Title
Current Alzheimer disease research highlights: evidence for novel risk factors

Journal
Chinese Medical Journal, 134(18)

ISSN
0366-6999

Authors
Brenowitz, Willa D
Xiang, Yang
McEvoy, Claire T
et al.

Publication Date
2021-09-20

DOI
10.1097/cm9.0000000000001706

Peer reviewed

Current Alzheimer disease research highlights: evidence for novel risk factors

Willa D. Brenowitz[1,2], Yang Xiang[3,4], Claire T. McEvoy[5,6], Cui Yang[3,4], Kristine Yaffe[1,2,6,7], Wei-Dong Le[3,4], Yue Leng[1,6]

[1]Department of Psychiatry and Behavioral Sciences, University of California, San Francisco, CA, USA;
[2]Department of Epidemiology and Biostatistics, University of California, San Francisco, CA, USA;
[3]Institute of Neurology, Sichuan Provincial People's Hospital, University of Electronic Science and Technology of China, Chengdu, Sichuan 610072, China;
[4]Chinese Academy of Sciences Sichuan Translational Medicine Research Hospital, Chengdu, Sichuan, China;
[5]Centre for Public Health, Queen's University Belfast, Belfast, UK;
[6]Global Brain Health Institute, University of California, San Francisco, San Francisco, CA, USA;
[7]Department of Neurology, University of California, San Francisco, CA, USA.

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 (Aβ), 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 Aβ, 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 (Aβ) 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

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000001706

Willa D. Brenowitz and Yang Xiang contributed equally to the work.

Correspondence to: Dr. Wei-Dong Le, Institute of Neurology, Sichuan Provincial People's Hospital, University of Electronic Science and Technology of China, Chengdu, Sichuan 610072, China
E-Mail: wdle@sibs.ac.cn;
Dr. Yue Leng, Department of Psychiatry and Behavioral Sciences, University of California, San Francisco, CA, USA
E-Mail: Yue.leng@ucsf.edu

Chinese Medical Journal 2021;134(18)
Received: 02-02-2021 **Edited by:** Yuan-Yuan Ji

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 Aβ, 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 Aβ deposition in healthy older adults, indicating the role of sleep as a useful biomarker for forecasting Aβ 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 Aβ 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 Aβ,[36] decreasing the degradation of Aβ,[37] reducing the clearance of Aβ,[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 amnestic 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 Aβ burden and tau hyperphosphorylation, alleviating neuroinflammation by decreasing astrogliosis and microgliosis, reducing proinflammatory cytokines, and elevating phagocytic markers in mouse mole of AD.[49] More recently, HBOT was shown to be able to reduce Aβ 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 Aβ25–35-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-κB 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 Aβ 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 Aβ42:Aβ40 ratio, but the fecal propionic acid and butyric acid are negatively correlated with Aβ42 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-Aβ, 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 Aβ 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 Aβ 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 supplement 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 Aβ 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 Aβ 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-κB 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 Aβ, glial activation, and inflammatory cytokines in the brain of AD mice.[101,102] Rapamycin not only reduces the level of Aβ 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* Aβ deposition,[120] while an autopsy study found an association between clinician rated hearing loss and tau neurofibrillary degeneration stage but not Aβ 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.

References

1. Leng F, Edison P. Neuroinflammation and microglial activation in Alzheimer disease: where do we go from here? Nat Rev Neurol 2021;17:157–172. doi: 10.1038/s41582-020-00435-y.
2. Arvanitakis Z, Shah RC, Bennett DA. Diagnosis and management of dementia: review. JAMA 2019;322:1589–1599. doi: 10.1001/jama.2019.4782.
3. Barnes DE, Yaffe K. The projected effect of riskfactor reduction on Alzheimer's disease prevalence. Lancet Neurol 2011;10:819–828. doi: 10.1016/S1474-4422(11)70072-2.
4. Chen J, Zhang F, Zhao L, Cheng C, Zhong R, Dong C, *et al*. Hyperbaric oxygen ameliorates cognitive impairment in patients

with Alzheimer's disease and amnestic mild cognitive impairment. Alzheimers Dement (N Y) 2020;6:e12030. doi: 10.1002/trc2.12030.
5. Ghosh TS, Rampelli S, Jeffery IB, Santoro A, Neto M, Capri M, *et al*. Mediterranean diet intervention alters the gut microbiome in older people reducing frailty and improving health status: the NU-AGE 1-year dietary intervention across five European countries. Gut 2020;69:1218–1228. doi: 10.1136/gutjnl-2019-319654.
6. Deschenes CL, McCurry SM. Current treatments for sleep disturbances in individuals with dementia. Curr Psychiatry Rep 2009;11:20–26. doi: 10.1007/s11920-009-0004-2.
7. Sexton CE, Sykara K, Karageorgiou E, Zitser J, Rosa T, Yaffe K, *et al*. Connections between insomnia and cognitive aging. Neurosci Bull 2020;36:77–84. doi: 10.1007/s12264-019-00401-9.
8. Leng Y, McEvoy CT, Allen IE, Yaffe K. Association of sleep-disordered breathing with cognitive function and risk of cognitive impairment: a systematic review and meta-analysis. JAMA Neurol 2017;74:1237–1245. doi: 10.1001/jamaneurol.2017.2180.
9. Tranah GJ, Blackwell T, Stone KL, Ancoli-Israel S, Paudel ML, Ensrud KE, *et al*. Circadian activity rhythms and risk of incident dementia and mild cognitive impairment in older women. Ann Neurol 2011;70:722–732. doi: 10.1002/ana.22468.
10. Leng Y, Blackwell T, Stone KL, Hoang TD, Redline S, *et al*. Periodic limb movements in sleep are associated with greater cognitive decline in older men without dementia. Sleep 2016;39:1807–1810. doi: 10.5665/sleep.6158.
11. Leng Y, Musiek ES, Hu K, Cappuccio FP, Yaffe K. Association between circadian rhythms and neurodegenerative diseases. Lancet Neurol 2019;18:307–318. doi: 10.1016/S1474-4422(18)30461-7.
12. Yaffe K, Laffan AM, Harrison SL, Redline S, Spira AP, Ensrud KE, *et al*. Sleep-disordered breathing, hypoxia, and risk of mild cognitive impairment and dementia in older women. JAMA 2011;306:613–619. doi: 10.1001/jama.2011.1115.
13. Leng Y, Redline S, Stone KL, Ancoli-Israel S, Yaffe K. Objective napping, cognitive decline, and risk of cognitive impairment in older men. Alzheimers Dement 2019;15:1039–1047. doi: 10.1016/j.jalz.2019.04.009.
14. Chen JC, Espeland MA, Brunner RL, Lovato LC, Wallace RB, Leng X, *et al*. Sleep duration, cognitive decline, and dementia risk in older women. Alzheimers Dement 2016;12:21–33. doi: 10.1016/j.jalz.2015.03.004.
15. Ma Y, Liang L, Zheng F, Shi L, Zhong B, Xie W. Association between sleep duration and cognitive decline. JAMA Netw Open 2020;3:e2013573. doi: 10.1001/jamanetworkopen.2020.13573.
16. Djonlagic I, Mariani S, Fitzpatrick AL, Van Der Klei VMGTH, Johnson DA, Wood AC, *et al*. Macro and micro sleep architecture and cognitive performance in older adults. Nat Hum Behav 2021;5:123–145. doi: 10.1038/s41562-020-00964-y.
17. Kang JE, Lim MM, Bateman RJ, Lee JJ, Smyth LP, Cirrito JR, *et al*. Amyloid-beta dynamics are regulated by orexin and the sleep-wake cycle. Science 2009;326:1005–1007. doi: 10.1126/science.1180962.
18. Xie L, Kang H, Xu Q, Chen MJ, Liao Y, Thiyagarajan M, *et al*. Sleep drives metabolite clearance from the adult brain. Science 2013;342:373–377. doi: 10.1126/science.1241224.
19. Ju YES, Lucey BP, Holtzman DM. Sleep and Alzheimer disease pathology – a bidirectional relationship. Nat Rev Neurol 2014;10:115–119. doi: 10.1038/nrneurol.2013.269.
20. Winer JR, Mander BA, Kumar S, Reed M, Baker SL, Jagust WJ, *et al*. Sleep disturbance forecasts β-Amyloid accumulation across subsequent years. Curr Biol 2020;30:4291–4298e3. doi: 10.1016/j.cub.2020.08.017.
21. Holth JK, Fritschi SK, Wang C, Pederson NP, Cirrito JR, Mahan TE, *et al*. The sleep-wake cycle regulates brain interstitial fluid tau in mice and CSF tau in humans. Science 2019;363:880–884. doi: 10.1126/science.aav2546.
22. Bubu OM, Pirraglia E, Andrade AG, Sharma RA, Gimenez-Badia S, Umasabor-Bubu OQ, *et al*. Obstructive sleep apnea and longitudinal Alzheimer's disease biomarker changes. Sleep 2019;42:zsz048. doi: 10.1093/sleep/zsz048.
23. Fultz NE, Bonmassar G, Setsompop K, Stickgold RA, Rosen BR, Polimeni JR, *et al*. Coupled electrophysiological, hemodynamic, and cerebrospinal fluid oscillations in human sleep. Science 2019;366:628–631. doi: 10.1126/science.aax5440.
24. Leng Y, Ackley SF, Glymour MM, Yaffe K, Brenowitz WD. Genetic risk of Alzheimer's disease and sleep duration in non-demented elders. Ann Neurol 2021;89:177–181. doi: 10.1002/ana.25910.
25. Blackman J, Swirski M, Clynes J, Harding S, Leng Y, Coulthard E. Pharmacological and non-pharmacological interventions to enhance sleep in mild cognitive impairment and mild Alzheimer's disease: a systematic review. J Sleep Res 2020;e13229. doi: 10.1111/jsr.13229.
26. Cordone S, Scarpelli S, Alfonsi V, Gennaro LD, Gorgoni M. Sleep-based interventions in Alzheimers disease: promising approaches from prevention to treatment along the disease trajectory. Pharmaceuticals (Basel) 2021;14:383. doi: 10.3390/ph14040383.
27. Zhang F, Zhong R, Li S, Wang R, Wang T, Huang Z, *et al*. Alteration in sleep architecture and electroencephalogram as an early sign of Alzheimer's disease preceding the disease pathology and cognitive decline. Alzheimers Dement 2019;15:590–597. doi: 10.1016/j.jalz.2018.12.004.
28. Yu JT, Xu W, Tan CC, Andrieu S, Suckling J, Evangelou E, *et al*. Evidence-based prevention of Alzheimer's disease: systematic review and meta-analysis of 243 observational prospective studies and 153 randomised controlled trials. J Neurol Neurosurg Psychiatry 2020;91:1201–1209. doi: 10.1136/jnnp-2019-321913.
29. Jendroska K, Poewe W, Daniel SE, Iwerssen-Schmidt H, Paulsen J, Barthel S, *et al*. Ischemic stress induces deposition of amyloid beta immunoreactivity in human brain. Acta Neuropathol 1995;90:461–466. doi: 10.1007/BF00294806.
30. Shi Y, Liu Z, Shen Y, Zhu H. A novel perspective linkage between kidney function and Alzheimer's disease. Front Cell Neurosci 2018;12:384. doi: 10.3389/fncel.2018.00384.
31. Daniele G, Dilucia S, Masci PG, Monte FD. Heart and brain: complex relationships for left ventricular dysfunction. Curr Cardiol Rep 2020;22:72. doi: 10.1007/s11886-020-01318-w.
32. Sharma RA, Varga AW, Bubu OM, Pirraglia E, Kam K, Parekh A, *et al*. Obstructive sleep apnea severity affects amyloid burden in cognitively normal elderly. A longitudinal study. Am J Respir Crit Care Med 2018;197:933–943. doi: 10.1164/rccm.201704-0704OC.
33. Nielsen RB, Egefjord L, Angleys H, Mouridsen K, Gejl M, Moller A, *et al*. Capillary dysfunction is associated with symptom severity and neurodegeneration in Alzheimer's disease. Alzheimers Dement 2017;13:1143–1153. doi: 10.1016/j.jalz.2017.02.007.
34. Tsarouchas N, Benedek K, Bezerianos A, Benedek G, Keri S. Effects of moderate hypobaric hypoxia on evoked categorical visuocognitive responses. Clin Neurophysiol 2008;119:1475–1485. doi: 10.1016/j.clinph.2008.02.021.
35. van der Post J, Noordzij LAW, de Kam ML, Blauw GJ, Cohen AF, van Gerven JMA. Evaluation of tests of central nervous system performance after hypoxemia for a model for cognitive impairment. J Psychopharmacol 2002;16:337–343. doi: 10.1177/026988110201600408.
36. Liu H, Qiu H, Yang J, Ni J, Le W. Chronic hypoxia facilitates Alzheimer's disease through demethylation of gamma-secretase by downregulating DNA methyltransferase 3b. Alzheimers Dement 2016;12:130–143. doi: 10.1016/j.jalz.2015.05.019.
37. Nalivaevaa NN, Fisk L, Kochkina EG, Plesneva SA, Zhuravin IA, Babusikova E, *et al*. Effect of hypoxia/ischemia and hypoxic preconditioning/reperfusion on expression of some amyloid-degrading enzymes. Ann N Y Acad Sci 2004;1035:21–33. doi: 10.1196/annals.1332.002.
38. Ashok A, Rai NK, Raza W, Pandey R, Bandyopadhyay S. Chronic cerebral hypoperfusion-induced impairment of Aβ clearance requires HB-EGF-dependent sequential activation of HIF1α and MMP9. Neurobiol Dis 2016;95:179–193. doi: 10.1016/j.nbd.2016.07.013.
39. Zhang CE, Yang X, Li L, Sui X, Tian Q, Wei W, *et al*. Hypoxia-induced tau phosphorylation and memory deficit in rats. Neurodegener Dis 2014;14:107–116. doi: 10.1159/000362239.
40. Liu H, Qiu H, Xiao Q, Le W. Chronic hypoxia-induced autophagy aggravates the neuropathology of Alzheimer's disease through AMPK-mTOR signaling in the APPSwe/PS1dE9 mouse model. J Alzheimers Dis 2015;48:1019–1032. doi: 10.3233/JAD-150303.
41. Wang CY, Wang ZY, Xie JW, Cai JH, Wang T, Xu Y, *et al*. CD36 upregulation mediated by intranasal LV-NRF2 treatment mitigates hypoxia-induced progression of Alzheimer's-like pathogenesis. Antioxid Redox Signal 2014;21:2208–2230. doi: 10.1089/ars.2014.5845.

42. Snyder B, Shell B, Cunningham JT, Cunningham RL. Chronic intermittent hypoxia induces oxidative stress and inflammation in brain regions associated with early-stage neurodegeneration. Physiol Rep 2017;5:e13258. doi: 10.14814/phy2.13258.
43. Jain K, Prasad D, Singh SB, Kohli E. Hypobaric hypoxia imbalances mitochondrial dynamics in rat brain hippocampus. Neurol Res Int 2015;2015:742059. doi: 10.1155/2015/742059.
44. Wang CY, Xie JW, Wang T, Xu Y, Cai JH, Wang X, *et al*. Hypoxia-triggered m-calpain activation evokes endoplasmic reticulum stress and neuropathogenesis in a transgenic mouse model of Alzheimer's disease. CNS Neurosci Ther 2013;19:820–833. doi: 10.1111/cns.12151.
45. Boussi-Gross R, Golan H, Volkov O, Bechor Y, Hoofien D, Beeri MS, *et al*. Improvement of memory impairments in poststroke patients by hyperbaric oxygen therapy. Neuropsychology 2015;29:610–621. doi: 10.1037/neu0000149.
46. Liu S, Shen G, Deng S, Wang X, Wu Q, Guo A. Hyperbaric oxygen therapy improves cognitive functioning after brain injury. Neural Regen Res 2013;8:3334–3343. doi: 10.3969/j.issn.1673-5374.2013.35.008.
47. Harch PG, Fogarty EF. Hyperbaric oxygen therapy for Alzheimer's dementia with positron emission tomography imaging: a case report. Med Gas Res 2018;8:181–184. doi: 10.4103/2045-9912.248271.
48. Hachmo Y, Hadanny A, Hamed RA, Daniel-Kotovsky M, Catalogna M, Fishlev G, *et al*. Hyperbaric oxygen therapy increases telomere length and decreases immunosenescence in isolated blood cells: a prospective trial. Aging (Albany NY) 2020;12:22445–22456. doi: 10.18632/aging.202188.
49. Shapira R, Solomon B, Efrati S, Frenkel D, Ashery U. Hyperbaric oxygen therapy ameliorates pathophysiology of 3xTg-AD mouse model by attenuating neuroinflammation. Neurobiol Aging 2018;62:105–119. doi: 10.1016/j.neurobiolaging.2017.10.007.
50. Choi J, Kwon HJ, Lee JE, Lee Y, Seoh JY, Han PL. Hyper-oxygenation revitalizes Alzheimer's disease pathology through the upregulation of neurotrophic factors. Aging Cell 2019;18:e12888. doi: 10.1111/acel.12888.
51. Tian X, Wang J, Dai J, Yang L, Zhang L, Shen S, *et al*. Hyperbaric oxygen and Ginkgo Biloba extract inhibit Aβ25-35-induced toxicity and oxidative stress in vivo: a potential role in Alzheimer's disease. Int J Neurosci 2012;122:563–569. doi: 10.3109/00207454.2012.690797.
52. Tian X, Zhang L, Wang J, Dai J, Shen S, Yang L, *et al*. The protective effect of hyperbaric oxygen and Ginkgo biloba extract on Aβ25-35-induced oxidative stress and neuronal apoptosis in rats. Behav Brain Res 2013;242:1–8. doi: 10.1016/j.bbr.2012.12.026.
53. Zhang LD, Ma L, Zhang L, Dai JG, Chang LG, Huang PL, *et al*. Hyperbaric oxygen and Ginkgo Biloba extract ameliorate cognitive and memory impairment via nuclear factor Kappa-B pathway in rat model of Alzheimer's disease. Chin Med J (Engl) 2015;128:3088–3093. doi: 10.4103/0366-6999.169105.
54. Zhao B, Pan Y, Wang Z, Xu H, Song X. Hyperbaric oxygen pretreatment improves cognition and reduces hippocampal damage via p38 mitogen-activated protein kinase in a rat model. Yonsei Med J 2017;58:131–138. doi: 10.3349/ymj.2017.58.1.131.
55. Estruch R, Ros E, Salas-Salvado J, Covas MI, Corella D, Aros F, *et al*. Primary prevention of cardiovascular disease with a Mediterranean diet supplemented with extra-virgin olive oil or nuts. N Engl J Med 2018;378:e34. doi: 10.1056/NEJMoa1800389.
56. Morris MC, Tangney CC, Wang Y, Sacks FM, Bennett DA, Aggarwal NT. MIND diet associated with reduced incidence of Alzheimer's disease. Alzheimers Dement 2015;11:1007–1014. doi: 10.1016/j.jalz.2014.11.009.
57. McEvoy CT, Hoang T, Sidney S, Steffen LM, Jacobs DR, Shikany JM, *et al*. Dietary patterns during adulthood and cognitive performance in midlife: the CARDIA study. Neurology 2019;92:e1589–e1599. doi: 10.1212/WNL.0000000000007243.
58. Wu J, Song X, Chen GC, Neelakantan N, van Dam RM, Feng L, *et al*. Dietary pattern in midlife and cognitive impairment in late life: a prospective study in Chinese adults. Am J Clin Nutr 2019;110:912–920. doi: 10.1093/ajcn/nqz150.
59. van den Brink AC, Brouwer-Brolsma EM, Berendsen AAM, van de Rest O, The Mediterranean . Dietary Approaches to Stop Hypertension (DASH), and Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diets are associated with less cognitive decline and a lower risk of Alzheimer's disease – a review. Adv Nutr 2019;10:1040–1065. doi: 10.1093/advances/nmz054.
60. Valls-Pedret C, Sala-Vila A, Serra-Mir M, Corella D, de la Torre R, Martinez-Gonzalez MA, *et al*. Mediterranean diet and age-related cognitive decline: a randomized clinical trial. JAMA Intern Med 2015;175:1094–1103. doi: 10.1001/jamainternmed.2015.1668.
61. McGrattan AM, McGuinness B, McKinkey MC, Kee F, Passmore P, Woodside JV, *et al*. Diet and inflammation in cognitive ageing and Alzheimer's disease. Curr Nutr Rep 2019;8:53–65. doi: 10.1007/s13668-019-0271-4.
62. Hendrickson RC, Schindler AG, Pagulayan KF. Untangling PTSD and TBI: challenges and strategies in clinical care and research. Curr Neurol Neurosci Rep 2018;18:106. doi: 10.1007/s11910-018-0908-5.
63. Bok E, Jo M, Lee S, Lee BR, Kim J, Kim HJ. Dietary restriction and neuroinflammation: a potential mechanistic link. Int J Mol Sci 2019;20:E464. doi: 10.3390/ijms20030464.
64. Patel NV, Gordon MN, Connor KE, Good RA, Engelman RW, Mason J, *et al*. Caloric restriction attenuates Aβ-deposition in Alzheimer transgenic models. Neurobiol Aging 2005;26:995–1000. doi: 10.1016/j.neurobiolaging.2004.09.014.
65. Wang J, Ho L, Qin W, Rocher AB, Seror I, Humala N, *et al*. Caloric restriction attenuates β-amyloid neuropathology in a mouse model of Alzheimer's disease. FASEB J 2005;19:659–661. doi: 10.1096/fj.04-3182fje.
66. Lazic D, Tesic V, Jovanoic M, Brkic M, Milanovic D, Zlokovic BV, *et al*. Every-other-day feeding exacerbates inflammation and neuronal deficits in 5XFAD mouse model of Alzheimer's disease. Neurobiol Dis 2020;136:104745. doi: 10.1016/j.nbd.2020.104745.
67. Zhuang ZQ, Shen LL, Li WW, Fu X, Zeng F, Gui L, *et al*. Gut microbiota is altered in patients with Alzheimer's disease. J Alzheimers Dis 2018;63:1337–1346. doi: 10.3233/JAD-180176.
68. Li B, He Y, Ma J, Huang P, Du J, Cao L, *et al*. Mild cognitive impairment has similar alterations as Alzheimer's disease in gut microbiota. Alzheimers Dement 2019;15:1357–1366. doi: 10.1016/j.jalz.2019.07.002.
69. Liu P, Wu L, Peng G, Han Y, Tang R, Ge J, *et al*. Altered microbiomes distinguish Alzheimer's disease from amnestic mild cognitive impairment and health in a Chinese cohort. Brain Behav Immun 2019;80:633–643. doi: 10.1016/j.bbi.2019.05.008.
70. Saji N, Murotani K, Hisada T, Tsuduki T, Sugimoto T, Kimura A, *et al*. The relationship between the gut microbiome and mild cognitive impairment in patients without dementia: a cross-sectional study conducted in Japan. Sci Rep 2019;9:19227. doi: 10.1038/s41598-019-55851-y.
71. Nagpal R, Neth BJ, Wang S, Craft S, Yadav H. Modified Mediterranean-ketogenic diet modulates gut microbiome and short-chain fatty acids in association with Alzheimer's disease markers in subjects with mild cognitive impairment. EBioMedicine 2019;47:529–542. doi: 10.1016/j.ebiom.2019.08.032.
72. Zhuang Z, Yang R, Wang W, Qi L, Huang T. Associations between gut microbiota and Alzheimer's disease, major depressive disorder, and schizophrenia. J Neuroinflammation 2020;17:288. doi: 10.1186/s12974-020-01961-8.
73. Nagpal R, Neth BJ, Wang S, Mishra SP, Craft S, Yadav H. Gut mycobiome and its interaction with diet, gut bacteria and Alzheimer's disease markers in subjects with mild cognitive impairment: a pilot study. EBioMedicine 2020;59:102950. doi: 10.1016/j.ebiom.2020.102950.
74. Parikh IJ, Estus JL, Zajac DJ, Malik M, Weng JM, Tai LM, *et al*. Murine Gut Microbiome Association With APOE Alleles. Front Immunol 2020;11:200. doi: 10.3389/fimmu.2020.00200.
75. Tran TTT, Corsini S, Kellingray L, Hegarty C, Gall GL, Narbad A, *et al*. APOE genotype influences the gut microbiome structure and function in humans and mice: relevance for Alzheimer's disease pathophysiology. FASEB J 2019;33:8221–8231. doi: 10.1096/fj.201900071R.
76. Weng JM, Parikh A, Naqib A, York J, Green SJ, Estus S, *et al*. Synergistic effects of APOE and sex on the gut microbiome of young EFAD transgenic mice. Mol Neurodegener 2019;14:47. doi: 10.1186/s13024-019-0352-2.
77. Del Rio D, Zimetti F, Caffarra P, Tassotti M, Bernini F, Brighenti F, *et al*. The gut microbial metabolite trimethylamine-N-oxide is

present in human cerebrospinal fluid. Nutrients 2017;9:E1053. doi: 10.3390/nu9101053.
78. Marizzoni M, Cattaneo A, Mirabelli P, Festari C, Lopizzo N, Nicolosi V, *et al*. Short-chain fatty acids and lipopolysaccharide as mediators between gut dysbiosis and amyloid pathology in Alzheimer's disease. J Alzheimers Dis 2020;78:683–697. doi: 10.3233/JAD-200306.
79. MahmoudianDehkordi S, Arnold M, Nho K, Ahmad S, Jia W, Xie G, *et al*. Altered bile acid profile associates with cognitive impairment in Alzheimer's disease – an emerging role for gut microbiome. Alzheimers Dement 2019;15:76–92. doi: 10.1016/j.jalz.2018.07.217.
80. Nho K, Kueider-Paisley A, MahmoudianDehkordi S, Arnold M, Risacher SL, Louie G, *et al*. Altered bile acid profile in mild cognitive impairment and Alzheimer's disease: relationship to neuroimaging and CSF biomarkers. Alzheimers Dement 2019;15:232–244. doi: 10.1016/j.jalz.2018.08.012.
81. Wickwire EM, Schnyer DM, Germain A, Williams SG, Lettieri CJ, McKeon AB, *et al*. Sleep, sleep disorders, and circadian health following mild traumatic brain injury in adults: review and research agenda. J Neurotrauma 2018;35:2615–2631. doi: 10.1089/neu.2017.5243.
82. Wang S, Jiang W, Ouyang T, Shen XY, Wang F, Qu YH, *et al*. Jatrorrhizine balances the gut microbiota and reverses learning and memory deficits in APP/PS1 transgenic mice. Sci Rep 2019;9:19575. doi: 10.1038/s41598-019-56149-9.
83. Wang Y, An Y, Ma W, Yu H, Lu Y, Zhang X, *et al*. 27-Hydroxycholesterol contributes to cognitive deficits in APP/PS1 transgenic mice through microbiota dysbiosis and intestinal barrier dysfunction. J Neuroinflammation 2020;17:199. doi: 10.1186/s12974-020-01873-7.
84. Chen D, Yang X, Yang J, Lai G, Yong T, Tang X, *et al*. Prebiotic effect of fructooligosaccharides from Morinda officinalis on Alzheimer's disease in rodent models by targeting the microbiota-gut-brain axis. Front Aging Neurosci 2017;9:403. doi: 10.3389/fnagi.2017.00403.
85. Zhou H, Tai J, Xu H, Lu X, Meng D. Xanthoceraside could ameliorate Alzheimer's disease symptoms of rats by affecting the gut microbiota composition and modulating the endogenous metabolite levels. Front Pharmacol 2019;10:1035. doi: 10.3389/fphar.2019.01035.
86. Wang X, Sun G, Feng T, Zhang J, Huang X, Wang T, *et al*. Sodium oligomannate therapeutically remodels gut microbiota and suppresses gut bacterial amino acids-shaped neuroinflammation to inhibit Alzheimer's disease progression. Cell Res 2019;29:787–803. doi: 10.1038/s41422-019-0216-x.
87. Cui B, Su D, Li W, She X, Zhang M, Wang R, *et al*. Effects of chronic noise exposure on the microbiome-gut-brain axis in senescence-accelerated prone mice: implications for Alzheimer's disease. J Neuroinflammation 2018;15:190. doi: 10.1186/s12974-018-1223-4.
88. Wang M, Cao J, Amakye WK, Gong C, Li Q, Ren J. Mid infrared light treatment attenuates cognitive decline and alters the gut microbiota community in APP/PS1 mouse model. Biochem Biophys Res Commun 2020;523:60–65. doi: 10.1016/j.bbrc.2019.12.015.
89. Leblhuber F, Steiner K, Schuetz B, Fuchs D, Gostner JM. Probiotic supplementation in patients with Alzheimer's dementia– an explorative intervention study. Curr Alzheimer Res 2018;15:1106–1113. doi: 10.2174/1389200219666180813144834.
90. Kim CS, Cha L, Sim M, Jung S, Chun WY, Baik HW, *et al*. Probiotic supplementation improves cognitive function and mood with changes in gut microbiota in community-dwelling elderly: a randomized, double-blind, placebo-controlled, multicenter trial. J Gerontol A Biol Sci Med Sci 2021;76:32–40. doi: 10.1093/gerona/glaa090.
91. Kim MS, Kim Y, Choi H, Kim W, Park S, Lee D, *et al*. Transfer of a healthy microbiota reduces amyloid and tau pathology in an Alzheimer's disease animal model. Gut 2020;69:283–294. doi: 10.1136/gutjnl-2018-317431.
92. Sun J, Xu J, Ling Y, Wang F, Gong T, Yang C, *et al*. Fecal microbiota transplantation alleviated Alzheimer's disease-like pathogenesis in APP/PS1 transgenic mice. Transl Psychiatry 2019;9:189. doi: 10.1038/s41398-019-0525-3.
93. Li Z, Zhu H, Guo Y, Du X, Qin C. Gut microbiota regulate cognitive deficits and amyloid deposition in a model of Alzheimer's disease. J Neurochem 2020;155:448–461. doi: 10.1111/jnc.15031.
94. Chen C, Ahn EH, Kang SS, Liu X, Alam A, Ye K. Gut dysbiosis contributes to amyloid pathology, associated with C/EBPβ/AEP signaling activation in Alzheimer's disease mouse model. Sci Adv 2020;6:eaba0466. doi: 10.1126/sciadv.aba0466.
95. Asl ZR, Sepehri G, Salami M. Probiotic treatment improves the impaired spatial cognitive performance and restores synaptic plasticity in an animal model of Alzheimer's disease. Behav Brain Res 2019;376:112183. doi: 10.1016/j.bbr.2019.112183.
96. Wang QJ, Shen YE, Wang X, Fu S, Zhang X, Zhang YN, *et al*. Concomitant memantine and Lactobacillus plantarum treatment attenuates cognitive impairments in APP/PS1 mice. Aging (Albany NY) 2020;12:628–649. doi: 10.18632/aging.102645.
97. Sun J, Xu J, Yang B, Chen K, Kong Y, Fang N, *et al*. Effect of Clostridium butyricum against microglia-mediated neuroinflammation in Alzheimer's disease via regulating gut microbiota and metabolites butyrate. Mol Nutr Food Res 2020;64:e1900636. doi: 10.1002/mnfr.201900636.
98. Lee HJ, Lee KE, Kim JK, Kim DH. Suppression of gut dysbiosis by Bifidobacterium longum alleviates cognitive decline in 5XFAD transgenic and aged mice. Sci Rep 2019;9:11814. doi: 10.1038/s41598-019-48342-7.
99. Agahi A, Hamidi GA, Daneshvar R, Hamdieh M, Soheili M, Alinaghipour A, *et al*. Does severity of Alzheimer's disease contribute to its responsiveness to modifying gut microbiota? A double blind clinical trial. Front Neurol 2018;9:662. doi: 10.3389/fneur.2018.00662.
100. Cattaneo A, Cattane N, Galluzzi S, Provasi S, Lopizzo N, Festari C, *et al*. Association of brain amyloidosis with pro-inflammatory gut bacterial taxa and peripheral inflammation markers in cognitively impaired elderly. Neurobiol Aging 2017;49:60–68. doi: 10.1016/j.neurobiolaging.2016.08.019.
101. Yulug B, Hanoglu L, Ozansoy M, Isik D, Kilic U, Kilic E, *et al*. Therapeutic role of rifampicin in Alzheimer's disease. Psychiatry Clin Neurosci 2018;72:152–159. doi: 10.1111/pcn.12637.
102. Budni J, Garcez ML, de Medeiros J, Cassaro E, Bellettini-Santos T, Mina F, *et al*. The anti-inflammatory role of minocycline in Alzheimer's disease. Curr Alzheimer Res 2016;13:1319–1329. doi: 10.2174/1567205013666160819124206.
103. Wang C, Yu JT, Miao D, Wu ZC, Tan MS, Tan L. Targeting the mTOR signaling network for Alzheimer's disease therapy. Mol Neurobiol 2014;49:120–135. doi: 10.1007/s12035-013-8505-8.
104. Lin FR, Niparko JK, Ferrucci L. Hearing loss prevalence in the United States. Arch Intern Med 2011;171:1851–1852. doi: 10.1001/archinternmed.2011.506.
105. Gold M, Lightfoot LA, Hnath-Chisolm T. Hearing loss in a memory disorders clinic. A specially vulnerable population. Arch Neurol 1996;53:922–928. doi: 10.1001/archneur.1996.00550090134019.
106. Loughrey DG, Kelly ME, Kelley GA, Brennan S, Lawlor BA. Association of age-related hearing loss with cognitive function, cognitive impairment, and dementia: a systematic review and meta-analysis. JAMA Otolaryngol Head Neck Surg 2018;144:115–126. doi: 10.1001/jamaoto.2017.2513.
107. Wei J, Hu Y, Zhang L, Hao Q, Yang R, Lu H, *et al*. Hearing impairment, mild cognitive impairment, and dementia: a meta-analysis of cohort studies. Dement Geriatr Cogn Dis Extra 2017;7:440–452. doi: 10.1159/000485178.
108. Lin FR, Albert M. Hearing loss and dementia – who is listening? Aging Ment Health 2014;18:671–673. doi: 10.1080/13607863.2014.915924.
109. Liu L, Shen P, He T, Chang Y, Shi L, Tao L, *et al*. Noise induced hearing loss impairs spatial learning/memory and hippocampal neurogenesis in mice. Sci Rep 2016;6:20374. doi: 10.1038/srep20374.
110. Livingston G, Huntley J, Sommerlad A, Ames D, Ballard C, Banerjee S, *et al*. Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. Lancet 2020;396:413–446. doi: 10.1016/S0140-6736(20)30367-6.
111. Lin FR, Ferrucci L, An Y, Goh JO, Doshi J, Metter EJ, *et al*. Association of hearing impairment with brain volume changes in older adults. Neuroimage 2014;90:84–92. doi: 10.1016/j.neuroimage.2013.12.059.
112. Rigters SC, Bos D, Metselaar M, Roshchupkin GV, Baatenburg de Jong RJ, Ikram MA, *et al*. Hearing impairment is associated with

smaller brain volume in aging. Front Aging Neurosci 2017;9:2. doi: 10.3389/fnagi.2017.00131.
113. Uchida Y, Nishita Y, Kato T, Iwata K, Sugiura S, Suzuki H, *et al*. Smaller hippocampal volume and degraded peripheral hearing among Japanese Community Dwellers. Front Aging Neurosci 2018;10:319. doi: 10.3389/fnagi.2018.00319.
114. Profant O, Skoch A, Balogova Z, Tintera J, Hlinka J, Syka J. Diffusion tensor imaging and MR morphometry of the central auditory pathway and auditory cortex in aging. Neuroscience 2014;260:87–97. doi: 10.1016/j.neuroscience.2013.12.010.
115. Castiglione A, Benatti A, Velardita C, Favaro D, Padoan E, Severi D, *et al*. Aging, cognitive decline and hearing loss: effects of auditory rehabilitation and training with hearing aids and cochlear implants on cognitive function and depression among older adults. Audiol Neurootol 2016;21 Suppl 1:21–28. doi: 10.1159/000448350.
116. Nguyen MF, Bonnefoy M, Adrait A, Gueugnon M, Petitot C, Collet L, *et al*. Efficacy of hearing aids on the cognitive status of patients with Alzheimer's disease and hearing loss: a multicenter controlled randomized trial. J Alzheimers Dis 2017;58:123–137. doi: 10.3233/JAD-160793.
117. Davis A, McMahon CM, Pichora-Fuller K, Russ S, Lin F, Olusanya BO, *et al*. Aging and hearing health: the life-course approach. Gerontologist 2016;56:S256–S267. doi: 10.1093/geront/gnw033.
118. Lim MYL, Loo JHY. Screening an elderly hearing impaired population for mild cognitive impairment using Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA). Int J Geriatr Psychiatry 2018;33:972–979. doi: 10.1002/gps.4880.
119. Hwang PH, Longstreth WT, Brenowitz WD, Thielke SM, Lopez OL, Francis CE, *et al*. Dual sensory impairment in older adults and risk of dementia from the GEM Study. Alzheimers Dement (Amst) 2020;12:e12054. doi: 10.1002/dad2.12054.
120. Golub JS, Sharma RK, Rippon BQ, Brickman AM, Luchsinger JA. The association between early age-related hearing loss and brain β-Amyloid. Laryngoscope 2021;131:633–638. doi: 10.1002/lary.28859.
121. Brenowitz WD, Besser LM, Kukull WA, Keene CD, Glymour MM, Yaffe K. Clinician-judged hearing impairment and associations with neuropathologic burden. Neurology 2020;95:e1640–e1649. doi: 10.1212/WNL.0000000000010575.
122. Brenowitz WD, Filshtein TJ, Yaffe K, Walter S, Ackley SF, Hoffmann TJ, *et al*. Association of genetic risk for Alzheimer disease and hearing impairment. Neurology 2020;95:e2225–e2234. doi: 10.1212/WNL.0000000000010709.
123. Gates GA, Anderson ML, McCurry SM, Feeney MP, Larson EB. Central auditory dysfunction as a harbinger of Alzheimer dementia. Arch Otolaryngol Head Neck Surg 2011;137:390–395. doi: 10.1001/archoto.2011.28.

How to cite this article: Brenowitz WD, Xiang Y, McEvoy CT, Yang C, Yaffe K, Le WD, Leng Y. Current Alzheimer disease research highlights: evidence for novel risk factors. Chin Med J 2021;134:2150–2159. doi: 10.1097/CM9.0000000000001706