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REVIEW

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Dietary factors and cognitive aging: Mapping epidemiological evidence and the role of gut microbiota

Hui Chen,[1,15,*] Jie Shen,[2,15] Xiaoran Liu,[3] Jiaqi Ni,[4,5,6] Shuang Rong,[7] Ju-Sheng Zheng,[8] Weili Xu,[9] Guowei Huang,[10] Benyan Luo,[1] Yan Zheng,[11] Marta Guasch-Ferré,[12,13,14] Jordi Salas-Salvadó,[4,5,6] and Changzheng Yuan[2,12,*]

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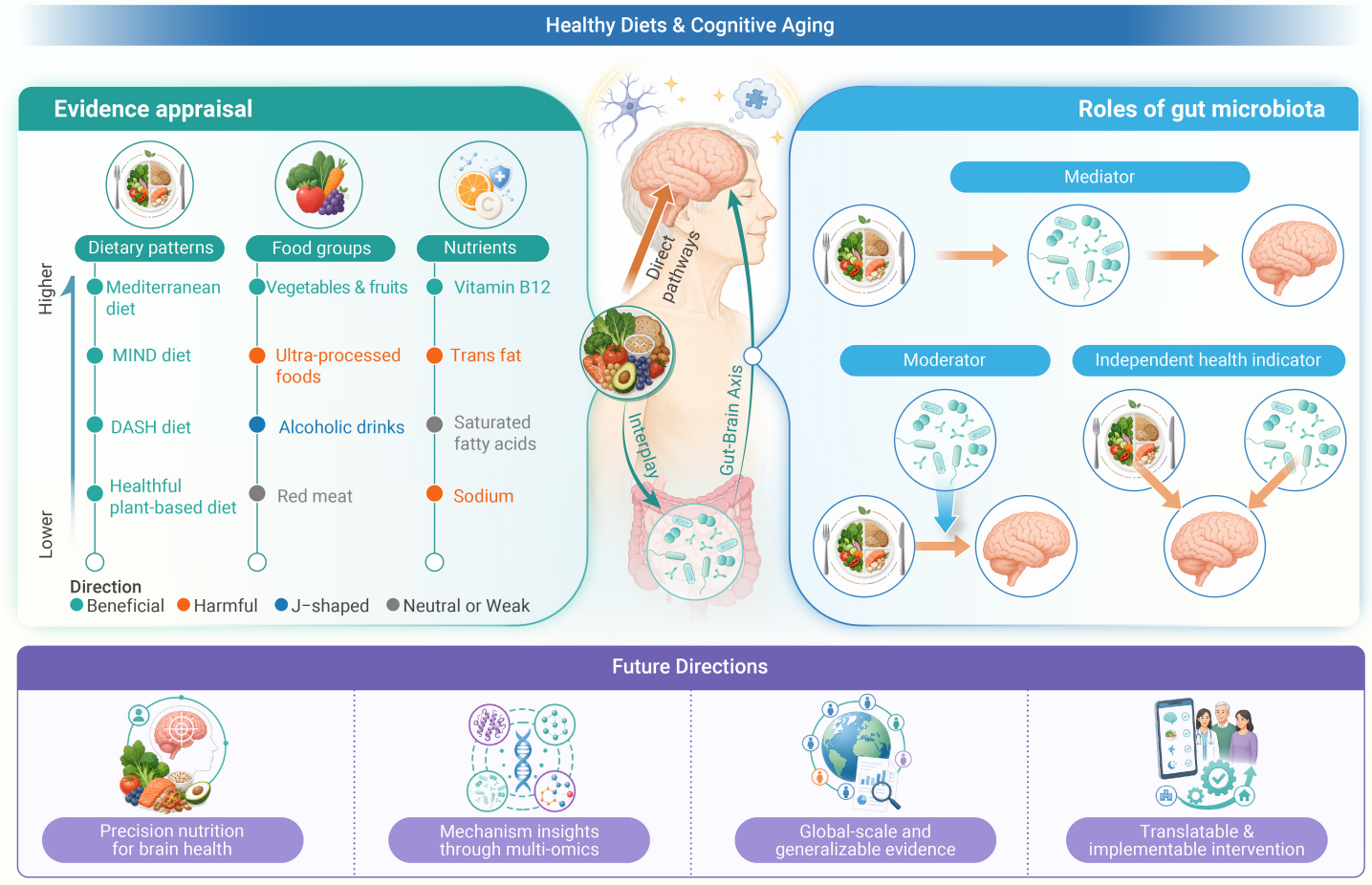
GRAPHICAL ABSTRACT



PUBLIC SUMMARY

- Healthy dietary patterns have generally been associated with better cognitive health.
- Evidence on specific dietary components and cognitive aging offers clues to diverse mechanistic pathways.
- Gut microbiota may act as a mediator, moderator, or health indicator in the associations of diet with cognition.
- Diet-microbiota-cognition research faces challenges in measurement, methodology, and generalizability.
- Further work should clarify causal pathways and personalize dietary strategies for dementia prevention.

REVIEW

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Dietary factors and cognitive aging: Mapping epidemiological evidence and the role of gut microbiota

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Dementia is a growing global health challenge with limited pharmacological treatments. Emerging evidence from randomized controlled trials and prospective cohort studies suggests that healthy dietary patterns may contribute to the prevention or delay of cognitive decline. This review summarizes current evidence on the relations of overall dietary patterns and specific foods and nutrients to cognitive aging, with a particular focus on the potential role of gut microbiota, which is largely shaped by diet. Certain healthy dietary patterns, such as the Mediterranean and the Mediterranean–DASH Intervention for Neurodegenerative Delay (MIND) diets, characterized by specific foods (e.g., vegetables and fruits) and dietary nutrients (e.g., n-3 fatty acids, B vitamins, and carotenoids) have shown potential benefits on cognitive health. However, inconsistencies across study findings necessitate further investigation. We review how the gut microbiota may mediate or moderate the diet-cognition association, or serve as a marker for cognitive health, particularly through mechanisms involving metabolic, immune, and neuroinflammatory pathways. Finally, we highlight key methodological challenges, including variability in exposure assessment, study design, and population heterogeneity, and propose a roadmap for future research, advocating for large-scale, multi-omics studies across diverse populations. These efforts are expected to facilitate the development of precision nutrition strategies for the prevention of cognitive decline and dementia.

INTRODUCTION

Dementia poses major and growing challenges for older adults, caregivers, and health systems, with an estimated 57 million people living with dementia worldwide in 2021.[1-3] Although recent pharmacological advances have brought hope for slowing progression in selected subtypes or at specific disease stages, particularly in early Alzheimer's disease (AD),[4] dementia remains largely irreversible. This places prevention at the center of clinical and public health strategy. In this context, the 2024 Lancet Commission estimated that around 45% of dementia cases are potentially preventable or delayed through modification of 14 risk factors.[1] While diet has been well recognized for its protective effects against cardiometabolic conditions,[5] which are considered major risk factors for dementia, evidence regarding the role of diet in cognitive aging remains debated due to methodological concerns.[6-7]

Over the past two decades, a large body of research has examined the associations between dietary patterns, nutrients, and foods, and cognitive outcomes, as well as placing them in a wider landscape of healthy aging.[8] In particular, healthy dietary patterns such as the Mediterranean, Dietary Approaches to Stop Hypertension (DASH), and Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diets, have shown promising associations with cognitive health.[9] Regionally distinctive dietary patterns, such as Chinese,[10] Japanese[11] and Nordic dietary patterns,[12] have also shown potential benefits for cognitive health in their respective populations. However, evidence on many other dietary factors remains uncertain, and even the most encouraging findings on diets have not been entirely consistent across populations and study designs.[9] Reported associations are often modest in magnitude and heterogeneous due to differences in dietary assessment, outcome definition, duration of follow-up, and population demographic and genetic characteristics. As such, the key challenges for the field extend to understanding the sources of inconsistent findings, identifying the individuals and settings in which dietary strategies may be most relevant, and addressing barriers to implementation, scalability, and reproducibility.

In this context, the role of gut microbiota in cognitive aging has been explored.[13–16] As a dynamic and functionally active ecosystem, the gut microbiota is strongly shaped by habitual diet, host health, and behaviors. It may influence host metabolism, immune and neural signaling, and the production of bioactive metabolites relevant to brain aging.[17-18] In this framework, it may act as a mediator that carries dietary signals to the brain, a moderator of inter-individual variability in response to the same diet, or a marker of individual health status in the diet-cognition relationship. This framework may help explain why associations between diet and cognitive outcomes differ across populations and settings, while providing a rationale for precision-prevention approaches.

Therefore, this narrative review aims to update the emerging evidence on the potential role of dietary factors in cognitive aging. We further review the possible roles of the gut microbiota as an interface between dietary exposures and cognitive health, emphasizing its dynamic and functional relevance. Finally, we discuss major limitations in the current evidence base and propose a roadmap for future experimental and mechanistic studies. Throughout this review, priority is given to evidence from systematic reviews and meta-analyses of human studies, with large-scale, long-term, randomized controlled trials (RCTs) and prospective cohort studies included where relevant to supplement or update the existing literature. Details of the literature research and evidence appraisal are presented in the Supplemental Information.

MAPPING EVIDENCE OF DIETARY FACTORS IN COGNITIVE AGING

Nutrition holds promise as a modifiable strategy to reduce dementia risk.

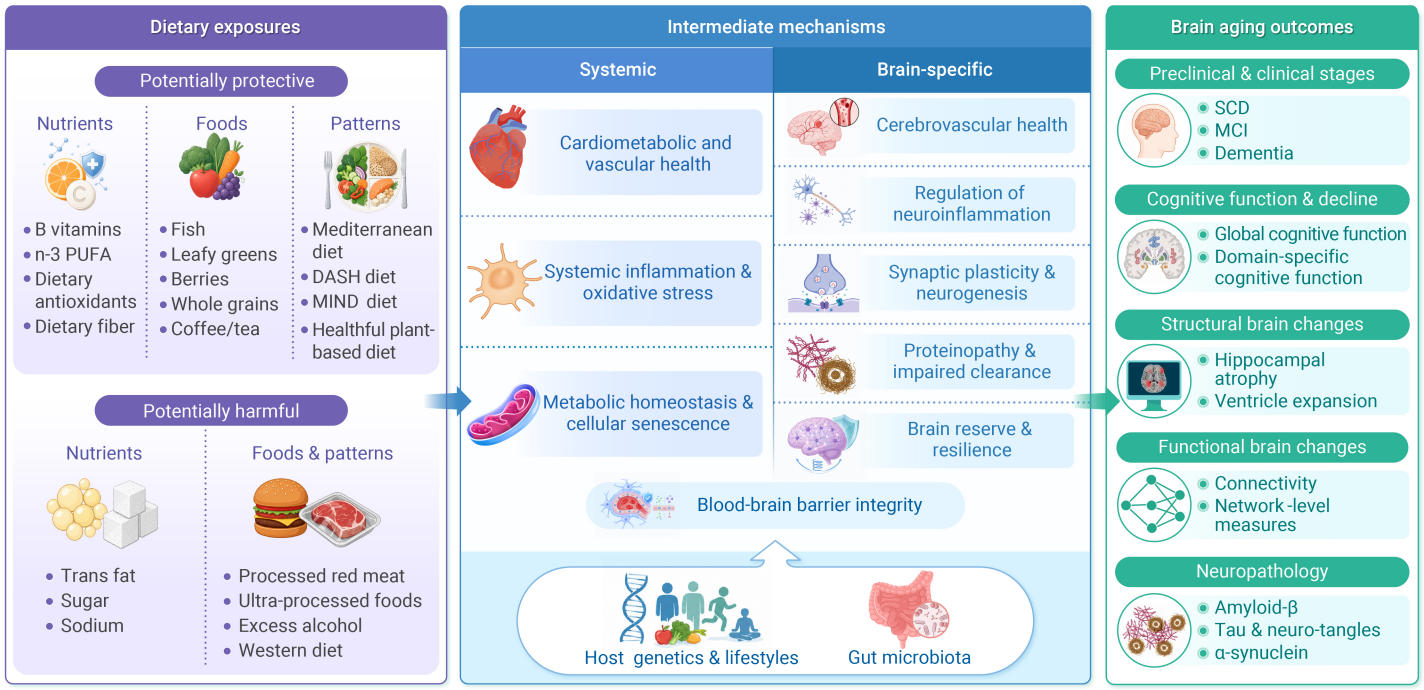

Figure 1. Conceptual framework of hypothesized intermediate processes linking dietary exposures to brain-aging outcomes Abbreviations: DASH, the Dietary Approaches to Stop Hypertension (DASH) diet; MCI, mild cognitive impairment; MIND, the Mediterranean–DASH Intervention for Neurodegenerative Delay; PUFA, polyunsaturated fatty acid; SCD, subjective cognitive decline.

Over the past decade, research attention has shifted from single nutrients or foods to dietary patterns, which better capture the multidimensional nature of diet and the complex interactions among foods and nutrients.[19-20] Nevertheless, the focus on individual foods and nutrients remains valuable for generating mechanistic insights and identifying microbiota-dependent pathways through which diet may influence cognitive health and cognitive aging (Figure 1).

Dietary patterns

Evidence from prospective cohort studies and clinical trials has generally supported associations between healthy dietary patterns and better cognitive outcomes. While claims for the established superiority of any one specific diet over others are still premature,[21] the dietary patterns of greatest interest in relation to cognitive aging are the Mediterranean diet, the DASH diet, and the MIND diet.

The **Mediterranean diet** is derived from the traditional eating habits of populations in the Mediterranean region, characterized by a high intake of plant-based foods (fruits, vegetables, legumes, whole grains, nuts), olive oil as the principal source of fat, low intake of red meat, and modest alcohol consumption during meals. In observational studies, its greater adherence was associated with better cognitive performance, slower cognitive decline, and a lower risk of dementia by 18%,[22–24] with potentially stronger associations in *APOE* ε4 homozygotes.[25] Evidence from two sub-studies of the PREDIMED (PREvención con DIeta MEDiterránea) trial further suggested that a Mediterranean diet supplemented with either extra-virgin olive oil or mixed nuts may improve cognitive performance over 4.1 to 6.5 years of follow-up, which provided causal evidence on the cognitive effects of the Mediterranean diet.[26-27]

The **DASH diet** was developed for blood-pressure control and has been examined in relation to broader cardiovascular and cognitive outcomes. It emphasizes fruits, vegetables, whole grains, low-fat dairy products, nuts, and legumes, while limiting sodium, red and processed meats, and sugar-sweetened foods and beverages. Given the close link between cardiovascular health and brain aging, observational studies also suggested its associations with better cognitive profiles in middle-aged and older adults.[28-29] However, evidence from trials has been less consistent. In the ENLIGHTEN trial, a 2×2 factorial trial involving 160 sedentary older adults with cardiovascular risk factors, the DASH diet showed no independent cognitive benefit beyond that achieved with aerobic exercise.[30] Nonetheless, another 4-month RCT reported that the DASH diet resulted in greater improvements in cognitive function.[31] Further research, especially large-scale and long-term RCTs, is needed to better understand the potential cognitive benefits of the DASH diet and its mechanisms of action.

The **MIND diet**, devised in 2015, integrates key elements of the Mediterranean and DASH diets while placing greater emphasis on foods and nutrients considered particularly relevant to brain health.[32-33] It encourages consumption of 10 food groups considered beneficial for brain health and limits 5 groups considered less healthy. Over the past decade, observational evidence for the MIND diet has been encouraging. Meta-analyses have linked its higher adherence to slower cognitive decline and a lower risk of dementia (17% lower risk comparing the highest vs. lowest adherence).[34–37] Greater MIND adherence has also been associated with slower brain atrophy over time[38–41] and lower burdens of brain pathology and pathology-independent cognitive reserve.[42–45] More recently, the MIND diet has been integrated into a multi-domain lifestyle intervention package for dementia prevention.[46] However, in a 3-year RCT of 604 older adults with overweight or obesity and a family history of dementia, while both the control group receiving mild caloric restriction and the MIND diet group showed improvements in cognitive function, no significant between-group difference was observed.[47] The use of an active control diet, the relatively short follow-up for detecting divergence in cognitive trajectories, and potential practice effects of cognitive testing may contribute to this finding.[48] Subsequent analyses from the MIND trial suggested that *APOE* ε4 carriers may derive greater cognitive benefits from higher circulating nutrient concentrations.[49]

Other dietary patterns have also attracted growing interest, although the evidence base remains less developed and is derived largely from observational studies. For example, broader dietary indices that reflect the overall healthfulness of the diet, such as the Alternative Healthy Eating Index (AHEI), have also been linked to cognitive health.[50] Regionally characterized diets, such as the Chinese,[10] Japanese[11] and Nordic dietary patterns,[12] have shown potential benefits for cognitive health; however, further replication across diverse populations is needed. Emerging dietary patterns of interest include plant-based dietary patterns, particularly healthful plant-based diets;[51-52] the planetary health diet,[53] which was designed to jointly promote human and environmental health; and data-driven dietary indices for predictions of inflammation, hyperinsulinemia[29,54-55] and dementia.[56] However, their compar-

ative efficacy, underlying mechanisms, and clinical relevance remain insufficiently established.

Food groups

Importantly, although these dietary patterns capture distinct constructs, they share several key food-based recommendations that are readily translated into intuitive and actionable public health messages. These generally include higher intake of minimally processed plant foods and selected sources of high-quality animal protein and fat; and lower intake of foods high in added sugars, sodium, and saturated fats. We hereby summarize the available evidence for major food groups in relation to cognitive aging.

Vegetables and fruits, recommended by multiple dietary patterns, are often rich in fiber, vitamins, minerals, and phytochemicals, and are widely considered candidate foods for cognitive health.[57-58] A meta-analysis of 16 observational studies reported that higher fruit and vegetable intake was associated with more favorable cognitive outcomes, with increasingly favorable outcomes at higher daily intakes.[59] Among sub-categories, cognitive benefits appeared stronger for green-leafy vegetables and berries, often rich in antioxidants and vitamins.[60-61] A study based on the Rush Memory and Aging Project (MAP) reported that consuming 1-2 servings per day of green-leafy vegetables was associated with a slower rate of cognitive decline, with an effect size equivalent to being approximately 11 years younger than participants who rarely or never consumed green leafy vegetables.[62]

Whole grains, often rich in dietary fiber, are associated with improved metabolic markers linked to cognitive function, including inflammation, glucose metabolism, blood pressure, and cholesterol. However, evidence on whole grain intake and cognitive outcomes varied.[63] This inconsistency may be partly attributable to food processing: some products marketed as whole-grain products may be ultra-processed, which may diminish the protective effects typically associated with intact whole grains. It may also reflect differences in population characteristics, such as ethnic background.[64]

Nuts and seeds are rich in monounsaturated fats (MUFAs), polyunsaturated fats (PUFAs) and protein. In particular, walnuts are abundant sources of α-linolenic acid, a plant-based n-3 fatty acid. Previous systematic reviews from RCTs and cohort studies, combined, suggest a potential cognitive benefit of mixed nut intake in populations at risk of cognitive decline.[65-66] However, another meta-analysis of five RCTs did not find a significant effect of nuts on cognitive performance.[67] For example, the Walnuts And Healthy Aging trial reported that walnut supplementation for 2 years had no effect on cognition in healthy elders.[68] **Soy products** are often rich in natural phytoestrogens and have been associated with a reduced likelihood of developing major neurocognitive disorders, with the association being more pronounced in individuals without a history of stroke.[69] Pooled results from five cohort studies further indicate that higher legume intake was associated with a lower risk of all-cause dementia.[70] These suggest that plant-protein foods may support cognitive health. However, evidence remains limited by heterogeneity in the specific foods evaluated, intake ranges, and study populations, and larger well-designed trials are needed to clarify the cognitive effects of individual plant-protein foods.

Meat and poultry are major sources of animal protein and provide essential amino acids required for multiple physiological processes. However, associations with cognitive health appear to differ by meat subtype. A cohort study of 133,771 US participants showed that higher intake of red meat, particularly processed red meat, was associated with an increased risk of dementia and worse cognitive performance.[71] Heme iron, saturated fat, and choline/betaine-microbiota interplay in trimethylamine N-oxide (TMAO) production have been hypothesized as potential mechanisms underlying these associations. However, evidence from previous meta-analyses has been less consistent, indicating that this association is not yet settled.[70,72] A more recent cohort analysis suggested that the associations for meat intake may differ by genetic background: higher total meat intake was associated with slower cognitive decline and lower dementia risk only among *APOE* ε4 carriers but not non-carriers.[73] For poultry, specifically, evidence remains limited and generally suggests neutral associations, with some studies reporting modest inverse trends that are not consistent across analyses.[72-73]

Compared with red meats, **fish and seafood** are usually considered higher-quality sources of protein and are rich in long-chain n-3 polyunsaturated fatty acids (PUFAs), with additional neuroprotective nutrients such as vitamin D, selenium, iodine, and B vitamins. Epidemiologic evidence suggests that higher fish intake may be associated more consistently with some cognitive domains, particularly processing speed.[74] A dose-response meta-analysis indicated that fish intake >1 serving per week was associated with slower cognitive and memory decline.[74] However, it remains unclear whether these findings may vary according to fish type, preparation methods, background dietary patterns, and presence of potential contaminants.[75]

Evidence for total **dairy and fermented dairy products (e.g., yogurt)** remains mixed. A meta-analysis of 15 prospective studies suggested a nonlinear inverse association between dairy intake and cognitive decline or incident dementia, with a lower risk observed at approximately 150 grams per day of total dairy intake; however, the association may differ by dairy product types and population characteristics.[76] Some observational studies have reported more favorable cognitive associations for cheese, but these findings should be interpreted cautiously given product-specific confounding and limited trial evidence.[77] By contrast, results for yogurt were less consistent, with two studies finding positive associations and one showing no association.[76] Differences in intake of fermented dairy products or characteristics in populations, as well as added sweeteners in yogurts, could contribute to these inconsistencies. In particular, host genetic background and gut microbiota may modify responses to dairy foods and their fermentation-derived metabolites.[78-79] Future studies integrating dietary assessment with host genomics and microbiome profiling may help clarify for whom and through which pathways dairy and fermented dairy products influence cognitive aging.

Coffee and tea have garnered attention due to their rich content in bioactive compounds, including caffeine and polyphenols. A meta-analysis of 38 cohorts showed that increased tea consumption was associated with a decreased risk of dementia and AD, and a non-linear relationship was found between coffee and dementia, with a protective association observed for 1 to 3 cups per day of coffee intake,[80] which was further supported by recent large-scale cohort studies.[81-82] These associations may be partly explained by the anti-inflammatory properties of polyphenols, as is supported by a recent study reporting the potential of coffee and tea consumption in mitigating systemic inflammation.[83] However, high caffeine intake may lead to disrupted sleep patterns[84] and blood pressure changes,[85] which may explain the potential risk of excessive consumption of coffee.

Olive oil, a key food product of the Mediterranean diet, is rich in monounsaturated fatty acids and polyphenols, which may contribute to the regulation of oxidative stress and attenuation of neuroinflammation.[86–88] Consistent with these potential mechanisms, a systematic review of cross-sectional studies, prospective cohort studies and RCTs reported that olive oil consumption may enhance cognitive function and reduce cognitive decline, although further large-scale studies are required to strengthen the evidence.[89] Although observational studies directly linking olive oil consumption to dementia incidence are limited, frequent olive oil consumption has been associated with a lower risk of dementia-related mortality compared with no olive oil consumption. In addition, substitution analyses showed that replacing margarine and mayonnaise with equivalent amounts of olive oil was associated with a lower risk of dementia mortality.[90]

Alcoholic beverages remain among the most debated components in cognitive health. Some observational studies and meta-analyses have reported non-linear associations between alcohol consumption and cognitive outcomes, with lower risks observed among individuals reporting low-to-moderate intake compared with abstainers or heavy drinkers.[91] However, these findings should be interpreted cautiously because alcohol use is strongly patterned by socioeconomic status, diet quality, social engagement, comorbidities, and other health-related behaviors. In addition, comparisons with abstainers may be affected by abstainer bias, including former drinkers who stopped drinking because of declining health, and reverse causation cannot be excluded. Similarly, another meta-analysis of 12 studies suggested an association between moderate wine consumption and slower cognitive decline, potentially due to its richness in bioactive compounds such as resveratrol, phenolic acids, and flavonoids.[92] However, as alcohol is a toxic and psychoactive substance with established health risks, future studies are needed to better address confounding and changes in drinking behavior over time to clarify whether the observed associations reflect causal effects of

alcohol, beverage-specific bioactive compounds, or correlated lifestyle factors.

Sugar-sweetened beverages (SSB), packaged snacks, and many fast foods, are commonly classified as **ultra-processed foods** (UPFs) and discouraged by most healthy dietary patterns. These products are often energy-dense and may adversely affect cardiometabolic health; higher UPF intake has also been associated with faster cognitive decline and a greater risk of dementia,[93] as indicated by a meta-analysis of ten observational studies.[94] Potential mechanisms may involve poorer nutrient profiles, food-matrix disruption, and exposure to certain additives or processing-related compounds. These pathways may include gut microbial dysbiosis and downstream neuroinflammation, vascular dysfunction, and brain insulin resistance.[94] However, the UPF construct, most commonly operationalized using the NOVA classification, remains contested.[95] Major concerns include the substantial nutritional heterogeneity within the UPF category (e.g., fortified products that may contribute meaningfully to nutrient adequacy) and challenges in accurately operationalizing NOVA using conventional food frequency questionnaires (FFQs) with limited information on product formulation, brand, and whether foods were commercially prepared or homemade. Associations with UPF intake may therefore partly reflect broader dietary-pattern characteristics, including Western-style dietary patterns, lower overall diet quality, and correlated lifestyle or socioeconomic factors.[96] Future research should evaluate UPF intake within the context of overall dietary patterns and food subgroups, rather than treating UPFs as a nutritionally homogeneous food category.

Nutrients and non-nutrient natural compounds

Understanding the effects of dietary patterns and food groups requires consideration of their underlying nutrient composition and bioactive constituents. Foods represent complex matrices in which macronutrients, micronutrients, and non-nutrient natural compounds may act independently or synergistically to influence biological pathways relevant to brain structure, function, and cognitive aging.

Macronutrients provide the structural basis and energy required for brain functioning and influence cognition through glucose and insulin metabolism, neurotransmitter systems, and cerebral oxidative and inflammatory processes. The current literature, although still mixed, highlights that the quality, food sources, and dietary context of macronutrients, rather than total quantity alone, are essential for cognitive health.

Carbohydrates are the primary fuel for the brain and may influence glucose metabolism and insulin signaling; however, existing evidence on total carbohydrate intake and cognitive outcomes remains inconsistent. Among subtypes, a larger body of evidence links higher intake of simple carbohydrates with worse cognition.[97] However, a recent cohort study of 27,786 participants reported that higher free sugar intake was not associated with overall dementia risk, but moderate intake was related to lower risk of vascular dementia.[98] This pattern was further observed in a recent multicohort study reporting that late-life (≥ 65 years) consumption of SSB was not associated with dementia risk.[99] However, given their detrimental effects on metabolic health and related chronic diseases during early life and midlife, the effects of early-life consumption of sugar and SSB on the risk of dementia warrant further investigation. In contrast, dietary complex carbohydrates (e.g., fiber), predominantly from less processed plant-based foods, appear beneficial.[100–103] In a study of 2729 Japanese individuals, dietary fiber intake, particularly soluble fiber, was inversely associated with risk of disabling dementia.[101] As dietary fiber is metabolized by the gut microbiota,[104] the potential benefits may depend on the host's microbial context, which provided preliminary clues for personalized dietary strategies.

Protein supplies amino acids needed for neurotransmitter synthesis, neuronal repair, and maintenance of brain structure and function during aging. In a large US cohort study of 49,493 women and 27,842 men followed for over 20 years, higher protein intake was associated with lower odds of subjective cognitive decline (SCD) when replacing carbohydrates.[105] Notably, plant-based protein sources showed a stronger inverse association with SCD than animal-based protein sources, with higher intakes of beans, legumes, fish, and lean poultry, rather than processed meat products, offering potential benefits. Nevertheless, epidemiological studies on total dietary protein intake and objective cognitive decline remain inconclusive.

Fat and fatty acids, of various lengths and saturation profiles, are essential for neuronal membranes, myelin integrity, and cell signaling. Different types of dietary fatty acids may differentially influence cognitive decline and neurodegeneration.[106] PUFAs, especially n-3 fatty acids, have long been considered contributors to brain health because of their roles in membrane fluidity, synaptic plasticity, and neuroinflammatory regulation.[107-108] A meta-analysis of 24 RCTs suggested that n-3 PUFA supplementation may provide modest benefits for executive function in middle-aged and older adults without dementia, particularly among those with low baseline intake of dietary docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA).[109] Cohort studies further revealed that the potential cognitive benefits of long-chain n-3 fatty acids tended to be stronger in *APOE* ε4 carriers.[110-111] Saturated fatty acids (SFAs), which have been extensively linked to worse vascular and metabolic health, have been associated with less favorable cognitive outcomes in previous meta-analyses[112] and a recent cohort analysis.[113] The evidence on MUFAs, however, is emerging and still inconsistent, although some large-scale studies have suggested potential cognitive benefits.[113–115] While overall trans fatty acids are associated with worse cognitive outcomes,[116] there is a certain level of heterogeneity, and residual confounding by unhealthy lifestyles cannot be excluded in existing studies.[107]

At the micronutrient level, vitamins, minerals, and bioactive compounds may influence brain aging through several interconnected biological pathways. The following sections focus on compounds selected for their roles in three pathways of particular relevance to cognitive aging: one-carbon metabolism and neurotransmitter synthesis; antioxidant and anti-inflammatory defense; and neuroendocrine and neuroimmune regulation.

Dietary B vitamins and choline are essential in one-carbon metabolism, methylation processes, homocysteine regulation, and neurotransmitter synthesis. B vitamins (e.g., folate, B6, B12) are central to homocysteine metabolism, and elevated homocysteine is a well-established risk factor for cognitive decline and dementia. A meta-analysis of 14 RCTs found that B vitamin supplementation may slow cognitive decline compared with placebo,[117] particularly in dementia-free populations receiving intervention for more than 12 months. Across individual B vitamins, higher folate intake (but not higher B12 or B6 intake) was significantly associated with a lower risk of incident dementia in older adults. Dietary choline shares many similarities with B vitamins and acts as a precursor of the neurotransmitter acetylcholine, with dietary intake serving as the primary source for circulating choline.[118] Recent studies revealed a non-linear pattern in its association with dementia,[119] which is mechanistically interesting because the same dietary choline that supplies acetylcholine synthesis can also be converted by trimethylamine (TMA)-producing gut bacteria into TMAO, a metabolite linked to vascular pathology. Nonetheless, other studies did not report a similar non-linearity,[120-121] which may emerge from the different levels of absolute intake.

Dietary antioxidants include a wide range of nutrients (e.g., **vitamins C and E**) and non-nutrient food ingredients (e.g., carotenoids and polyphenols).[122] Despite strong biological plausibility and potential for reducing oxidative stress, the evidence on vitamin E and AD remains debated,[7,123] with a recent study showing that higher vitamin E intake from dietary sources alone was associated with slower cognitive decline.[124] A meta-analysis of 11 cohort studies (N = 35,954) found that ≥ 75 mg per day of dietary vitamin C was associated with reduced AD risk, but no significant association was observed for vitamin E intake or supplementation.[125] **Carotenoids**, a family of compounds that cannot be synthesized by humans and can only be obtained through diet or supplements, are fat-soluble plant pigments commonly found in dark-colored vegetables and fruits.[126] A meta-analysis of nine clinical trials reported that carotenoid supplementation improved cognitive performance in healthy adults aged 45-78 years.[127] Studies on its dietary intake[128-129] and circulating levels[130] reported similar beneficial associations. Emerging evidence suggests stronger associations for non-provitamin A carotenoids (lutein-zeaxanthin and lycopene) compared with provitamin A subtypes (α-carotene, β-carotene and β-cryptoxanthin)[131-132] and potentially greater benefits in *APOE* ε4 carriers.[49] **Polyphenols** may also act, to varying degrees, against neuroinflammation, loss of synaptic plasticity, mitochondrial dysfunction, and reduced cerebral blood flow.[133] Flavonoids and other polyphenols have shown promising associations with slower cognitive

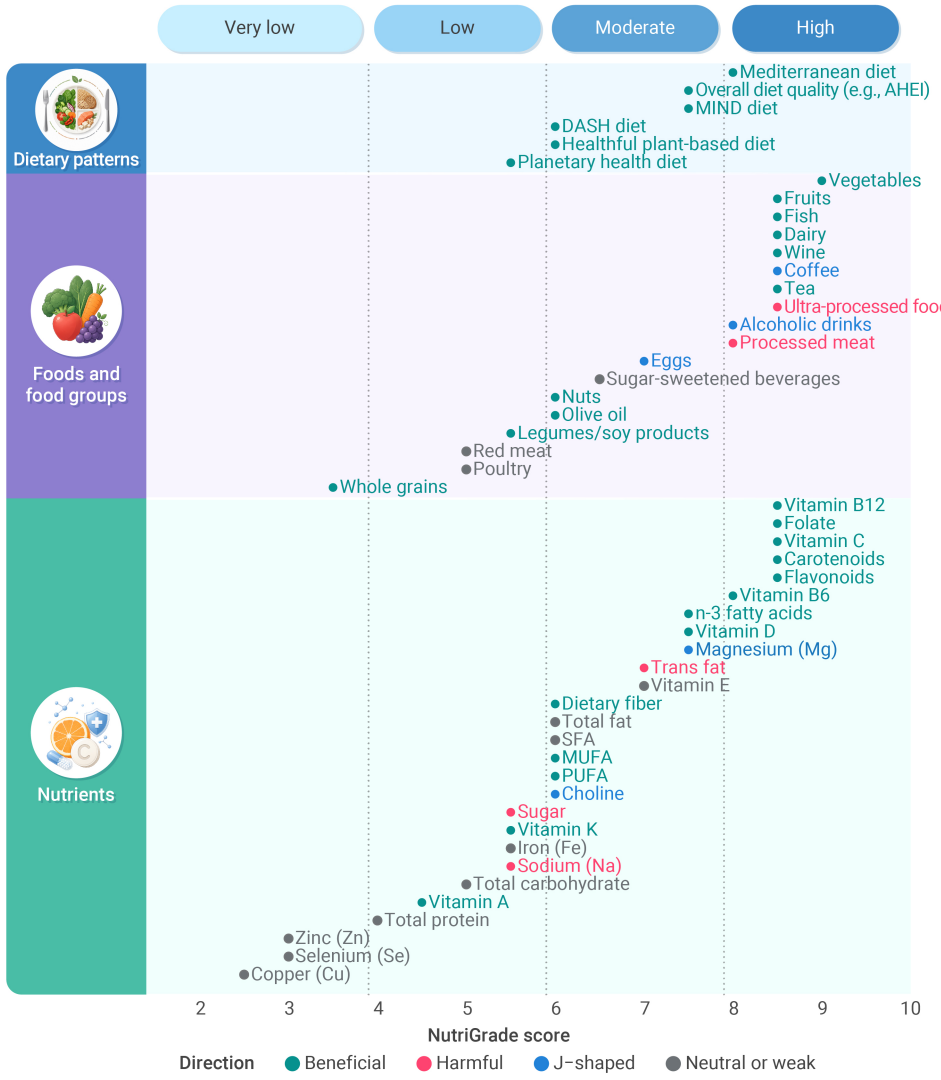

Figure 2. Evaluating the evidence level of existing literature on associations of major dietary factors with cognitive outcomes based on the NutriGrade* framework Abbreviations: AHEI, Alternative Healthy Eating Index; DASH, the Dietary Approaches to Stop Hypertension (DASH) diet; MIND, the Mediterranean–DASH Intervention for Neurodegenerative Delay; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; SFA, saturated fatty acid. * NutriGrade is a nutrition-specific scoring system developed to assess the credibility and certainty of evidence from meta-analyses of randomized controlled trials (RCTs) and cohort studies. For each dietary exposure, we identified the most relevant and up-to-date systematic review or meta-analysis of human studies examining cognitive outcomes. When multiple eligible meta-analyses were available, we prioritized those that included prospective cohort studies and/or RCTs, included the largest number of participants or events, and reported dose-response analyses where available. Details of the scoring could be found in the Supplementary Materials. The evidence for wine and alcoholic beverages, while suggestive of potential inverse associations with cognitive outcomes at low-to-moderate levels of intake, should be interpreted with particular caution because of substantial abstainer bias, reverse causation, and the established health risks of alcohol.

decline. A systematic review of 37 studies reported that a higher flavonoid intake was associated with better cognitive function and lower odds of cognitive impairment.[134] However, individual compounds in the broad family of polyphenols warrant separate investigations for their specific effects.

Vitamin D is also involved in neuroendocrine regulation. Although partially synthesized endogenously by humans and obtained from a limited number of dietary sources, it is frequently deficient in older adults and has been linked to dementia risk in numerous observational studies. A meta-analysis of 24 RCTs concluded that vitamin D supplementation improves global cognition, with benefits most pronounced in vulnerable populations and those with proven vitamin D deficiency.[135] Another meta-analysis of 23 observational studies of middle-aged and older adults reported nonlinear relationships between vitamin D intake and risk of dementia and AD, suggesting that the 25(OH)D concentration associated with the lowest observed dementia risk was approximately 77.5-100 nmol/L.[136]

Within a NutriGrade framework,[137] we evaluated the evidence level of existing literature for major dietary factors (Figure 2 and Table S1). In general, while the literature presents encouraging evidence on the impact of dietary factors such as B vitamins, PUFAs, fiber, and specific dietary patterns like the Mediterranean and MIND diets, the findings remain mixed. Inconsistencies in study designs, population characteristics, and dietary assessment methods warrant further research to establish more definitive conclusions on the role of diet in cognitive aging.

POTENTIAL ROLES OF THE GUT MICROBIOME IN DIET-COGNITION ASSOCIATIONS

Variability and inconsistencies in human studies on diet and cognition may reflect substantial heterogeneity in individual responsiveness to dietary interventions. Evidence from pilot trials suggests that individuals may respond differently to the same dietary pattern.[15] One plausible source of this inter-individual variability is the gut microbiota, which may modify the metabolic, inflammatory, and further neurological consequences of dietary exposures and influence downstream effects on brain health.[16]

The gut microbiota is a dynamic and functionally plastic ecosystem, profoundly shaped by diet and, in turn, potentially modulates host brain health.[138-149] However, a fundamental gap in understanding the diet-microbiota-gut-brain axis is determining the bio-behavioral processes that occur between dietary habits and their effects on cognitive aging.[14–16] The gut microbiota may act as: (1) a potential mediator through which diet may influence brain health, (2) a moderator that alter how dietary factors influence brain health, or (3) a marker reflecting host health or aging status rather than representing a direct causal pathway between diet and cognition, as illustrated in Figure 3.

Potential Pathways Linking the Gut Microbiota with Cognitive Health

Several candidate metabolic, immune, endocrine, and neural pathways have been proposed, supported to varying degrees by experimental models, human mechanistic studies, and observational data.[150–152] Diet is the dominant modifiable input to the substrates reaching the colon, from which microbial metabolites are produced and, consequently, which signaling pathways are engaged.[13-14,153] Several diet-related microbiota pathways have received the most empirical attention to date.[154-155]

Short-chain fatty acids (SCFAs), primarily acetate, propionate, and butyrate, are the main products of microbial fermentation of dietary fiber in the colon.[156] These metabolites reach the brain via the systemic circulation, crossing the blood-brain barrier (BBB) through monocarboxylate transporters expressed on endothelial cells.[157] In a previous mapping of gut microbiome and brain phenotypes in a human cohort, gut bacteria were associated with cognitive functions and brain structure via acetic acids.[158] The peripheral actions of butyrate and propionate on enteric neurons, gut endocrine cells, and circulating immune cells are also plausible routes by which these SCFAs influence the brain.[159] Experimental studies suggest that SCFAs may influence BBB integrity, microglial activation, neuroinflammatory signaling, and neurotrophic pathways.[160-161] Fiber-rich foods are the primary

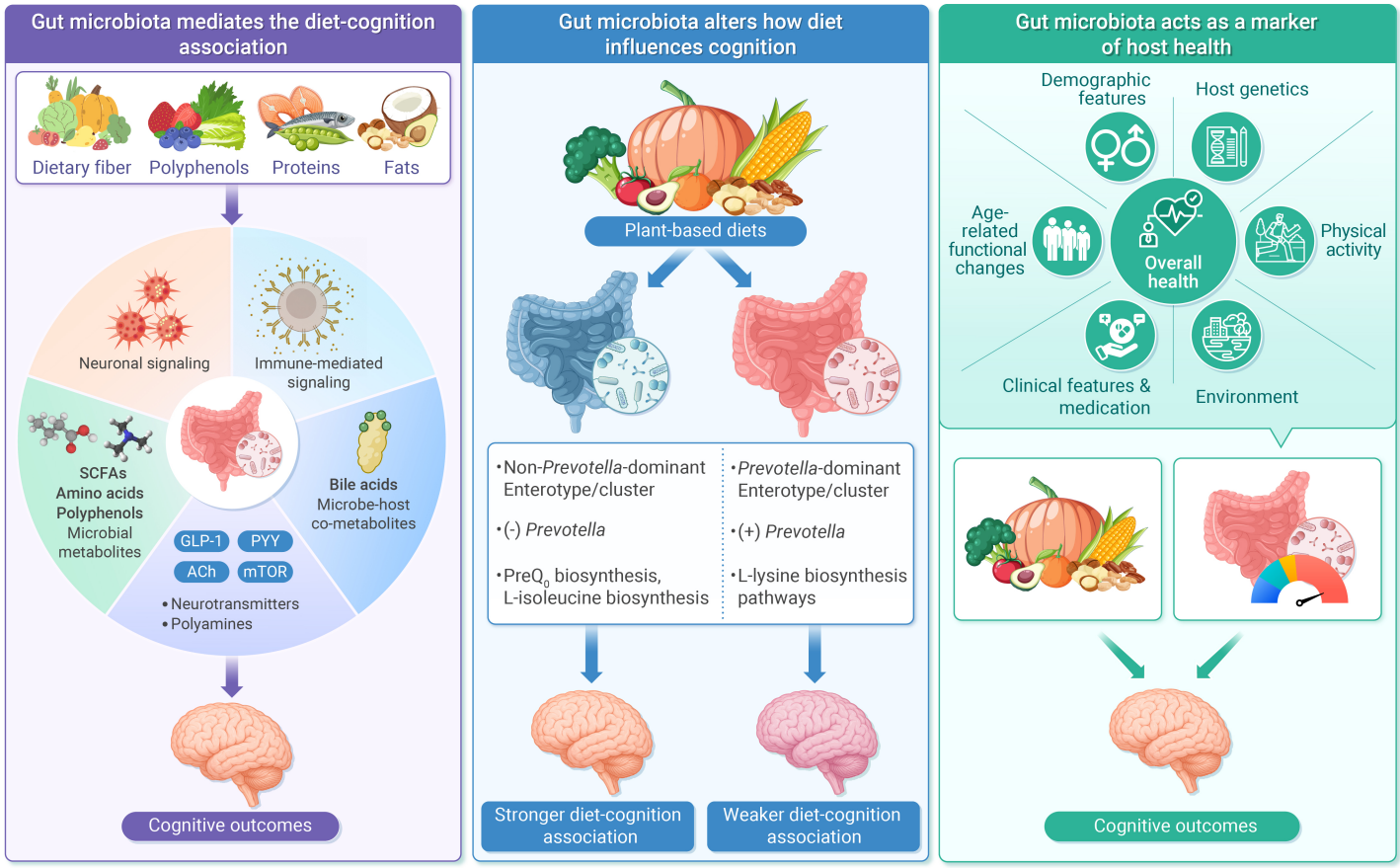

Figure 3. Potential roles of the gut microbiome in diet-cognition associations Abbreviations: ACh, Acetylcholine; GLP-1, glucagon-like peptide 1; mTOR, mechanistic target of rapamycin; PYY, peptide YY; SCFAs, short chain fatty acids.

substrates for SCFA production, and higher fiber intake correlates with greater fecal SCFA concentrations.[162] In contrast, low-fiber, high-fat dietary patterns have been associated with lower abundance of some SCFA-producing taxa and lower butyrate availability, potentially contributing to cognitive aging.

TMAO metabolism represents another important pathway linking diet, gut microbiota, vascular dysfunction, and cognitive aging.[163] TMAO is produced when gut bacteria convert dietary choline, L-carnitine, and betaine (abundant in red meat, eggs, and shellfish) into TMA, which is then oxidized to TMAO in the liver.[164] Elevated circulating TMAO concentrations have been associated with atherosclerosis, endothelial dysfunction, and other adverse vascular processes, which may in turn contribute to cognitive impairment.[163] Therefore, the TMAO pathway connects diet, microbiota, and brain health.[165] TMAO production depends not only on dietary intake but also on gut microbiota composition, as certain bacterial taxa (e.g., those with the *CutC/CntA* gene cluster) influence TMA production.[166]

Bile acids and tryptophan-derived metabolites are involved in gut-brain signaling through neuroactive, metabolic, and immune pathways.[154,155] Primary bile acids synthesized in the liver are secreted into the intestine with food intake and subsequently transformed by colonic bacteria into secondary bile acids, including deoxycholic and lithocholic acids. These metabolites signal through farnesoid X receptor (FXR) and TGR5 in peripheral tissues, vagal afferents, and the brain, with potential effects on glucose homeostasis, inflammation, and neuronal survival.[167] The gut microbiota may also influence how dietary tryptophan, an essential amino acid, is partitioned among several metabolic routes. These include host serotonin synthesis, the kynurenine pathway, and microbial conversion into indole derivatives.[168] Diets rich in fermentable fiber and polyphenols may support microbial production of indole derivatives and other potentially beneficial tryptophan metabolites,[169] whereas dietary patterns associated with intestinal inflammation or dysbiosis may enhance indoleamine 2,3-dioxygenase activity and shift tryptophan metabolism toward the kynurenine pathway, potentially promoting neuroinflammatory processes.[170-171]

Additionally, the gut microbiota affects gut barrier integrity, a multilayered defense system that includes the mucus layer, epithelial tight junctions, and local immune mechanisms. For example, low-fiber, high-sugar, or high-saturated-fat dietary patterns may reduce butyrate-producing bacteria and alter mucin-associated microbial communities, potentially impairing mucus-layer function, epithelial integrity, and intestinal permeability.[172-173] Increased permeability may permit bacterial lipopolysaccharide (LPS) and other microbe-associated molecular patterns to translocate into the circulation, contributing to chronic low-grade endotoxaemia.[174] Activation of Toll-like receptors on immune cells elevates pro-inflammatory cytokines, which may cross the BBB, activating microglia and promoting neuroinflammation, synaptic dysfunction, and cognitive decline.[151] In addition, microbial metabolites can influence gut-brain communication through neuroendocrine and neural pathways related to gut hormones, including glucagon-like peptide-1 (GLP-1) and serotonin, which regulate appetite, glucose homeostasis, inflammation, and neural signaling.[175] These signals can also activate vagal afferents, providing a rapid bidirectional communication route between the gut and brain that may influence stress responses and neuroinflammation. Preliminary observational evidence has also linked fungal functional features, including riboflavin-related pathways, to brain structural phenotypes; these findings require replication.[176] Emerging evidence further suggests that the gut virome may also be associated with brain-health outcomes.[177]

Understanding the roles of diet-microbiota interactions in cognitive aging requires a functional approach. While taxonomic profiling identifies which microbial taxa are present, many biological activities and processes are shared across phylogenetically diverse organisms, whereas closely related taxa may exhibit substantially different metabolic capabilities. Thus, functional readouts may provide more biologically meaningful insights into the mechanisms. The following sections explore the gut microbiota's role in diet-cognition relationships as a mediator, moderator, and marker of host health and ageing from a functional perspective (Table 1).

Table 1. Examples of studies linking dietary factors, gut microbiota, and cognitive outcomes.

Dietary factors	Cognitive outcomes	Study name & design	Participant characteristics	Microbiome-related findings
Dietary patterns				
Healthful plant-based diet	Cognitive function	Rugao Longitudinal Aging Study (China), cohort analysis	N=784, mean age 80 years; 53% female	Higher modified healthful plant-based diet index was associated with better global cognition, with a stronger association in participants with non-*Prevotella*-dominant enterotypes than in those with a *Prevotella*-dominant enterotype. Implicated pathways included preQ0 and L-isoleucine biosynthesis. The diet-cognition association was mediated by microbiota-derived SCFAs and amino acids.[138]
Mediterranean diet	Six-year cognitive decline	PREDIMED-Plus Trial (ISRCTN89898870, Spain), cohort analysis	N=746, mean age 65 ± 5 years, 48% female	A 20-taxa microbiota score of the Mediterranean diet, including positively weighted short-chain fatty acid-producers (e.g., *Barnesiella*, *Butyricicoccus*) and negatively weighted pro-inflammatory taxa (e.g., *Eggerthella*), was associated with 6-year global cognitive decline.[139]
Modified Mediterranean-ketogenic diet (MMKD)	AD CSF biomarkers	BEAM Trial (NCT2984540, USA), RCT	N=17, mean age: 65 ± 6 years, 71% female	The abundance of Enterobacteriaceae, *Akkermansia*, *Slackia*, *Christensenellaceae* and *Erysipelotriaceae* increased while that of *Bifidobacterium* and *Lachnobacterium* decreased with the MMKD intervention. The MMKD intervention modulated the gut microbiome and metabolites in association with improved AD biomarkers in CSF.[140]
	Cognitive function		N=20, mean age 64 ± 6 years, 75% female	The MMKD group had lower levels of GABA-producing microbes Alistipes sp. CAG:514 and GABA, and higher levels of GABA-regulating microbes Akkermansia muciniphila, which was correlated with cognitive performance.[141]
Food groups and nutrients				
Nuts	Six-year cognitive change	PREDIMED-Plus Trial (ISRCTN89898870, Spain), cohort analysis	N=747, mean age 65 ± 5 years, 48% female	Nut consumption was related to abundance of 13 taxa, including *Lachnospiraceae* UCG-004, which was further associated with slower 6-year cognitive decline.[142]
Olive oil	Two-year cognitive change		N=656, mean age 65 ± 5 years, 48% female	The overall gut microbial community composition (first principal component) mediated the association between total olive oil and executive function change. *Adlercreutzia* mediated the association of virgin olive oil consumption with 2-year changes in general cognitive function by 20%.[143]
Dietary fiber	MCI, subjective cognitive impairment (SCI)	CANN (NCT02525198, UK) and COMBAT trials (NCT03679533, UK), RCTs	N=170, mean age 66 ± 6 years, 56% female	Dietary fiber may differentially affect the gut microbiota composition and subsequent metabolites (i.e. SCFAs). Dietary fiber-induced changes in the microbiome and resulting serum metabolites were associated with a lower risk of cognitive decline, primarily in non-*APOE* ε4 carriers.[144]
	Cognitive function	Hong Kong osteoporosis cohort (Hong Kong, China), cohort analysis	N=252, mean age 87 years, 54% female	Higher dietary fiber intake correlated with higher cognitive scores and higher abundance of fermenting bacteria. *Eubacterium ventriosum* mediated the association of dietary fiber intake with dementia risk by 12.7%.[145]

Gut microbiota as a candidate mediator of diet-cognition associations

Diet is a major determinant of inter-individual variation in gut microbiota in both short term and long term.[147-148] For example, dietary fiber and resistant starch support saccharolytic and butyrate-producing taxa, whereas protein fermentation can generate branched-chain fatty acids and, depending on substrate source and colonic location, potentially harmful metabolites such as ammonia, phenols, and indoles.[13] Dietary fat alters bile acid secretion and may reshape microbial composition, while polyphenol-rich foods can selectively inhibit pathogens and promote beneficial taxa.[14] Diet also modifies the gut environment through effects on luminal pH, transit time, and mucosal integrity. Food processing and additives, including emulsifiers, artificial sweeteners, and preservatives in ultra-processed foods, may further impair barrier function or alter microbial activity even without substantial taxonomic changes.[13]

These diet-induced changes in microbial composition may in turn influence cognitive health. A growing body of evidence supports the microbiota's role as a mediator in diet-cognition associations.[14] For example, the PREDIMED-Plus cohort found that adherence to the Mediterranean diet increased gut microbial diversity and SCFA-producing taxa like *Barnesiella* and *Butyricicoccus*, which in turn correlated with better cognitive function.[139] A trial comparing a Modified Mediterranean-Ketogenic Diet to a heart-healthy diet in individuals at risk for AD showed that diet-induced microbial changes (e.g., increased *Akkermansia muciniphila*) were linked to improved cognitive outcomes.[141]

At the food group level, *Eubacterium ventriosum* accounts for part of the association of higher dietary fiber intake with lower risk of dementia,[145] potentially through SCFA production.[178] Nuts and virgin olive oil, rich in polyphenols, unsaturated fats, and fiber, can enhance SCFA production and related species. A 2-year study within the PREDIMED-Plus trial found that the genus *Adlercreutzia* mediated the association of higher virgin olive oil with greater improvement in cognitive function.[143] Nut consumption was linked to certain butyrate-producing taxa, such as *Lachnospiraceae UCG-004*, which is associated with slower cognitive decline.[142] Another study reported that habitual coffee drinkers had higher relative abundance of *Cryptobacterium* and *Eggerthella* species and lower levels of the metabolites indole-3-propionic acid, indole-3-carboxyaldehyde, and γ-aminobutyric acid, which correlate with cognitive performance.[179]

Taken together, these converging lines of evidence indicate that overall dietary patterns and individual components may be related to cognitive function in part through microbiota-dependent mechanisms. However, the nature of the evidence remains largely associative rather than causal.

Gut microbiota potentially modulates how diet influences cognitive health

Inter-individual differences in gut microbial composition and function may modify the cognitive response to plant-forward diets. This moderating role is biologically plausible: variation in microbial enzymatic capacity (e.g., fiber-fermenting versus proteolytic profiles) can alter the quantity and spectrum of neuroactive metabolites generated from the same dietary input.[14] A recent study based on 784 Chinese older adults showed that the association between a healthful plant-based diet and cognitive function was stronger in participants with non-*Prevotella*-dominant enterotypes than in those with a *Prevotella*-dominant enterotype.[138] Such enterotype-associated differences in microbial metabolic pathways, including preQ0 and L-isoleucine biosynthesis, parallel the heterogeneity in cognitive benefits.[138] This echoes a previous study reporting the *Prevotella*-dependent association between Mediterranean diet and cardiometabolic disease risk,[180] and another study showing gut microbiota-dependent metabolic responses to dietary fiber.[181-182] While the concept of enterotypes may simplify a more nuanced, gradient-like ecological reality, it may nonetheless capture a microbial functional state that reflects how individuals biologically respond to the same dietary exposures.[183]

Another example is the potential role of microbial metabolism of meat and choline, which, via TMAO-producing bacteria, can influence vascular health, although direct evidence for cognitive outcomes remains lacking. Elevated TMAO levels, produced by gut bacteria from dietary choline and L-carnitine, have been linked to cognitive decline through vascular contributions.[163-164] A study of 307 healthy men showed that inter-individual differences in gut microbial composition can modify how red meat and choline intake relate to circulating TMAO levels and cardiometabolic risk markers, underscoring that the impact of dietary precursors on metabolic biomarkers depends on microbiota metabolic capacity.[153] This suggests that individual microbiota profiles, particularly those capable of TMAO production, may alter the health effects of meat and choline consumption, although direct evidence for cognitive outcomes remains lacking.

The inter-individual variability in metabolic and neurobiological responses to diet has driven a paradigm shift toward precision nutrition.[184] However, direct evidence rigorously testing the modifying role of the gut microbiota, through formal diet-microbiota interaction analyses for cognitive outcomes, remains limited and is discussed further below.

Gut microbiota as a marker of host health status

In some contexts, the gut microbiome is an independent transducer of personal and external environmental signals, which may primarily reflect host health or aging status, rather than representing a direct causal pathway from diet to cognition.[14] Age-related alterations in the gut microbiome are influenced by individual-level factors, including progressive physiological deterioration through aging, as well as by lifestyle-linked factors such as diet, medication use, physical activity, and social contact. The age-related and disease-related deterioration in the gut microbiome of older people reflects overlapping, interactive, yet distinct processes. For example, studies of centenarians across various geographies and nationalities found lower abundance of typically health-associated symbionts (e.g., *Faecalibacterium* spp.), alongside elevated abundance of both alternative health-associated taxa (e.g., *Akkermansia* spp.) and disease-associated pathobionts.[185] Medication-induced dysbiosis, such as that caused by long-term proton pump inhibitor use, which alters gut pH, can also confound diet-cognition associations, as these drugs are common in older adults and independently affect microbial composition.[186] Thus, a given microbial signature might serve as an integrated biomarker of cumulative health insults that are themselves independent risk factors for cognitive decline, and distinguishing the microbiota as a causal mediator from an epiphenomenal marker remains a major challenge.

CHALLENGES AND FUTURE DIRECTIONS IN DIET-MICROBIOTA-COGNITION RESEARCH

Data collection and measurements

A major challenge in diet-microbiota-cognition research is that its three central domains, i.e., diet, gut microbiota, and cognition, are each intrinsically complex, dynamic, and difficult to measure with precision. Consequently, substantial uncertainty may arise at multiple stages of study design, data collection, analysis, and interpretation.[187]

Assessment of habitual dietary intake in humans has long been a major methodological challenge.[188-189] Most large population-based studies rely on self-reported dietary data collected through FFQ, 24-hour recalls, or diet records, all vulnerable to measurement error.[188,190] Although FFQs can capture long-term habitual intake, they rely on pre-specified food lists that may not adequately assess degree of processing. They are also prone to recall and portion-size estimation errors, and these errors may be especially pronounced in older adults with subtle cognitive changes.[187,191-192] Further complexity arises from its relative nature.[188] Dietary pattern scores often depend on predefined cutoffs, investigator-driven food grouping decisions, and cultural adaptations; while FFQ-based measures often emphasize internal ranking within a population,[193] such measures may reduce comparability across studies and populations.[194]

In contrast, 24-hour recalls provide detailed quantitative information on recent intake but are limited in their ability to capture long-term dietary habits or changes in diet over time.[190,195] This limitation is particularly relevant in research on cognitive aging, because both diet and cognitive function may evolve over years or decades.[196] Bias may therefore be amplified when diet is assessed only once at baseline, as a single measurement may fail to capture cumulative exposure, dietary trajectories, or potentially important exposure windows across the life course. Diet records can provide highly precise estimates of dietary intake because foods and beverages are recorded in real time. However, they require substantial participant effort and adherence, may influence usual eating behaviors, and are therefore more difficult to implement in large-scale epidemiological studies among cognitively impaired older individuals.[188]

Microbiome assessment represents another major source of heterogeneity and uncertainty. Most human studies rely on stool samples, which are practical and non-invasive but provide only a partial representation of the gut microbial ecosystem and may not fully reflect regional differences along the gastrointestinal tract.[197] Similar to diet, the gut microbiome is dynamic and changes over time.[198–200] A single stool sample therefore captures only a snapshot and may not reflect longer-term configurations that are more relevant to brain aging or neurodegeneration.[201] Interpretation is further complicated by methodological variability arising from sample collection, storage, DNA extraction, sequencing platforms, bioinformatic pipelines, taxonomic reference databases, and quality-control processing.[202-203] Consequently, microbial signatures identified and confirmed in one cohort can sometimes fail to replicate in another.

Cognitive aging is multidimensional, involving changes in memory, executive function, attention, language, and processing speed, yet these domains are often collapsed into broad summary measures.[204] Dementia is similarly heterogeneous, encompassing diverse clinical presentations and underlying pathologies that may differ in their relations to diet and the microbiome.[205] Although diagnostic criteria of AD have evolved toward an integrated clinical-biological framework,[206–209] many epidemiologic studies still rely on brief cognitive screening instruments that lack sensitivity to subtle or domain-specific changes. This limits the ability to distinguish normal cognitive aging from preclinical or prodromal neurodegenerative disease and to clarify the biological pathways linking diet-microbiota interactions with cognitive decline. Case ascertainment based solely on medical records or administrative codes may also introduce misclassification and obscure early disease stages.[210] Another important limitation is insufficient attention to timing. Most studies assess cognition in later life without considering life-course processes,[211-212] despite the likelihood that dietary and microbial exposures accumulate over decades and exert stage-specific effects.

Methodological challenges

Even when dietary, microbial, and cognitive data are well measured, drawing valid inferences from their joint analysis poses substantial methodological challenges.

Confounding is prevalent in diet-microbiota-cognition research because multiple factors influence all three domains.[187,196,213-215] Genetic background[216-217] and lifestyle factors like physical activity,[218] sleep[219] and smoking[220] affect both gut microbiota and cognitive health. Chronic conditions are linked to altered microbiota, modified diet, and accelerated cognitive decline, compli-

cating the disentangling of dietary effects from disease-driven confounding.[13,221-222] Medications, including antibiotics, also reshape microbiota and may influence cognition.[186,222] In older adults, frailty and functional limitations can restrict diet, alter gut physiology, and reflect neurodegeneration.[223-224] These interconnected factors make it challenging to isolate the specific contributions of diet-microbiota pathways to cognitive outcomes.

Reverse causation represents another concern, especially given that existing evidence is primarily based on cross-sectional or short-term cohort studies. Preclinical cognitive decline and sensory changes may emerge decades before clinical diagnosis and alter dietary behaviour.[225] Individuals in the early stages of neurodegeneration may simplify their eating patterns, shift toward energy-dense convenience foods, or lose interest in meal preparation. They may also experience reduced gastric motility, slower intestinal transit, and a greater medication burden. These changes may in turn reshape the gut microbiota, creating a spurious chain driven by incipient disease. This concern is not confined to cross-sectional studies; it may also affect prospective studies when the lag between microbiota and cognitive assessments is insufficient to exclude prodromal influences.[226]

Finally, the high dimensionality of microbiome and related multi-omics data introduces statistical challenges. A typical microbiomic study generates hundreds to thousands of microbial features, genes, or functional pathways, while the integration of metabolomic, transcriptomic, proteomic, or metagenomic data further increases the complexity and dimensionality of the analyses.[17,184] Most diet-microbiota-cognition studies, however, are based on cohorts that have modest sample sizes relative to the number of features tested.[11,141,227] This imbalance increases the risk of false discoveries due to multiple testing and capitalization on chance associations. As there is currently no consensus on best practices for multiple-testing correction or compositionality-aware statistical methods in microbiome research,[228–230] reported associations between specific taxa and cognitive outcomes may be difficult to replicate across independent cohorts. An additional related challenge is publication bias and the limited reporting of null findings in diet-microbiota-cognition research. Studies reporting statistically significant associations between dietary exposures, microbial features, and cognitive outcomes may be more likely to be published than those reporting no association, particularly given the high dimensionality of microbiome data and the large number of potential analytical choices. Consequently, the apparent consistency of findings for specific taxa, metabolites, or dietary components may be overstated, whereas genuinely null or heterogeneous effects may remain underrecognized.

These limitations underscore the importance of external replication and validation, transparent pipelines, and longitudinal and interventional studies to improve the robustness and reproducibility of findings in the field.

Representativeness and generalizability

Another critical challenge facing diet-microbiota-cognition research is ensuring the representativeness and generalizability of findings across diverse populations.[231] While much of the current evidence base has been derived from studies in high-income Western countries,[139,141–143] there is a growing body of evidence from Asian populations that deserves recognition, such as those from Japan,[11] China,[232] and Singapore[79] that differ substantially from Western patterns. However, the relative paucity of studies from South and Southeast Asia, Africa, and Latin America remains a major limitation.[233] The vast differences between regions, in terms of culture, diet, socioeconomic status, and healthcare access, significantly shape gut microbiome and cognitive outcomes.[234] It is thus unclear whether the existing research findings may be applicable to individuals in these relatively less represented populations.

Distinct dietary patterns across regions, together with other correlated lifestyle and environmental factors, including physical activity, sedentary behavior, medication use, sanitation, and urbanization, may differentially shape the gut microbiome.[235-236] For example, in Western countries where processed and animal-based products dominate the diet, individuals typically have a lower intake of dietary fiber, and members of the *Bacteroides* and *Prevotella* genera and the *Firmicutes* phylum are the dominant enterosignatures.[237] In contrast, non-Western populations consuming traditional plant-forward diets tend to exhibit greater bacterial diversity and microbial richness that breaks down a wider range of plant fibers.[237] Genetic variations between populations may also affect how individuals metabolize nutrients, respond to dietary interventions,[231,238] or how their microbiomes interact with their genes.[239-240] To date, few studies have evaluated the reproducibility and context-specificity of associations across dietary cultures, and geographic settings, and genetic backgrounds.

Future directions and recommendations

These challenges underscore the need for a more rigorous, integrative, and globally relevant research framework for studying diet-microbiota-cognition relationships. Progress in this field will depend on the adoption of improved methodological approaches that are better able to capture the measurement, longitudinal, multidimensional, and mechanistic complexity of these interrelated systems (Figure 4).

Longitudinal and dynamic assessment of diet, the gut microbiota, and cognition across the life course would help reduce exposure misclassification, distinguish long-term patterns from short-term fluctuations, and identify potentially responsive periods during which dietary or microbial factors may exert particularly important effects on cognitive health. Biomarkers of dietary intake and omics-based data may increase the objectivity of dietary assessment and reduce the potential influence of misreporting.[241–244] A life-course framework is especially relevant for cognitive aging, as the pathways linking diet, metabolism, inflammation, and neurodegeneration are likely to unfold over decades.[149] Emerging tools may help facilitate this shift, including digital dietary assessment platforms, image-assisted and app-based food recording, scalable remote cognitive assessment tools, and more stable biospecimen collection strategies that make repeated microbiome sampling more feasible in large-scale longitudinal studies.

Second, deeper phenotyping and biological characterization through multi-omics integration are needed to better identify the functional pathways involved.[14,184] Taxonomic descriptions of the microbiota alone are unlikely to fully explain how diet influences cognitive health. Future studies should integrate metagenomics, metabolomics, transcriptomics, proteomics, and host genetic data to better capture microbial function, host response, and the molecular intermediates that connect dietary exposures to brain aging.[228,184] Advanced biomarkers of brain and cognitive aging should also be incorporated when feasible to provide important complementary dimensions of biological characterization. Structural and functional neuroimaging and indicators of vascular brain injury may help clarify which pathways are most relevant to different stages and phenotypes of cognitive decline.[230]

As data depth and dimensionality increase, strengthening causal inference should become a central and practical priority.[245] Future research would benefit from broader application of causal inference methods, such as target trial emulation, quasi-experimental approaches,[246-247] and biologically grounded Mendelian randomization.[248–250] Meanwhile, well-designed feeding trials and microbiota-targeted interventions will be needed to determine whether modifying diet, microbial composition, or microbial function can causally alter cognitive trajectories.

To overcome the limitations in generalizability, future research needs to expand beyond homogeneous populations and include participants from diverse geographic regions, ethnic backgrounds, and socioeconomic statuses.[238] Collaborating across regions and including multinational cohorts will also improve our understanding of how environmental, dietary, genetic, and lifestyle factors shape the microbiome and cognitive health. Such efforts will be critical to developing universally effective dietary guidelines and interventions for cognitive aging.

Ultimately, these efforts should support a precision prevention framework aimed at identifying who is most likely to benefit from intervention, and at what stage the intervention appears most effective.[184] Future studies should therefore examine the effect heterogeneity according to factors such as genetic predisposition, baseline microbiota composition or function, and metabolic status. The optimal timing of intervention also warrants greater attention, as the goals of prevention in cognitively healthy adults may differ from those of resilience enhancement in at-risk individuals or progression slowing in those with established impairment. Realizing this vision will require rigorous longitudinal data, standardized methods, diverse populations, and careful validation of predictive tools across settings.

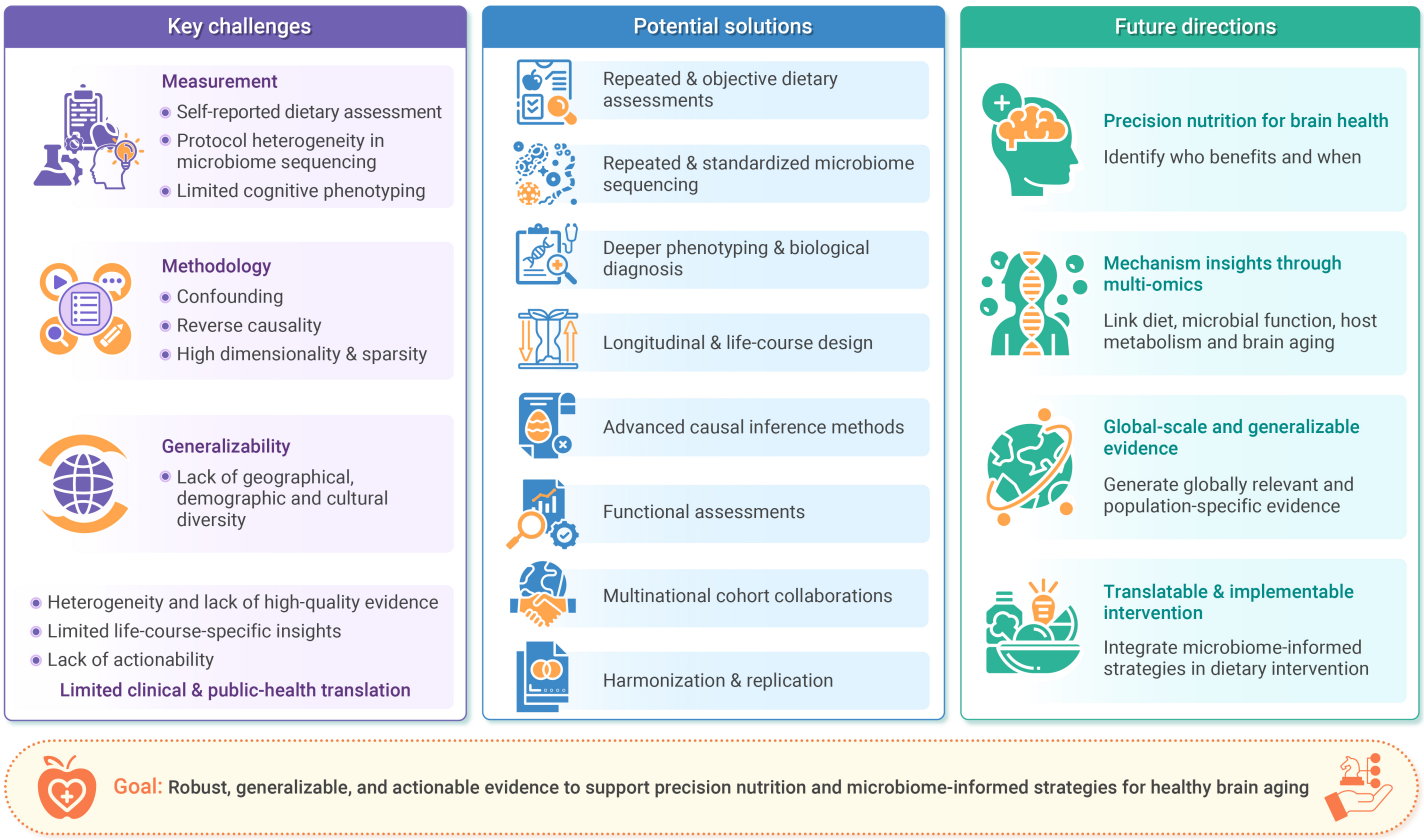

Figure 4. Potential solutions to key challenges and future directions in diet-microbiota-cognition research.

CONCLUSION

In this review, we synthesized evidence suggesting that diet may be a modifiable target for preserving cognitive health, particularly through healthy dietary patterns. The gut microbiota provides a plausible and increasingly studied framework for understanding heterogeneity in diet-cognition associations. However, inconsistencies persist in the associations observed across different populations and study designs, and many questions remain, particularly regarding the mechanisms through which diet and microbiota affect cognition and the precise interventions needed.

A key next step for research is to move beyond association-based studies and focus on defining the causal mechanisms based on more rigorous and biologically informed study designs. This includes integrating longitudinal and experimental approaches capable of disentangling temporal relationships and minimizing residual confounding, and addressing barriers to implementation, scalability, and reproducibility. The next phase of research should define who is most likely to benefit, when intervention is most effective, and which mechanisms are most amenable to modification. In this sense, diet-microbiota research is moving beyond epidemiologic association toward biologically grounded precision prevention and translational strategies for cognitive decline and dementia.

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Conception and design, H.C., J.S., and C.Y.; literature search & evidence appraisal, H.C. and J.S.; manuscript drafting, H.C. and J.S.; manuscript review, X.L., J.N., S.R., J.-S. Z, W.X., G.H., B. L., Y.Z., M.G.F., J.S.S.; study supervision, H.C. and C.Y.

DECLARATION OF INTERESTS

Hui Chen is a Youth Editorial Board member of The Innovation Nutrition and was blinded from reviewing or making final decisions on the manuscript. Peer review was handled independently of this member and their research group. The other authors declare no conflicts of interest.

DATA AND CODE AVAILABILITY

No new data were created or analyzed in this study.