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Current Alzheimer disease research highlights: evidence for novel risk factors

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Abstract

Alzheimer disease (AD) is the most common type of dementia characterized by the progressive cognitive and social decline. Clinical drug targets have heavily focused on the amyloid hypothesis, with amyloid beta (A β), and tau proteins as key pathophysiologic markers of AD. However, no effective treatment has been developed so far, which prompts researchers to focus on other aspects of AD beyond A β , and tau proteins. Additionally, there is a mounting epidemiologic evidence that various environmental factors influence the development of dementia and that dementia etiology is likely heterogenous. In the past decades, new risk factors or potential etiologies have been widely studied. Here, we review several novel epidemiologic and clinical research developments that focus on sleep, hypoxia, diet, gut microbiota, and hearing impairment and their links to AD published in recent years. At the frontiers of AD research, these findings and updates could be worthy of further attention.

Keywords: Alzheimer disease; Sleep; Hypoxia; Diet; Gut microbiota

Introduction

As one of the most common neurodegenerative diseases and causes of dementia, Alzheimer disease (AD) is a critical topic for biomedical research. The main clinical manifestation of AD is the progressive decline of cognitive function and activities of daily living, and the pivotal pathological features of AD are amyloid beta (A β) deposition, neurofibrillary tangles, neuroinflammation, synaptic degeneration, and neuronal loss.^[1] While research on AD has been ongoing for >100 years, our understanding of AD is also constantly enriched by the new research directions. However, there are still no effective treatments to delay, halt, or even reverse the process of AD.

In the past few decades, researchers have gradually shifted their attention from treatments to the early diagnosis and prevention of AD.^[2] There is an interest in identifying the novel risk factors for AD as well as the novel biomarkers to help detect AD before the symptom onset. Several potential

risk factors for AD have been studied extensively, including cardiovascular disease (CVD), diabetes, obesity, low education, social isolation, and depression.^[3] However, recent epidemiologic and clinical studies are expanding our understanding of potential AD markers and risk factors to other health behaviors and conditions, such as sleep, diet, and hearing loss. For example, sleep disturbance has a complex association with AD and may be either a preclinical biomarker or potential modifiable risk factor for AD. In particular, hypoxia, often caused by severe obstructive sleep apnea syndrome (OSAS), significantly promotes the development of AD, inspiring the attempts to treat AD using the hyperbaric oxygen treatment (HBOT).^[4] Dietary patterns are associated with cognition in older adults, and the Mediterranean-style diet (MD) is associated with reduced risk of AD. Gut microbiota may be an intriguing potential mediator

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between diet and AD.^[5] Also, hearing impairment which is often ignored in clinical practice has strong associations with the risk of AD.

Here, we review the latest developments and especially the epidemiological evidence on sleep, hypoxia, diet, gut microbiota, and hearing impairment in the research field of AD published in recent years. These topics are receiving increasing research interest and may point to novel areas for intervention in the treatment and prevention of AD. As the frontiers of AD research, these findings and updates could be worthy of further attention.

Recent Progress in the Research of AD

In this section, we will review and summarize the recent progress in the research of AD focusing on five novel potential risk factors or early disease indicators such as sleep, hypoxia, diet, gut microbiota, and hearing impairment. As these factors are relatively novel, this review focuses on the epidemiologic evidence with some discussion of potential mechanisms as well as areas for future research.

Sleep and AD

One of the most exciting recent highlights in Alzheimer research is the bi-directional relationship between sleep disturbances and the risk of AD. Patients with AD frequently experience sleep disturbances, including insomnia, abnormal sleep duration, poor nighttime sleep quality, excessive daytime sleepiness, and disrupted circadian rhythms.^[6] These sleep problems subsequently reduce patient quality of life and increase the risk for premature institutionalization.

Importantly, growing evidence from the epidemiological studies has suggested that 50% to 80% increased risk of dementia is associated with sleep disturbances, including insomnia, sleep-disordered breathing (SDB), disrupted circadian rhythms, and sleep-related movement disorders.^[7-12] Excessive daytime napping has also been associated with an increased risk of cognitive impairment in older men, although the underlying mechanisms are less clear.^[13] Several studies have found a U-shaped association between sleep duration and risk of dementia,^[14,15] indicating the effects of both short and long sleep duration on cognitive aging. Furthermore, one recent study discovered 23 macro- and micro-physiological architecture metrics of sleep, including rapid eye movement sleep duration, features of the electroencephalography power spectra derived from multivariate analysis, and spindle and slow oscillation morphology and coupling, which were all strongly linked with cognitive performance in older adults.^[16] Sleep disturbances are increasingly recognized as a preclinical marker or potential modifiable risk factor for AD.

Over the past decade, emerging evidence from animal and human studies has begun to uncover the nature of the association between sleep disturbances and AD. Since the earlier animal studies that identified a close link between sleep-wake cycle and the pathogenesis of AD,^[17,18] a

growing body of research has suggested sleep deprivation as both a result and trigger of A β , the hallmark pathological feature of AD.^[19] Prospective analysis also showed that baseline measures of non-rapid eye movement (NREM) sleep slow-wave activity and sleep quality are sensitive in predicting longitudinal trajectory of A β deposition in healthy older adults, indicating the role of sleep as a useful biomarker for forecasting A β pathological progression before the clinical cognitive impairment.^[20] Furthermore, sleep-wake cycle was found to regulate brain interstitial fluid (ISF) tau, and chronic sleep deprivation might increase ISF and cerebrospinal fluid (CSF) tau as well as tau pathology spreading.^[21] It was also suggested that SDB might lead to increased tau levels over time in those with normal cognition or mild cognitive impairment (MCI).^[22] Interestingly, one recent study found a coherent pattern of electrophysiological, hemodynamic, and CSF oscillations during human NREM sleep, suggesting a link in the neurophysiology of sleep and waste clearance in the brain.^[23]

In addition to the use of neuroimaging and biomarkers, recent studies are also starting to use novel statistical approaches, such as Mendelian randomization (MR), to overcome the limitations of observational epidemiological studies and to reveal the causal relationship between sleep and AD. For instance, using the MR approach, it was found that higher genetic risk for AD might predict shorter sleep duration, suggesting that short sleep duration could be part of the AD disease process and thus serve as an early marker for AD.^[24] Meanwhile, another MR study showed no causal effect of self-reported or accelerometer-measured sleep traits on AD risk. Given the growing evidence that indicates a bi-directional relationship between sleep disturbances and AD, emerging studies are underway to examine the use of sleep interventions in the prevention and treatment of AD. One recent review summarized the effects of several sleep interventions that have been studied in patients with MCI or mild dementia, including Cognitive Behavioral Therapy-Insomnia (CBT-I), a structured limbs exercise program, aromatherapy, phase locked loop acoustic stimulation, transcranial stimulation, suvorexant, melatonin, donepezil, galantamine, rivastigmine, tetrahydroaminoacridine, and Continuous Positive Airway Pressure (CPAP) and concluded that CBT-I, melatonin, suvorexant, and CPAP for OSA hold the most promises.^[25] Since medications might further impair cognition, non-pharmacological interventions are of particular interest for older adults who are at high risk for dementia. Cordone *et al*^[26] highlighted several promising techniques to enhance NREM sleep oscillations that have solid scientific basis for preventing or slowing down AD pathology but remain to be tested in clinical settings.

Overall, while it remains inconclusive whether sleep disturbances are early signs or risk factors for AD, recent research highlights the importance of sleep among older adults. Changes in sleep architecture and electroencephalogram might be considered as a valuable marker of AD before the onset of cognitive symptoms and help with the early detection of the disease.^[27] Future research is needed to test whether sleep disturbances could be the risk factors for AD and to explore the use of sleep interventions in patients at high risk for AD.^[25]

Hypoxia and AD

Hypoxia can be caused by CVD, hematological diseases, chronic kidney diseases (CKD), respiratory dysfunction, and environmental conditions, which could influence the central nervous system and induce neurodegeneration.^[28-33] Acute hypoxia can be induced by stroke, while OSAS, capillary dysfunction, and CKD may lead to chronic hypoxia. Cognitive impairment may also occur in normal adults after hypoxia.^[34,35]

Hypoxia is associated with AD.^[28-33] Both acute and chronic hypoxia intervention in experimental animals can result in the aggravation of cognitive dysfunction and the AD-type pathological alterations including A β deposition, hyperphosphorylation of tau protein, synaptic degeneration, and neuronal loss.^[36] Increasing evidence suggests that hypoxia facilitates the pathogenesis of AD through multiple pathways including increasing the production and accelerating the accumulation of A β ,^[36] decreasing the degradation of A β ,^[37] reducing the clearance of A β ,^[38] elevating the hyperphosphorylation of tau,^[39] inhibiting the autophagic function,^[40] aggravating neuroinflammation^[41] and oxidation stress,^[42] ruining the mitochondria function,^[43] and causing the stress of endoplasmic reticulum.^[44] As mentioned above, it is rational to propose that hypoxia is one of the essential factors contributing to the pathogenesis of AD.

Given that hypoxia contributes to the pathogenesis of AD, the development of prevention and treatment targeting hypoxia is promising. HBOT is a safe, effective, and routinely used medical procedure. Growing evidence suggests that HBOT can induce the neuroplasticity and improve the cognitive function in patients suffering from neurocognitive impairment due to stroke and brain injuries.^[45,46] Moreover, HBOT cannot only improve cognitive functions and ameliorate the brain glucose metabolism in AD and amnesic MCI (aMCI) patients^[4,47] but also induce significant senolytic effects including significantly increasing telomere length and clearance of senescent cells in the aging individuals.^[48]

Besides, HBOT is capable of improving the cognitive behavioral performance, reducing A β burden and tau hyperphosphorylation, alleviating neuroinflammation by decreasing astrogliosis and microgliosis, reducing pro-inflammatory cytokines, and elevating phagocytic markers in mouse model of AD.^[49] More recently, HBOT was shown to be able to reduce A β accumulation and hippocampal neuritic atrophy, increase hippocampal neurogenesis, and profoundly improve the cognitive deficits through the upregulation of neurotrophic factors.^[50] Moreover, HBOT has been proved to inhibit A β ₂₅₋₃₅-induced toxicity, oxidative stress, and neuronal apoptosis.^[51,52] In addition, both the cognitive impairment and hippocampal damage can be attenuated by HBOT via NF- κ B signaling pathway^[53] or p38 mitogen-activated protein kinase (MAPK) in the animal model of AD.^[54] However, there is still no research report on whether HBOT has the capacity of preventing or delaying the occurrence of AD in high-risk groups at an early stage. Besides, further experiments are still warranted because of

the possibility of oxygen toxicity, even though HBOT itself seems to be beneficial to cognition.

Diet and AD

As poor diet contributes to several AD risk factors including obesity, hypertension, and diabetes, modifying the dietary behavior could be an effective public health strategy to protect against age-related neurodegeneration and AD in late life.

A growing body of evidence has linked several foods (eg, green vegetables, berries, fish, and olive oil), nutrients (eg, B-vitamins, vitamin E, and omega-3 fatty acids), and plant bioactives (eg, flavanoids) to reduce dementia risk. Consuming these nutrients and foods in combination as a dietary pattern is likely to exert greater synergistic effects on the physiological processes underlying neurodegeneration. The MD rich in antioxidants and flavonoids and characterized by high intake of fruits, vegetables, whole grains, olive oil, nuts, and legumes; moderate intake of fish, poultry, and alcohol, and low intake of red meat have proven cardiometabolic benefits^[55] and remain the most frequently studied dietary pattern for neuroprotection during ageing. Evidence from prospective studies indicate beneficial associations among MD adherence, slower rate of cognitive decline, and reduced risk of cognitive impairment, in Western^[56,57] and Asian^[58] populations. However, findings have not been consistent likely because of the differences in populations studied, measures of MD and cognition, length of follow-up, and adjustment for important confounders such as cardiovascular morbidity and baseline cognitive function. To date, only a small number of studies have examined the relationship between diet and incident AD.^[59] Among older cognitively healthy U.S. adults, those in the highest tertile of MD adherence had 40% to 54% reduced AD risk compared to those in the lowest MD tertile, but results have not been replicated in French or Swedish populations^[59] making it difficult to draw firm conclusions.

The neuroprotective mechanisms of a healthy diet are not fully elucidated, but multiple antioxidants, anti-inflammatory, and vascular pathways are likely to be important. The MD improves vascular function and insulin resistance^[55,60] that contribute to the cognitive decline and AD. Experimental and preclinical studies have shown that dietary antioxidants and flavonoids have a direct effect on the brain by inhibiting oxidative stress, cytokine production and pro-inflammatory cell signaling pathways, and suppressing neuroinflammatory processes implicated in AD. Emerging data suggest that diets rich in fruit, vegetables, whole grains, and fiber promote biodiversity of the gut microbiome and decreased pro-inflammatory gut-derived bacteria and toxins are shown to contribute to early neuroinflammatory changes, and AD pathology.^[5,60] Evidence from observational studies report a link between greater MD adherence and favorable brain structures and functions that protect against neurodegeneration as well as less A β accumulation in AD-vulnerable regions of the brain.^[61] Furthermore, dietary restriction^[62] achieved by calorie restriction (30%–40%) or intermittent fasting may provide neuroprotection by attenuating neuroinflamma-

tion and insulin resistance and promoting synaptic plasticity and neurogenesis.^[63] Beneficial effects of DR on AD pathology have been demonstrated in some^[64,65] but not all^[66] transgenic animal models, and it is not yet clear on how the findings translate to humans.^[63]

The effect of diet on AD risk is not yet known; however, randomized controlled trial data evaluating the effect of diet on cognitive performance demonstrated less decline in global cognition, memory, and executive function in response to a MD >4 to 6 years^[60] with no convincing benefit for shorter-term MD interventions (up to 12 months)^[59] in cognitively healthy older adults, suggesting that several years of dietary exposure may be needed to detect changes in intermediate cognitive tests of AD risk in general populations.

Overall, accumulating data suggest a role for diet in AD prevention but larger adequately powered intervention and prospective studies in diverse populations with clinically relevant endpoints incorporating incident AD, MCI as well as sensitive neurocognitive tests and brain biomarkers associated with preclinical AD risk are required to understand the effect of diet on AD from the earliest to later stages of disease.

Gut microbiota and AD

Given the complex bidirectional communication system that exists between the gut and brain, there is a growing interest in the gut microbiome as a novel and potentially modifiable risk factor for cognitive impairment and AD. Gut dysbiosis has been implicated in the pathogenesis and progression of AD.

Compared with the normal controls, the *Bacteroidetes*, *Actinomyces*, *Ruminococcus*, and *Selenomonas* in AD patients are significantly different.^[67] The cognitively normal elderly do not have an AD-type pattern of gut microbiota compared with patients at the early stage of AD,^[68] and specific gut microbiota, especially enriched *Enterobacteriaceae*, are associated with AD patients compared with aMCI and cognitively healthy controls,^[69] indicating the potential of gut microbiota in the differential diagnosis of AD. Besides, the alteration of gut microbiota tends to occur several years before the onset of dementia, even at the early stage of MCI.^[68] A cross-sectional study showed that an increase in *Bacteroidetes* in non-dementia patients is independently associated with the presence of MCI.^[70] The abundance increase of *Enterobacteriaceae*, *Akkermansia*, *Slackia*, *Christensenellaceae*, and *Erysipelotriaceae* in MCI patients suggests that this special gut microbiota composition may indicate the presence of MCI.^[71]

To investigate the causal relationship between gut microbiota and AD, a clinical study found that gamma-aminobutyric acid (GABA) and serotonin may play an important role in the gut microbiota–host interaction in AD patients.^[72] A pilot study revealed the characteristics of the MCI-specific gut fungi (mycobiome) signatures and elucidated that the diet-regulated mycobiome are associated with AD markers and fungal–bacterial co-regulation networks in MCI patients.^[73] A clinical study showed that

Proteobacteria is positively correlated with A β 42:A β 40 ratio, but the fecal propionic acid and butyric acid are negatively correlated with A β 42 level in MCI patients with the MD.^[71] Intriguingly, the gut microbiota composition is strongly correlated with apolipoprotein E (ApoE) genotype. The relative abundance of different bacterial groups is significantly different under the influence of ApoE genotype,^[74] which is also related to the specific gut microbiota composition of human and ApoE-targeted replacement mice, especially the *Prevotellaceae* and *Ruminococcaceae* and several butyrate-producing genera.^[75] Moreover, the relative abundance of *Prevotella* and *Ruminococcus* in female ApoE4-familial Alzheimers disease (FAD) mice is higher than that of female ApoE3-FAD mice, whereas the relative abundance of *Sutterella* in male ApoE4-FAD mice is significantly higher than that of female ApoE3-FAD mice, implying a synergistic effect of ApoE and sex on gut microbiota of AD.^[76]

The metabolites of gut microbiota are particularly critical in the mechanism of the gut–brain axis. Trimethylamine-n-oxide (TMAO), a kind of gut microbiota metabolites, can be found in human CSF.^[77] It was suggested that the gut microbiota metabolites, such as lipopolysaccharide (LPS) and short chain fatty acids, could mediate the systemic inflammation and intracerebral amyloidosis through endothelial dysfunction.^[78] A multicenter clinical study found that the serum concentration of primary bile acid (BA) is significantly decreased, whereas the concentrations of secondary BA, deoxycholic acid, and its conjugated form of glycine and taurine are increased in AD patients compared with cognitively normal elderly.^[79] Moreover, it was found that the certain blood BA-related indicators are associated with CSF-A β , CSF-p-tau 181, CSF-t-tau, glucose metabolism, and brain atrophy in patients with MCI and AD, respectively.^[80]

Additionally, there are also many studies exploring the effect and mechanism of different types of intervention on AD using gut microbiota as a potential mediator. High dose of Jatrorrhizine,^[81] an essential component of coptidis rhizome, a Chinese traditional herb, is capable of improving the learning and memory ability, reducing A β deposition, and altering the abundance of certain gut microbiota composition such as *Firmicutes* and *Bacteroidetes* in APP/PS1 mice.^[82] Besides, 27-hydroxycholesterol can aggravate AD-type pathological alterations, gut microbiota dysbiosis, and intestinal barrier dysfunction.^[83] The fructooligosaccharides derived from *Morinda officinalis* improves the learning and memory abilities of rats by regulating the interaction between intestinal ecosystem and brain.^[84] Xanthoceraside can alleviate the symptoms of AD by affecting the composition and endogenous metabolites of gut microbiota in rats.^[85] GV-971, an oligosaccharide sodium, has the capacity of inhibiting gut microbiota dysbiosis and related phenylalanine/isoleucine accumulation, alleviating neuroinflammation, and reversing cognitive dysfunction.^[86]

Environmental factors may also influence the pathogenesis of AD through gut microbiota. Long-term exposure to noise alters gut microbiota composition and accelerates age-related neurochemical and inflammatory regulation

disorders, resulting in the aggravated AD-type pathological changes in the brain of senescence-accelerated prone mice.^[87] Treatment of mid infrared light of peak wavelength 7.7 to 10 mm can attenuate the decline of learning and memory, reduce A β deposition, and alter the gut microbiota composition.^[88]

Due to the importance of gut microbiota in the pathogenesis of AD, many studies assessed its potential therapeutic value. Clinical studies have found that supplementation of multiple probiotics alters the gut microbiota composition and serum tryptophan metabolism in AD patients,^[89] and promotes the mental plasticity and stress relief in healthy elderly.^[90] A multicenter study published recently has also shown that the MD can alter the composition of the gut microbiota and improve cognitive function in older adults.^[5]

In animal study, it revealed that the transplantation of feces from normal wild type mice to AD transgenic mice significantly reduces A β burden and tau pathology, attenuates the glial activation, learning and memory impairment, and abnormal expression of genes related to intestinal macrophage activity, and restores the circulating inflammatory monocytes and synaptic plasticity in AD mice.^[91,92] The gut microbiota alteration can promote A β deposition by activating the MAPK signaling pathway and C/enhancer binding protein β (EBP)/asparagine endopeptidase (AEP) signaling pathway in the brain of AD transgenic mice.^[93,94] In addition, the probiotics have the capacity of improving the maze navigation, restoring the long-term potential, and balancing the antioxidant/oxidative biomarkers in mice.^[95] In detail, *Lactobacillus plantarum* inhibits the synthesis of TMAO and reduces the clusterin level.^[96] *Clostridium butyricum* and its metabolites inhibit microglia-mediated neuroinflammation.^[97] *Bifidobacterium longum* regulates NF- κ B activation via inhibiting LPS production.^[98] Of note, however, clinical studies have found that probiotics supplement does not significantly improve the cognitive and biochemical indicators in patients with severe AD.^[99]

Unlike the intestinal probiotics, the effects of antibiotics on AD are more complicated. Antibiotics, such as streptozotocin, can promote the growth of proinflammatory gut microbiota sub-types in animals, leading to learning and memory impairment, as has been used to establish sporadic AD models.^[100] Rifampicin and minocycline could decrease the levels of A β , glial activation, and inflammatory cytokines in the brain of AD mice.^[101,102] Rapamycin not only reduces the level of A β and the activation of microglia but also decreases the phosphorylation of tau protein.^[103] Nevertheless, despite some encouraging results in the animal studies, the clinical efficacy of antibiotics in patients with AD remains controversial so far.

Hearing impairment and AD

There is an emerging interest in the role of age-related hearing impairment on development of AD and other dementias. Hearing impairments can be caused by changes in the inner ear (eg, peripheral hearing) and/or dysfunction

in auditory processing (eg, central hearing). Hearing impairments are common among older adults: affecting up to 40% of adults aged 65 and up to 90% of adults aged >90.^[104] Hearing difficulty is commonly reported by patients with AD.^[105] Observational studies have found a consistent association between hearing loss and risk of dementia and cognitive decline.^[106,107] This work raises the question whether hearing loss may cause AD and dementia; however, alternative mechanisms could also explain this association.^[108]

Hearing impairments may directly affect dementia risk through brain atrophy by impairing cognitive processing abilities or by increasing cognitive load.^[108] In animal studies, noise-induced (peripheral) hearing loss is associated with increased neurodegeneration in the hippocampus, decreased neurogenesis, and poor memory function.^[109] Hearing impairments may also affect “psychosocial wellbeing” including social engagement, mental health, and physical activity,^[109] which could lead to increased dementia risk.^[110] In epidemiologic studies, peripheral hearing loss measured by pure tone audiometry may offer some of the stronger evidence that hearing loss may cause dementia, since pure tones are less affected by AD-neurodegeneration than central hearing.^[110] Peripheral hearing impairment has also been associated with decreased whole brain volumes, reduced temporal lobe or auditory cortex volumes,^[111,112] or reduced hippocampal volume.^[113] But there are conflicting results.^[114]

Hearing loss can often be corrected or mitigated, which could in turn also reduce dementia burden if hearing loss causes dementia. The Lancet commission on dementia prevention in 2020 suggested that treating hearing loss may reduce dementia burden by up to 8%.^[110] However, this estimate is based on observational studies which may be biased. Evidence from several small clinical trials has been mixed; some studies are suggestive that treatment of hearing impairments may improve cognition in non-demented patients,^[115] but this was not found in AD patients.^[116] Although studies often include important confounders in statistical models, unmeasured or residual confounder may remain. Both hearing and cognitive impairments are strongly associated with age, tend to have a gradual onset, and may have shared etiologies, including neurodegeneration, vascular and metabolic diseases, and aging processes.^[117] Some studies even question a biologic between hearing and cognition, as many cognitive tests rely on hearing and poor hearing may lead to more errors in hearing-based cognitive tests.^[118]

Relatively few studies have examined associations between hearing and AD specifically; one study on dementia subtypes have found associations between hearing impairment and clinical AD but not vascular dementia.^[119] One neuroimaging study found an association with pure tone and word recognition hearing loss and *in vivo* A β deposition,^[120] while an autopsy study found an association between clinician rated hearing loss and tau neurofibrillary degeneration stage but not A β plaque frequency.^[121] Higher genetic risk for AD also is associated with increased difficulty hearing in noise in older adults, suggesting a shared biologic pathway and

Table 1: Summary of current evidence and promising future research directions for novel factors related to AD.

Items	Summary of main evidence	Priorities for future research
Sleep	There exists a bi-directional relationship between sleep disturbances and dementia, but it remains unclear whether sleep disturbances are early signs or risk factors for AD.	Future research to uncover potential mechanisms and to explore the use of sleep interventions for the prevention and treatment of AD among high-risk older adults.
Hypoxia	Chronic hypoxia is one of the important environmental factors contributing to the pathogenesis of AD.	Further research is needed to determine whether prospective prevention and treatment of hypoxia may be helpful to delay or ameliorate the progression of AD by any mechanism.
Diet	Certain nutrients (eg, antioxidants) and dietary patterns (eg, Mediterranean diet) might have neuroprotective effects, but results have been inconsistent.	Larger adequately powered intervention and prospective studies in diverse populations with clinically relevant endpoints as well as sensitive neurocognitive tests and brain biomarkers associated with preclinical AD risk are required to understand the effect of diet on AD from the earliest to later stages of disease.
Gut microbiome	Numerous evidences have been obtained on the relationship between gut microbiota and AD from clinical studies, animal experiments, and mechanism exploration.	Whether some specific bacteria or combinations of bacteria in the gut microbiota have a role in the prevention and treatment of AD remains to be further clarified.
Hearing loss	Peripheral and central hearing loss are associated with lower regional brain volumes and dementia risk	Studies to determine mechanisms and direction of associations. Clinical trial to test if hearing rehabilitation affects cognition.

AD: Alzheimer disease.

that central hearing loss such as difficulty hearing in noise may be a preclinical marker for AD.^[122] Neurodegeneration in AD affects anatomical structures including the auditory pathways: neuritic plaques and tangles have been found in auditory association cortex as well as subcortical auditory pathways, which includes the medial temporal lobe. Several studies find that central auditory processing dysfunction is strongly associated with AD and precedes dementia diagnosis.^[123]

Older adults with hearing impairments are a higher risk for dementia and may be an important subgroup for referral for dementia evaluation. Treating hearing impairment may also help to prevent dementia; however, further research is needed to clarify the relationships between hearing impairments, AD, and dementia. Regardless, treatment for hearing impairments should be prioritized to improve quality of life of older adults with hearing loss.

Perspectives

There is no denying that the clinical treatment of AD is currently facing significant bottlenecks. The failure of many clinical trials suggests the importance of early diagnosis and prevention. Therefore, in recent years, researchers have been interested in thinking about AD from a broad perspective and in evaluating novel potential risk factors beyond those traditionally associated with AD such as CVD, diabetes, and education. These findings of the effects of oxygen metabolism, inflammation, and gut microbiota provide novel evidence that systemic effects may impact brain aging. Furthermore, our review highlights the potential importance of underappreciated health

factors to healthy aging such as sleep, diet, and hearing. This new research adds further evidence to support a shift from amyloid focused drug targets to multi-domain interventions that may help prevent AD and slow cognitive decline.

However, there is still a lot of work to be done in these areas. In Table 1, we present main evidence for each topic in our review as well as list key next steps for research. In particular, studies are needed to clarify the causal directions of the association between these potential novel risk factors and AD and to understand the underlying mechanisms and how they are related to AD neuropathogenesis. The clinical application of the study of oxygen metabolism and AD, such as the attempt to treat AD with HBOT; development of new intestinal probiotics; the prevention and treatment effect of specific diet components on AD. As the future direction of AD research, these works will require more multidisciplinary collaboration and the use of innovative research methods.

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