:10.3389/fphar.2022.888333
61. Angelucci F, Cechova K, Amlerova J, Hort J. Antibiotics, gut microbiota, and Alzheimer's disease. *J Neuroinflammation*. 2019;16(1):108. doi:10.1186/s12974-019-1494-4
62. Markowiak-Kopeć P, Śliżewska K. The effect of probiotics on the production of short-chain fatty acids by human intestinal microbiome. *Nutrients*. 2020;12(4):1107.
63. Kobyliak N, Falalyeyeva T, Tsyryuk O, et al. New insights on strain-specific impacts of probiotics on insulin resistance: evidence from animal study. *J Diabetes Metab Disord*. 2020;19(1):289-296.
64. Kim YA, Keogh JB, Clifton PM. Probiotics, prebiotics, synbiotics and insulin sensitivity. *Nutr Res Rev*. 2018;31(1):35-51.
65. Ballini A, Gnoni A, Vito DD, et al. Effect of probiotics on the occurrence of nutrition absorption capacities in healthy children: a randomised double-blinded placebo-controlled pilot study. 2019;23(19):8645-8657.

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APPENDIX A: Showing search procedure on MEDLINE database

Search number	Query	Filters	Search details	Results	Time
1	[gut microbiota[Title/Abstract]] AND [[vitamins[Title/Abstract]] OR [vitamins[MeSH Terms]]] AND [[observationalstudy[Filter] OR randomizedcontrolledtrial[Filter]] AND [2012:2023[pdat]]]	Observational Study, Randomized Controlled Trial	["gut microbiota"[Title/Abstract] AND ["vitamins"[Title/Abstract] OR "vitamins"[MeSH Terms]] AND [["observational study"[Publication Type] OR "randomized controlled trial"[Publication Type]] AND 2012/01/01:2023/12/31[Date - Publication]]] AND [observationalstudy[Filter] OR randomizedcontrolledtrial[Filter]]	10	14:00:41
2	[gut microbiota[Title/Abstract]] AND [[antibiotics[Title/Abstract]] OR [antibiotics[MeSH Terms]]] AND [[observationalstudy[Filter] OR randomizedcontrolledtrial[Filter]] AND [2012:2023[pdat]]]	Observational Study, Randomized Controlled Trial	["gut microbiota"[Title/Abstract] AND ["antibiotics"[Title/Abstract] OR "antibacterial agents"[MeSH Terms]] AND [["observational study"[Publication Type] OR "randomized controlled trial"[Publication Type]] AND 2012/01/01:2023/12/31[Date - Publication]]] AND [observationalstudy[Filter] OR randomizedcontrolledtrial[Filter]]	86	14:01:16
3	[gut microbiota[Title/Abstract]] AND [dementia[Title/Abstract]]	Observational Study, Randomized Controlled Trial	["gut microbiota"[Title/Abstract] AND "dementia"[Title/Abstract]] AND [observationalstudy[Filter] OR randomizedcontrolledtrial[Filter]]	2	14:02:01
4	[[gut microbiota[Title/Abstract]] AND [[vitamins[Title/Abstract]] OR [vitamins[MeSH Terms]]] AND [[observationalstudy[Filter] OR randomizedcontrolledtrial[Filter]] AND [2012:2023[pdat]]] AND [observationalstudy[Filter] OR randomizedcontrolledtrial[Filter]]] AND [dementia[Title/Abstract]]	Observational Study, Randomized Controlled Trial	["gut microbiota"[Title/Abstract] AND ["vitamins"[Title/Abstract] OR "vitamins"[MeSH Terms]] AND [["observational study"[Publication Type] OR "randomized controlled trial"[Publication Type]] AND 2012/01/01:2023/12/31[Date - Publication]] AND ["observational study"[Publication Type] OR "randomized controlled trial"[Publication Type]] AND "dementia"[Title/Abstract]] AND [observationalstudy[Filter] OR randomizedcontrolledtrial[Filter]]	0	14:02:54
5	[[gut microbiota[Title/Abstract]] AND [[antibiotics[Title/Abstract]] OR [antibiotics[MeSH Terms]]] AND [[observationalstudy[Filter] OR randomizedcontrolledtrial[Filter]] AND [2012:2023[pdat]]]AND [observationalstudy[Filter] OR randomizedcontrolledtrial[Filter]]] AND [dementia[Title/Abstract]]	Observational Study, Randomized Controlled Trial	["gut microbiota"[Title/Abstract] AND ["antibiotics"[Title/Abstract] OR "antibacterial agents"[MeSH Terms]] AND [["observational study"[Publication Type] OR "randomized controlled trial"[Publication Type]] AND 2012/01/01:2023/12/31[Date - Publication]] AND ["observational study"[Publication Type] OR "randomized controlled trial"[Publication Type]] AND "dementia"[Title/Abstract]] AND [observationalstudy[Filter] OR randomizedcontrolledtrial[Filter]]	0	14:03:24
6	[dementia[Title/Abstract]] AND [[antibiotics[Title/Abstract]] OR [antibiotics[MeSH Terms]]] AND [[observationalstudy[Filter] OR randomizedcontrolledtrial[Filter]] AND [2012:2023[pdat]]]	Observational Study, Randomized Controlled Trial	["dementia"[Title/Abstract] AND ["antibiotics"[Title/Abstract] OR "antibacterial agents"[MeSH Terms]] AND [["observational study"[Publication Type] OR "randomized controlled trial"[Publication Type]] AND 2012/01/01:2023/12/31[Date - Publication]]] AND [observationalstudy[Filter] OR randomizedcontrolledtrial[Filter]]	13	14:05:43

(Continues)

Search number	Query	Filters	Search details	Results	Time
7	[dementia[Title/Abstract]] AND [[vitamins[Title/Abstract]] OR [vitamins[MeSH Terms]]] AND [[observationalstudy[Filter] OR randomizedcontrolledtrial[Filter]] AND [2012:2023[pdat]]]	Observational Study, Randomized Controlled Trial	["dementia"[Title/Abstract] AND ["vitamins"[Title/Abstract] OR "vitamins"[MeSH Terms]] AND [["observational study"[Publication Type] OR "randomized controlled trial"[Publication Type]] AND 2012/01/01:2023/12/31[Date - Publication]]] AND [observationalstudy[Filter] OR randomizedcontrolledtrial[Filter]]	21	14:06:09