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Nutrition, Gut Microbiota, and Alzheimer's Disease

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Nutrition is known to play an important role in the pathogenesis of Alzheimer's disease. Evidence is obtained that the gut microbiota is a key player in these processes. Dietary changes (both adverse and beneficial) may influence the microbiome composition, thereby affecting the gut-brain axis and the subsequent risk for Alzheimer's disease progression. In this review, the research findings that support the role of intestinal microbiota in connection between nutritional factors and the risk for Alzheimer's disease onset and progression are summarized. The mechanisms potentially involved in these processes as well as the potential of probiotics and prebiotics in therapeutic modulation of contributed pathways are discussed.

Keywords: nutrition, gut microbiota, cognitive function, dementia, Alzheimer's disease

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INTRODUCTION

Over 50 million people worldwide were living with dementia in 2019 and their number is expected to rise to 152 million in 2050 (1). Dementia, particularly Alzheimer's disease (AD), as the major cause of disability and dependence in elderly persons lead to a significant negative socioeconomic impact (2). In 2015, the global costs of dementia increased to 818 billion of US dollars and estimated costs in 2030 can reach about 2 trillion US dollars (3). Among the multiple risk factors identified for AD the presence of potentially modified cardiometabolic risk factors opens the opportunities to impact them through dietary modification (4, 5). Moreover, recent evidence indicates that imbalances in the gut microbiota (GM) can be also associated with the neurodegeneration (6, 7). So, the GM appears to be an attractive aim for prevention or treatment of AD (8–10). In this context, modulation of the GM composition offers diet a strong potential (6, 11).

NUTRITION AND ALZHEIMER'S DISEASE

In the last decades, the influence of dietary factors on cognitive function has become the subject of active research in pre-clinical and clinical studies. Various nutritional approaches have demonstrated a potential impact to prevent or slow down neurodegeneration or improve certain cognitive capacities. Accordingly, some benefits for cognitive performance may be found for vitamins E, D, B-group vitamins, various polyphenols, carotenoids, capsaicin, n-3 polyunsaturated fatty acids (PUFAs) and monosaturated fatty acids (MUFAs), some food and dietary patterns (12, 13).

Food Group

The relationships between the consumption of various food groups and cognitive health has been investigated for many years. Currently, studies of the various foods impact on cognitive performance mostly report mixed data. Vegetable intake was correlated with better cognitive score in a prospective cohort study or with larger cortical thickness in a cross-sectional study (14, 15). Consumption of vegetables was also shown to improve orientation ability in cognitively healthy adults or adults with mild cognitive impairment (MCI) (16). Positive impact of vegetables on cognitive performance is thought to be attributed to high content of carotenoids, polyphenols, other antioxidants and fiber.

Animal protein food is of interest as it is a significant source for the formation of neurotransmitters or neurotoxic substances by the GM (17). However, fish consumption seems to affect cognitive function positively. In cognitively healthy elderly individuals higher fish intake was associated with larger cortical thickness or larger total gray matter volume (15, 18). Elderly adults with fish consumption ≥1 servings/week had a slower rate of cognitive decline (19). Nevertheless, in other study no evidence was found for fish to prevent age-related cognitive impairment (20). In meta-analysis by Bakre et al. a 20–30% decrease in the risk of dementia and AD in people who eat fish was reported (21). The potential benefits of fish intake are considered to be linked to the n-3 PUFAs content in marine fish (12). N-3 PUFAs were shown to diminish amyloid-beta (Aβ) peptide aggregation, increase Aβ clearance, modulate synaptic plasticity and Tau phosphorylation, and decrease neuroinflammation (22–26). Existing findings indicate that n-3 PUFAs may also influence the GM composition and intestinal barrier integrity (27, 28). Interestingly, cognitive changes induced by dietary n-3 PUFAs deficiency correlated with microbiota composition and inflammatory status in an animal study (29). However, in the systematic review by Rangel-Huerta et al. evidence that n-3 PUFAs supplementation can prevent or slow down AD in older adults appeared to be inconclusive (30).

Consumption of dairy and meat is thought to impact negatively on cognition, as a high intake of this protein sources is part of the unhealthy Western-style diet. Nonetheless, Ngabirano et al. found that elderly people who consumed meat ≤1 time/week were at an increased AD risk. Moreover, low meat consumers also ate less fish, fruit and vegetables, therefore, they could have low dietary intake in general and some nutritional deficiencies (31). No strong association between meat consumption and cognitive decline was observed in the meta-analysis by Zhang et al. (32).

Currently, several reviews failed to find a dose-response effect of milk and dairy consumption on cognitive performance (33, 34). In part, the mixed findings can be explained by methodological heterogeneity of studies included and the existence of opposing consumption patterns in countries with different dairy cultures such as Japan and the US, for example (35, 36). Concerns about dairy consumption are related to their D-galactose content since excess D-galactose has been shown to impair neuronal function (37). Interestingly, interventions with probiotics (38) or antioxidants (39, 40) may attenuate D-galactose-induced brain senescence in animal studies.

Dietary Pattern

Accumulating evidence indicates that combinations of foods and nutrients might have a synergistic effect and thus more benefits on cognitive function than individual components. This may be due to the improved micronutrient intake and overall health and, of course, better microbiota composition in people adherent to healthy diet. Some dietary patterns such as Mediterranean diet (MeD), Dietary Approaches to Stop Hypertension (DASH) and Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) were associated with improved cognitive scores in population aged ≥40 y (12, 41, 42). MeD, DASH and MIND are plant-based diets with moderate to high consumption of fish, whole grains, vegetables and fruit, nuts and limited amount of red meat and sweets. Some differences between these diets lie in the amounts of other foods and nutrients (41–44). Higher adherence to MeD was associated with lower brain atrophy in non-demented elderly adults (15, 18). In the meta-analysis by van den Brink et al. higher MeD adherence decreased AD risk in case-control and longitudinal studies (42). The longitudinal studies showed a lower AD risk for high adherence to the DASH and MIND diets and for moderate adherence to the MIND diet (45, 46). Of note, the mentioned dietary patterns are high in fiber promoting the growth of healthy GM. Moreover, these diets contain nutrients associated with antioxidant and anti-inflammatory properties and suppression of Aβ deposition, including n-3 PUFAs, vitamin E, folate, carotenoids, and polyphenols (44, 47). Elevated MUFAs consumption as part of MeD and MIND diets is also considered to be beneficial for reducing the dementia risk (12, 48).

GUT MICROBIOTA COMPOSITION AND ALZHEIMER'S DISEASE

The previous data showed that the detrimental changes in the GM composition result in increase of intestinal permeability and systemic inflammation, which negatively affects the blood-brain barrier integrity (49–51). Further, bacterial lipopolysaccharides (LPS) and proinflammatory cytokines may activate microglia and accelerate neuroinflammation which contributes to a neuronal loss (7, 52–54). Activation of intestinal NLRP3 by gut flora was also shown to be involved into AD pathogenesis. In animal model upregulation of NLRP3 inflammasome after fecal microbiota transplantation (FMT) from AD patients lead to activation of systemic inflammation and neuroinflammation in the hippocampus (55). The most discussed potential mechanisms of GM impact on AD risk are associated with active metabolites and signaling molecules such as: trimethylamine N-oxide (TMAO) (56, 57), bile acids (58, 59), dysregulated P-glycoprotein (60), kynurenine (61), and nuclear factor-κB-sensitive microRNA-146a (62).

In addition, bacterial amyloid proteins prime the immune system, thus triggering an immune response to the brain amyloids and promoting the alpha-synuclein aggregation (63, 64). Therefore, an increasing number of studies are devoted to the relationship between AD and GM. Significant changes in the GM were demonstrated in many studies on AD

mouse models. For example, 27 bacterial species from six phylogenetic groups differed in SAMP8 mice compared to the control (65). Significant differences in the GM composition were also revealed for AD patients, both at the phylum and species levels. Quantitative differences between AD patients and healthy participants were found in 13 bacterial genera. In particular, AD patients showed an increase in the number of bacteria belonging to *Proteobacteria* and *Bacteroidetes* phyla, together with a decrease in the representatives of *Firmicutes* and *Actinobacteria* phyla. Additionally, researchers demonstrated an association between the presence of some genera in the gut and AD markers, such as Aβ42/Aβ40 and Aβ/p-tau ratio (66). Noted remarkable differences in the bacterial diversity in the AD patients' intestines compared to healthy people were revealed in terms of taxonomic groups such as *Bacteroides*, *Actinobacteria*, *Ruminococcus*, *Lachnospiraceae*, and *Selenomonadales* (67). An increase of genera *Escherichia–Shigella,* a member of *Enterobacteriaceae,* and reduction of SCFA-producing genera was found by Hou et al. (68). In another study, AD patients showed higher prevalence of proinflammatory taxa and lower abundance of butyrate-producing species, such as members of the *Butyrivibrio* and *Eubacterium* genera, as well as *Clostridium sp.* strain SY8519, *Roseburia hominis*, and *Faecalibacterium prausnitzii* (60). Notably, infection with certain pathogens including representatives of the oral or gut microbiome such as *Helicobacter pylori*, *Porphyromonas gingivalis, Candida albicans*, *Candida glabrata,* and others were found to be associated with AD risk (69).

Due to obvious differences in the microbiome composition, the first attempts to use microbial signatures as markers of AD are being made (70). For example, a model that uses 20 typical predominant genera can effectively distinguish patients with AD and MCI from healthy individuals. Moreover, five functional orthologs which differed in AD patients were identified by using metagenomic data. The samples obtained from AD patients showed a deficit of orthologs engaged into the biosynthesis of the amino acids involved in the metabolism of neurotransmitters (71). These results are in line with other studies which revealed the dysregulation of tryptophan metabolic pathways in AD patients (72, 73).

MICROBIOTA-MEDIATED LINK BETWEEN NUTRITION AND ALZHEIMER'S DISEASE

Nutrition is one of the main factors that influence the GM composition throughout the life course (74, 75). In turn, microbiota mediate interplay between habitual diet and various processes of a host organism, including cognitive performance (6, 10). In this context the GM may interact with dietary factors by contributing to energy homeostasis and metabolic risk factors and modulating systemic inflammatory response through dietary metabolites and also affecting the availability of nutrients which are important for brain functioning (49, 50, 52, 76). **Figure 1** summarizes the potential effects of nutrition and the GM on the AD risk.

Short-Chain Fatty Acids

A positive impact of GM on neuronal homeostasis is associated with short-chain fatty acids (SCFAs) derived from non-digested polysaccharides (77). SCFAs were shown to affect brain functions directly by improving blood-brain barrier integrity and affecting glial cells or indirectly by modulating the immune response, and activating vagal and humoral pathways of the gut-brain axis (78–81). SCFAs such as acetate, propionate, and butyrate regulate many cellular functions via binding to G-protein-coupled receptors (82). Moreover, acetate and butyrate are also well-known inhibitors of histone deacetylases, which activity is associated with cellular aging (83, 84). Anti-inflammatory and neuroprotective capacities of SCFAs were found mainly in animal studies or *in vitro* (85–87). In contrast, in one study increased Aβ plaque deposition was demonstrated in germ free AD mice fed with SCFAs (88). In human studies acetate and valerate as well as bacterial LPS were connected with an enhanced amyloid deposition in the brain. Conversely, a high serum level of butyrate was found to be associated with fewer amyloid plaques (89).

Polyphenols

Current findings indicate that GM closely interacts with dietary polyphenols using them as a food source for its own growth and providing new microbiota-derived metabolites. Thus, dietary polyphenols were shown to promote growth of *Lactobacillus spp.* and *Bifidobacterium spp.* and inhibited potentially pathogenic species (90, 91). On the other hand, GM potentially enhances the bioavailability of phenolic metabolites to the host (92, 93). Benefits of polyphenols and their metabolites in prevention of cognitive decline associated with its anti-inflammatory properties were reported previously (94–97). For example, gallic acid, which is a bacterial-derived metabolite of anthocyanins, was shown to decrease Aβ deposition, reduce neuroinflammation and oxidative stress in brain of AD mice (98). Noteworthy that polyphenols and their metabolites may enhance the intestinal barrier integrity and thus decrease the local and systemic inflammation (99–101). Accordingly, the GM activity contributes to cognitive promotion effect of polyphenol-rich dietary patterns like MeD, DASH, and MIND. Particularly, a positive association between certain phenolic compounds and abundance of a butyrate-producing *Faecalibacterium prausnitzii* was found in healthy adults adherent to MeD (102).

Trimethylamine-N-oxide

TMAO, which is a bacterial-derived metabolite of dietary choline, betaine and l-carnitine, was shown to be related to cognitive decline and AD (56, 57). An increased TMAO level in cerebrospinal fluid was found in individuals with MCI as well as with AD. Moreover, elevated TMAO in the cerebrospinal fluid was associated with markers of neurodegeneration (57). It is suggested that the TMAO blood level may depend on various factors, including the diet, GM composition, liver enzymes activity and urinary excretion (103, 104). However, the interaction between TMAO, its precursors, and neurodegeneration remains not fully understood. All of TMAO dietary substrates were previously found to be beneficial for

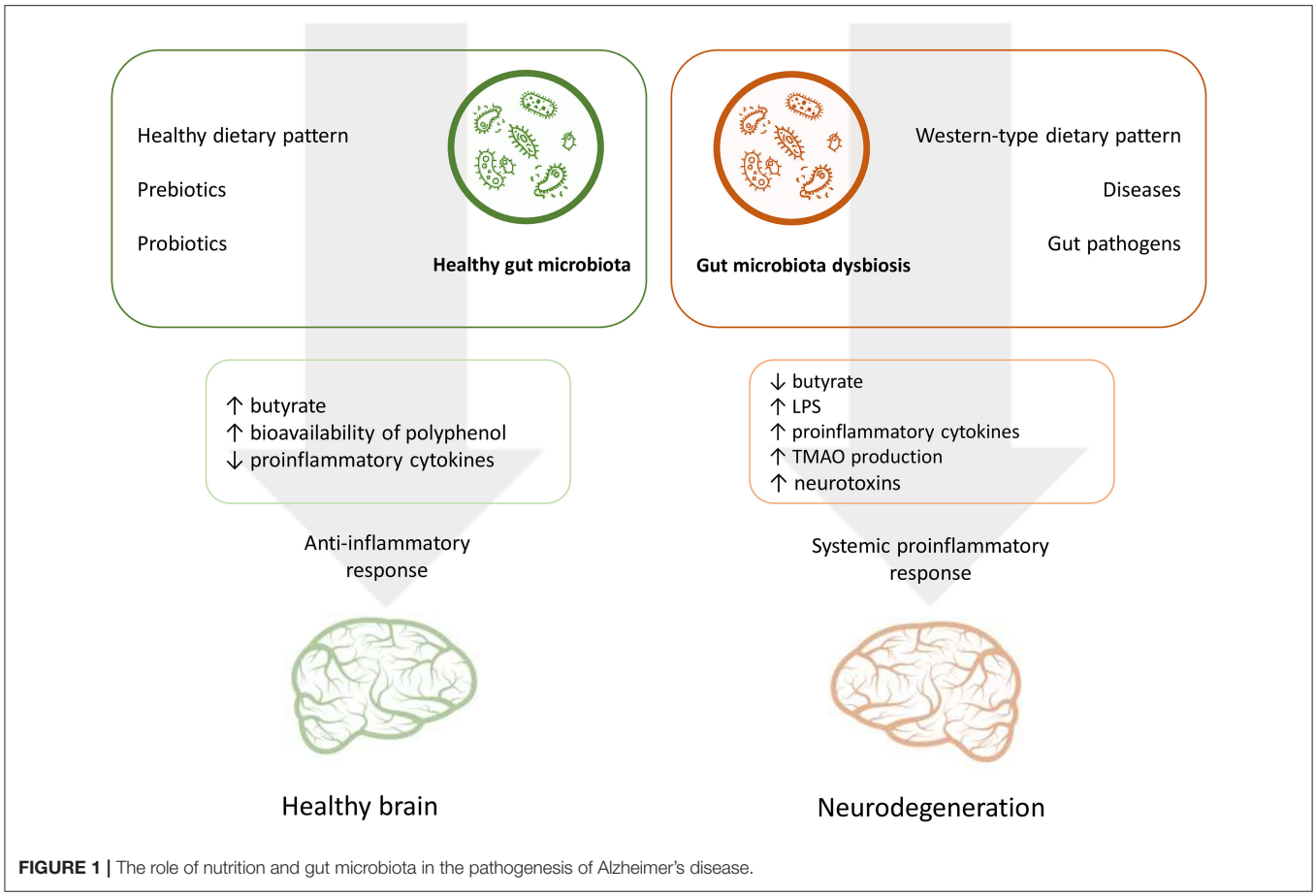

FIGURE 1 | The role of nutrition and gut microbiota in the pathogenesis of Alzheimer's disease.

the cognitive function (105–110). Systematic reviews and meta-analyses elucidating the impact on cognition of food rich in TMAO precursors such as meat, eggs, dairy products, and marine fish demonstrated mixed results, although fish intake seemed to improve cognitive performance (12, 21, 32–34). Interestingly, marine fish already contains an increased amount of TMAO (103, 111). Studies with food or supplements rich in TMAO precursor failed to increase fasting plasma TMAO in young healthy adults (112, 113). Despite this, a concomitant increase in plasma choline, betaine and gamma-butyrobetaine was observed in study by Berge et al. (112). Switching to the MeD did not affect fasting TMAO, choline, betaine, and carnitine in healthy adults with an increased colon cancer risk (114). However, in another study daily red meat consumption (meat protein was 12% of daily energy) elevated TMAO concentration in plasma and urine. Moreover, red meat intake decreased TMAO renal excretion (115). Thus, it remains unclear whether consumption of TMAO precursors should be restricted for better cognitive performance.

Current findings showed that the impact of microbiota on TMAO metabolism may be related to an abundance of strains producing trimethylamine (TMA). Among the TMA-producing species belonging to *Firmicutes* and *Proteobacteria* phyla the representatives of *Clostridium*, *Escherichia*, and *Proteus* genera were identified (116). It is notable that cognitive impaired patients with Aβ deposition had higher abundance of the genus *Escherichia/Shigella* as compared to Aβ negative patients and healthy controls (117). In other studies, healthy individuals with a higher *Firmicutes* to *Bacteroidetes* ratio demonstrated an increased production of TMAO from choline and carnitine rich food (118, 119). Negative correlation was found between the *Akkermansia mucinophilia* presence and fasting plasma TMAO in healthy adults at risk for colon cancer (114). Additionally, the GM was shown to regulate TMAO production via the impact on converting enzyme activity in the liver (117). However, in other neurodegenerative diseases lower plasma TMAO was reported to have worse prognostic implications (120, 121). Altogether, the existing data indicate that the interaction between TMAO, its precursors and cognitive impairment is more complex than a direct link and GM may play in it one of the key roles.

Prebiotics and Probiotics

The modulation of systemic inflammatory response with prebiotics and probiotics can be part of a comprehensive approach to slow down the cognitive decline through an impact on gut-brain axis (122, 123). A positive effect on cognitive performance for diets rich in fiber and polyphenols can partially be attributed to the prebiotic properties of the mentioned nutrients. Studies on AD mouse models revealed neuroprotective effects for some non-digested fermentable carbohydrates, such as mannan oligosaccharide (124), *Morinda*

officinalis oligosaccharides (125), xylooligosaccharides (126), yeast β-glucans (127), lactulose and trehalose (128). Currently, human studies of prebiotics impact on cognitive function in AD patients are scarce.

Animal studies on probiotics showed that feeding with *Bifidobacterium breve* A1 restored the impaired cognitive behavior and suppressed neuroinflammation in the hippocampus of AD mice (129). Human interventions with *Bifidobacteria spp.* revealed an improvement in cognitive scores under up to 6 months supplementation in elderly adults with MCI (130, 131). The interventions with probiotics in AD individuals as of today are quite limited but still promising. Shot-term supplementation with multispecies probiotic did not change cognitive scores in AD patients but affected the microbiome leading to an increase in *Faecalibacterium prausnitzii* and decreased intestinal permeability. A concomitant increase in serum neopterin and tryptophan breakdown marker could indicate the stimulation of the immune system (132). In small research of supplementation with probiotic-fermented milk AD individuals demonstrated a decrease in inflammatory and oxidative responses, reduction of DNA damage and apoptosis in peripheral blood leucocytes (133). In another study, probiotic stains plus selenium supplementation resulted in a better cognitive score in AD patients. Moreover, probiotics enhanced the selenium effect on the reduction of high sensitive C-reactive protein and an increase in total antioxidant capacity and the glutathione level (134).

FECAL MICROBIOTA TRANSPLANTATION

FMT is a transfer of fecal material from a healthy donor into the patient's gastrointestinal tract. This procedure is a powerful means of regulating the GM and is being actively studied for many diseases at the moment. Despite this approach being promising, we have very limited data on the use of this method for AD (135). FMT from WT mice into ADLP^{APT} mice improved intestinal barrier integrity and decreased the formation of amyloid plaques and neurofibrillary tangles in animal brains (136). In another AD mouse model FMT from healthy individual following FMT from AD patients decreased the expression of pro-inflammatory cytokines in blood and hippocampus and improved cognitive ability of animals (55). One case study reported long-term improvement in the mental acuity of 82-year-old patient after FMT (137).

CONCLUSION

Existing evidence suggests that dietary lifestyle changes may affect cognitive function. Certain nutrients appear to be beneficial in maintaining neuronal homeostasis and slowing cognitive decline. Along with it, the most convincing evidence was reported for whole-diet approaches such as MeD, DASH, and MIND. One of the key roles in the diet impact on cognitive performance and AD risk belongs to the composition and functional activity of the GM. It has now been shown that microbiota affects brain functions through various metabolites with potentially positive or, conversely, toxic properties. Moreover, by converting food precursors, the intestinal flora regulates the availability of nutrients important for cognition. It seems that the GM involvement in the SCFA and polyphenols metabolism may contribute to the cognitive promotion effect of healthy dietary patterns. In addition, the use of probiotics can be part of a comprehensive approach to delay neurodegeneration. However, for a long-term GM modification, a whole-diet may have advantages over nutrients alone or in combination. Overall, the GM is an important factor to be considered in future research of dietary effects on cognitive function. Thus, the underlying mechanisms of interaction between nutrition, microbiota, and the host require additional studies for developing effective dietary strategies within integrated AD prevention and control.

AUTHOR CONTRIBUTIONS

AV conceptualized the structure and wrote the first draft. MR, AK, and VK co-wrote the first draft. MR edited the final version of the manuscript. All authors approved the final version of the manuscript.

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