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REVIEW

A review of variable risk factors affecting the development of mild cognitive impairment in older adults

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Abstract

Mild cognitive impairment (MCI) is considered to be a transitional state in which cognitive function gradually deteriorates from normal to dementia, which is mainly characterized by reduced functioning in several cognitive domains, such as executive function, memory, language, processing speed, and attention. Currently, the clinical treatment of dementia is unsatisfactory, so we shifted our research focus to MCI to find variable risk factors, potential mechanisms, and effective preventive measures for the occurrence of MCI in older adults, to reduce the incidence of dementia and alleviate the health and economic burden on the family and society. Currently, we found that the variable risk factors affecting the occurrence and development of MCI in older adults are cardiovascular and respiratory diseases, endocrine-metabolic diseases, social life factors, and psychological factors. We mainly review the effects of these risk factors on cognitive function and the potential mechanisms of action, and propose interventions to improve cognitive function.

Keywords: Mild cognitive impairment, risk factors, type 2 diabetes, hypertension, intervention

Introduction

Mild cognitive impairment (MCI) is an excess stage between normal cognition and dementia and a precursor to Alzheimer's disease (AD). It is characterized primarily by impaired subjective memory and moderate deficits in at least one of the cognitive domains, such as executive function, memory, language, processing speed, or attention [1]. Neurobiological features are reflected in hypoperfusion and hypometabolism in the temporoparietal cortex, atrophy of the medial temporal lobe, elevated tau and phosphorylated tau, and decreased Aβ42 in the cerebrospinal fluid, and cerebral Aβ42 deposition [2]. MCI is currently divided into amnestic MCI (aMCI) and non-amnestic MCI (naMCI) [3]. aMCI is the most common subtype of MCI, manifesting as situational memory impairment, and is more likely to progress to typical AD, whereas naMCI affects impairment of cognitive domains other than memory and is more likely to progress to atypical AD (including vascular dementia or other types of dementia) [3]. The transition from normal cognition to MCI to AD is a continuous process in the development of cognitive impairment, and thus patients with MCI are considered to be at high risk of developing AD [4]. In China, 15.2%-15.9% of the elderly population over the age of 60 suffer from MCI, and the incidence of the disease is around 6.36% per year [5], with aMCI accounting for more than 80% of all MCI patients [3]. Meanwhile, the average annual conversion rate from MCI to AD is as high as 18.4% [6]. In terms of gender, the prevalence of MCI is higher in women than in men [7], and the gender difference is attributed to differences in socioeconomic status (*e.g.*, education and occupation) and health status between men and women [3]. In addition, regarding social development, the prevalence of MCI is significantly lower in most developed countries than in developing countries [8]. Cognitive impairment causes a serious economic burden to individuals, families, and society, but the current treatment for AD patients is still unsatisfactory, and MCI as a precursor of AD has become a new direction of current research. Multiple risk factors can affect the development and transformation of MCI; therefore, this review mainly lists the risk factors (Figure 1), pathogenesis, and interventions of MCI to reduce the incidence of MCI and block its transformation to AD.

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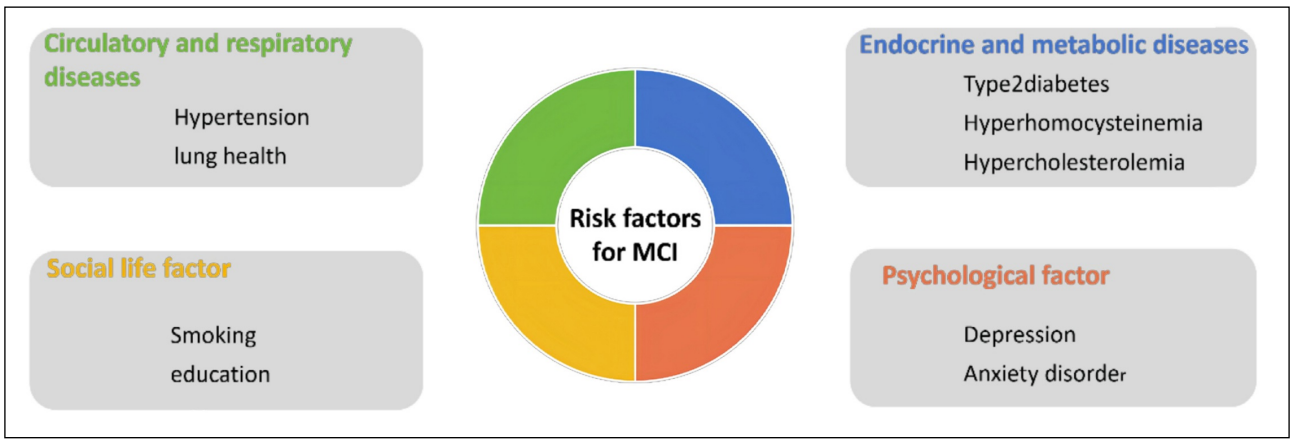

Figure 1. Risk factors affecting MCI.

Risk factors, mechanisms, and interventions

Type 2 diabetes

Diabetes mellitus is a group of metabolic disorders characterized by chronic hyperglycemia caused by multiple etiologies, which can lead to chronic progressive lesions in multiple organs and systems. An estimated 537 million people will already have diabetes in 2021, and this number is expected to reach 643 million by 2030 and 783 million by 2045 [9]. This means that in the next 20 years, an average of 1 in 10 people worldwide will have diabetes, and more than 90% of them will have type 2 diabetes. It is now well established that type 2 diabetes is one of the modifiable risk factors for the development of MCI [5, 10, 11]. In a follow-up study of diabetic patients for more than 10 years [10], the mean MCI prevalence in the diabetic group was found to be 30.66 ± 3.09%, which was significantly higher than that in the non-diabetic group, which was 22.32 ± 2.75%. In a meta-analysis, the prevalence of MCI in patients with type 2 diabetes mellitus was even 45% worldwide [12]. There are two conclusions regarding whether mild cognitive functioning progresses to dementia in patients with type 2 diabetes: a few researchers have suggested that although diabetes raises the prevalence of MCI, it seems to have no effect on its progression [10, 13]; however, the majority of scholars have suggested that the prolonged presence of diabetes may increase the risk of conversion of MCI to dementia [14-16]. There is a relatively significant difference between the two findings, which may be related to the sample size, age of the participants, and duration of follow-up, and needs to be demonstrated by further study follow-up. The incidence of MCI may be higher when type 2 diabetes is combined with other conditions than type 2 diabetes alone. In addition, hyperlipidemia, hypertension, diabetic nephropathy, and macrovascular and microvascular lesions are thought to significantly increase the risk of MCI in patients with diabetes [11, 17].

There may be multiple causes of MCI due to type 2 diabetes: cerebrovascular disease is the primary cause, and chronic hyperglycemia may lead to thickening of the basement membrane of the cerebrovascular muscle, which reduces cerebral blood circulation, leading to inadequate cerebral perfusion and white matter disease, and ultimately to MCI or dementia [11, 18]. Second, galactose lectin 3 (Gal3) and inflammatory responses play an important role in the progression of cognitive impairment in diabetes. Elevated circulating levels of Gal3 and some inflammatory markers, such as serum soluble vascular adhesion molecule (svcAM-1) and high-sensitivity C-reactive protein (Hs-CRP), may be associated with the development of MCI in type 2 diabetes patients [19, 20]. Third, type 2 diabetic patients with MCI exhibit significantly reduced amplitude of diffuse low-frequency fluctuations (ALFF) in various brain regions significantly associated with cognitive performance, such as the bilateral insula, the left middle frontal gyrus, the left precuneus, and significantly elevated ALFF in the temporal gyrus and the fusiform gyrus [21]. Fourth, dipeptidyl peptidase IV (DPP-IV) has been shown to affect cognitive function through both enzymatic and non-enzymatic pathways. DPP4 may contribute to cognitive dysfunction in diabetic patients by combining with PAR2 in the hippocampus, activating GSK-3β, and downregulating peroxisome proliferator-activated receptor gamma coactivator 1α expression, leading to mitochondrial dysfunction [22]. In addition, advanced glycosylation end products (AGEs), vascular endothelial dysfunction, abnormal insulin regulation, and neuroinflammation may also be engaged in the pathogenesis of MCI in diabetic patients [17].

Some glucose-lowering drugs have been shown to improve cognitive function in patients. Recent studies have found that glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and DPP-IV inhibitors are effective in ameliorating cognitive impairment in diabetic patients [23]. GLP-1 acts as a physiological modulator of the central nervous system and enhances learning and memory function by restoring insulin signaling [24]. DPP-IV inhibitors ameliorate diabetes-mediated cerebrovascular dysfunction by lowering plasma endothelin-1 (ET-1) levels and decreasing cerebrovascular hyperreactivity [25]. DPP-IV inhibitors may also improve cognitive performance by inhibiting Aβ aggregation [26]. Some other drugs, such as epalrestat, donepezil, and empagliflozin, prevent cognitive impairment through antioxidant and anti-inflammatory ef-

fects [27, 28]. The traditional Chinese exercise Tai Chi is an increasingly popular multimodal mind-body exercise that combines physical, cognitive, social, and meditative activities to promote brain health while controlling blood glucose [29].

Hypertension

According to authoritative epidemiological surveys, the number of hypertensive patients aged 30–79 years worldwide increased from 648 million between 1990 and 2019 to 1,278 million in 2019, but the global rate of hypertension control by 2019 was only 23% in women and 18% in men [30]. Hypertension impairs cerebral blood supply by impairing the structure and function of the cerebral microcirculation, promoting microvascular thinning, cerebral microvascular endothelial dysfunction, and neurovascular uncoupling. At the same time, hypertension disrupts the blood-brain barrier, contributing to neuroinflammation and exacerbating amyloidosis [31, 32]. Hypertension-induced endothelial dysfunction is associated with cognitive decline [33]. Vascular endothelial cells are subjected to a combination of intravascular shear stress, turbulence, increased free radicals, and decreased NO signaling, ultimately leading to the development of atherosclerosis. Intracranial and extracranial atherosclerosis promotes cognitive decline [32]. Proteomic studies have identified reduced synaptic regulation and plasticity as well as abnormal myelination as potential signaling mechanisms leading to cognitive decline in patients with hypertension combined with atherosclerosis [34]. Cerebrovascular self-regulation ensures adequate cerebral perfusion during fluctuations in blood pressure by maintaining relatively constant cerebral blood flow. The mechanisms of hypertension-induced alterations in cerebrovascular self-regulation involve structural changes in the cerebral vasculature (sclerosis and remodeling) and alterations in the responsiveness of vascular smooth muscle cells to increases in transmural pressure [35]. Activation of AngII type 1 receptors (AT1R) in brain endothelial cells by chronic hypertension via AngII is necessary for blood-brain barrier disruption [36]. A recent study showed that damage to endothelial Kir2.1 channels, involving endothelial hyperpolarization and vasodilation under neural activity, mediates neurovascular coupling defects in BPH mice [37, 38]. In animal models, hypertension has been found to mediate Aβ deposition, disruption of the blood-brain barrier, and cognitive function through activation of AGE receptors and modulation of β- and γ-secretase activity. In addition, neuroradiological markers such as white matter hyperintensities, lacunar infarcts, micro hemorrhages, and enlarged perivascular gaps are associated with the development of cognitive impairment [31, 39].

Thus, hypertension has been identified as a variable risk factor for cognitive dysfunction, including MCI [40, 41]. A multicenter study shows that the prevalence of cognitive impairment is higher in hypertensive patients than in the general population, with executive function and semantic memory being the cognitive domains most affected [42]. In a meta-analysis of 47,179 participants, Qin *et al*. showed that the overall prevalence of MCI in hypertensive patients was in the range of 30% and was significantly higher than in non-hypertensive older adults [43]. Wang *et al*. further found in a 7-year retrospective cohort study that different grades and durations of hypertension had different outcomes on the occurrence of MCI: subjects with hypertension grade 1 or duration [40]. This result may be due to a compensatory effect of early-stage hypertension on vascular lesions and inadequate cerebral perfusion. Also, hypertension is a risk factor for the conversion of cognitive function to AD in patients with MCI [44].

Hypertension treatment reduces cognitive decline to some extent [45-47]. A recent randomized clinical trial showed that intensive blood pressure control (systolic blood pressure target < 120 mmHg) versus standard blood pressure control (systolic blood pressure target < 140 mmHg) in patients found that control of blood pressure reduced the risk of MCI, with less increase in cerebral white matter lesion volume in the intensive treatment group [48, 49]. Although decreased renal function, as measured by eGFR, may be a factor in the increased risk of MCI, it is not related to the presence or absence of intensive treatment of hypertension, *i.e*., intensive treatment of hypertension does not lead to a decrease in eGFR [50]. Antihypertensive drugs, especially calcium channel blockers and renin-angiotensin system blockers (ACEIs and ARBs), may help to prevent cognitive decline by lowering blood pressure and through neuroprotective mechanisms [46].

Hypercholesterolemia

Elevated plasma cholesterol is associated with a variety of health conditions, and it may be related to the pathogenesis of MCI. A large study based on a Chinese population (n = 46,011) demonstrated that hyperlipidemia is a risk factor for MCI [5]. The accumulation of cholesterol in neurons contributes to amyloid deposition in the brain by accelerating the cleavage of amyloid precursor proteins into amyloid-like components, whereas keeping cholesterol low in neurons may inhibit Aβ accumulation. Another meta-analysis reported that elevated cholesterol levels in midlife may increase the risk of cognitive impairment in later life, while elevated cholesterol levels in later life were not associated with dementia or cognitive impairment [51]. The possible reasons for this phenomenon may be: cholesterol is essential for synaptic maturation and maintenance of synaptic plasticity, and as the body ages, the cholesterol level in the brain gradually decreases, causing a decrease in the role of cholesterol in the maintenance of synaptic plasticity, leading to a decline in cognitive function, while those patients with normal cognition have cholesterol levels that are still sufficient to maintain synaptic plasticity; Meanwhile, cholesterol is also an important component of the cell membrane, playing a role as an ion-permeable regulator and a regulator of signal transduction, which may also impair this function to some extent [52]. At the same time, cholesterol is an important component of cell membranes, acting as an ion-permeable regulator and a regulator of signal transduction, which may be impaired

to some extent by lower cholesterol levels.

Although statins are the most commonly used cholesterol-lowering drugs, it is not established whether they can be used to prevent cognitive decline. It has been suggested that individuals taking statins, especially purist ApoE4 carriers, have a slower progression of cognitive decline [53]. Simvastatin was found to be beneficial in maintaining white matter microstructure in cognitively normal middle-aged adults, suggesting that simvastatin has the potential to prevent MCI. However, another prospective study reported no difference in the rate of decline on cognitive tests between the pravastatin group and the control group during 3 years of follow-up [54]. These conflicting results result from the lack of harmonized biomarkers and adequate intervention time. Addressing these issues may help us to further our understanding of the effects of lipid-lowering drugs on cognitive function in older adults.

Hyperhomocysteinemia (HHcy)

Homocysteine (Hcy) is a non-essential sulfur-containing amino acid that is produced *in vivo* by the demethylation of methionine and plays a central role in the methionine and folate cycles. HHcy is associated with a variety of cognitive dysfunctions, including MCI [55, 56]. In a follow-up study of 592 patients with acute stroke, patients with higher Hcy levels were found to be more likely to be cognitively impaired 1 month after stroke than those with lower Hcy levels [57]. A dose-response meta-analysis of 29 prospective cohort studies found that for every 5 mol/L increase in blood Hcy levels, the relative risk of AD increased by 15% [58]. It has been found that Hcy is capable of autoxidation in the presence of oxygen molecules and promotes the formation of reactive oxygen species (*e.g.*, hydrogen peroxide, hydroxyl, and thiol radicals), which may have cytotoxic effects when the concentration of reactive oxygen species in the body is elevated [59]. Endothelial inflammation under HHcy conditions can impair vascular endothelial function, promote vascular injury, lead to cerebral small vessel disease, and alter the permeability of the blood-brain barrier, which in turn leads to cognitive dysfunction [60]. Meanwhile, Hcy can have direct toxic effects on neurons by promoting DNA damage and altering NMDA receptor expression, leading to dysregulation of calcium homeostasis, mitochondrial function, neuronal autophagy, and apoptosis [61].

The study found that supplementation with B vitamins can significantly reduce Hcy levels, which may reduce age-related cognitive decline and the risk of AD and overall dementia [62]. Hcy produced by the human body is metabolized by three main pathways [63]: (1) remethylation elimination, in which Hcy is remethylated to methionine with the aid of vitamins B2 and B12; (2) transsulfuration, in which Hcy is first converted to cystathionine (with vitamin B6 acting as a cofactor), which is metabolized to cysteine and α-keto-butyric acid, and ultimately excreted from the body; and (3) release into the extracellular fluid. Abnormalities in any of these metabolic pathways elevate plasma Hcy concentrations. In contrast, Hcy metabolism is heavily dependent on B vitamins, including folate, vitamin B12, and vitamin B6. Folic acid provides methyl for Hcy methylation, while vitamin B12 functions as a coenzyme for methionine synthase in the process of Hcy methylation. Vitamin B6 activates the transsulfuration pathway, transferring sulfur from homocysteine to cysteine, which can use the transferred sulfur to synthesize glutathione with itself, and the reduction of glutathione enhances the antioxidant activity of the organism [64]. Clinically, older adults are more likely to be deficient in B vitamins and show an increasing trend with age. Supplementation with folic acid, vitamin B6, and vitamin B12 not only reduces plasma Hcy concentrations but also prevents cognitive decline in patients with MCI [65]. In a 24-month randomized trial, Gong *et al*. found that in MCI patients with left frontal lobe atrophy, B vitamins may be more effective in slowing cognitive decline [66]. And the combination of folic acid and vitamin B12 demonstrated better efficacy than their use alone [67].

Smoking

Smoking is bad for brain health and increases the risk of cognitive impairment [53]. In elderly patients with MCI, functional performance declines more rapidly in smokers than in nonsmokers, which is associated with a more rapid decline in endonasal cortical mass over time [68]. Sleep plays an important mediating role in the relationship between smoking and MCI [69]. One of the sleep problems is sleep deprivation, which leads to short sleep duration, and fatigue, causing cognitive decline and reduced sleep duration [70, 71]. The study found an inverted U-shaped relationship between sleep duration and cognitive scores, and a positive linear relationship between sleep quality and cognitive scores, so too much or too little sleep and sleep quality may lead to cognitive decline [72]. Long-term smoking is associated with elevated brain oxidative stress, which plays an important role in reducing sleep duration [73], as well as decreasing melatonin secretion by the pineal gland, which can persistently impair cognitive function in animals and humans [74]. Smoking also alters the composition of the nicotinic acetylcholine receptor subunit, increases the expression of the glutamate receptor subunit GluR2, reduces neurogenesis, and alters Akt and ERK1/2 activity, causing mitochondrial dysfunction in the hippocampus and cortex [75]. In addition, smoking-induced inefficiencies in Aβ removal may also contribute to the development of MCI. Smoking affects the function of cortico-striatal circuits, with increased functional connectivity between dorsal striatal and parietal regions in cognitively normal smokers compared to non-smokers. Compared with cognitively normal smokers and MCI non-smokers, MCI smokers showed reduced functional connectivity between the dorsal striatum and parieto-occipital regions and increased functional connectivity between the ventral striatum and frontal cortex, suggesting that smoking affects the functioning of cortico-striatal circuits in patients with MCI and that such an effect may disrupt the functioning of the cortico-striatal circuits by exacerbating Aβ pathology. Smoking also affects visual attention through cortico-striatal circuits, further contributing to

memory loss in MCI patients [76]. The cortico-striatal circuit may be a potential therapeutic target for smoking [77]. It has also been suggested that chronic nicotine exposure may lead to disruption of functional connectivity between the Meynert's basal ganglia and the precuneus in patients with MCI, and it has been hypothesized that the precuneus may also be an important target for the cognitive effects of smoking in MCI [78]. Therefore, smoking cessation can reduce the damage to cognitive function caused by smoking through multiple pathways and improve cognitive status.

Lung health

There is growing evidence of an association between lung function decline, chronic obstructive pulmonary disease (COPD) and cognitive function [79, 80]. One of the most common causes of impaired lung function is COPD. COPD is a progressive disease, but treatable and preventable. The global prevalence of COPD among people aged 30–79 years is 10.3% (391 million people), with the majority of cases occurring in low- and middle-income countries and a slightly higher prevalence in high-income countries [81]. COPD is expected to be the third leading cause of death by 2030 [82]. A recent systematic review and meta-analysis found a strong correlation between COPD and increased incidence of MCI (OR = 2.11, 95%CI: 1.32-3.38) [83]. Other researchers have suggested that the prevalence of cognitive dysfunction in COPD patients is about 56.7%, four times higher than in non-COPD patients, including attention, learning, processing speed, visuospatial memory, language, and executive functioning [84]. COPD is characterized by partially irreversible chronic obstruction of pulmonary airflow, resulting in abnormally low blood oxygen levels, which may lead to cognitive dysfunction [85]. COPD-induced pulmonary dysfunction reduces cerebral oxygen supply, affects cerebral energy metabolism, and thus promotes cerebral ischemia-induced oxidative stress, leading to oxidative stress-mediated injury and accelerated vascular damage and degenerative disease. Long-term chronic hypoxia leads to impaired neurovascular coupling, apoptosis, transcription factor-mediated inflammation as well as Aβ accumulation and tau phosphorylation as causes of neurocognitive deficits. In addition, structural brain changes of hippocampal and cortical atrophy, ventricular enlargement, senile plaques, and neurogenic fiber tangle deposition can be observed under chronic hypoxia [86]. Olaparib [87] and dimethyl fumarate [88] have been found to inhibit the systemic inflammatory response to protect cognitive function in animal experimental models of acute lung injury, and thus inflammation may be able to be a target for the treatment of cognitive deficits induced by lung health problems. Long-term physical activity not only exercises respiratory muscle movement and improves ventilation, but also achieves systemic anti-inflammatory effects [89, 90].

Education

Educational attainment is an important factor influencing the occurrence of MCI, with healthy older adults with higher education having better cognitive performance than those with lower levels of education [91, 92]. Even very low levels of education (1–4 years) are associated with reduced odds of cognitive impairment compared with no formal education [92]. Cognitive reserve (CR) is the accumulation of neural resources, influenced by genetic and/or environmental factors, that mitigate cognitive function impairments caused by aging or disease [93]. Highly educated people are better able to withstand cognitive decline caused by pathological changes in the brain than those with low levels of education. That is, highly educated people have better CR. High levels of CR were found to be neuroprotective during EEG activity, possibly by enhancing rsEEGα source activation [94]. However, another study found that education was only associated with baseline levels of cognitive function. It is not associated with slow cognitive decline, late cognitive decline, and residual cognitive decline. This contradicts most CR theories [95]. The fact that education can prevent MCI can also be explained by the brain reserve (BR) theory. BR is a passive threshold model that emphasizes support for the structural integrity of cognitive performance and volumetric quantitative measures [7]. In other words, the brain responds to the pathology of cognitive impairment by enriching neurons and synapses [96]. Grey matter volume, cortical thickness, and surface area of the hippocampal and amygdala subregions of the brain increased after receiving higher education. Higher levels of education are associated with higher white matter integrity in several brain regions associated with AD [97]. Education also improves neural resources in childhood and young adulthood by increasing synaptic density, which then mitigates the effects of neurodegeneration caused by aging or age-related diseases [98]. This predicts that investing in education at an early stage of life may reduce the risk of cognitive impairment and dementia in later life, lowering the associated personal and societal costs and enabling them to withstand more cognitive decline [99]. In conclusion, in the majority of researchers' opinion, education not only reduces the incidence of MCI but also reduces the rate of conversion of MCI to dementia and protects against further deterioration of cognitive function in the early stages of cognitive impairment [92, 100, 101]. Thus, early education can benefit our cognitive function to some extent.

Depression

Depression is a common psychiatric symptom in people with MCI and dementia, with a prevalence of 32 percent in MCI and 37 percent in dementia [102]. Studies have shown that depression increases the risk of MCI in cognitively normal people [103, 104]. The Lancet Dementia Commission further reported that if late-life depression were eliminated, there would be a corresponding 4 percent reduction in the prevalence of dementia [105]. After performing diffusion tensor imaging (DTI) in patients with early MCI (EMCI) without depression, patients with mild depression in EMCI (EMCID), and patients with late MCI (LMCI) without depression, Feng *et al*. found that

the mean controllability of the DMN was significantly higher in the EMCI group and the LMCI group than in the EMCID group [106]. On the imaging side, patients with depression and MCI have reduced volumes in areas such as the insula, superior temporal gyrus, inferior frontal gyrus, amygdala, hippocampus, and thalamus [103]. Cognitive decline in old age was greater in people with depression than in those without depression, and memory loss, executive function, and information processing speed were found to decline over time in these individuals [107]. On cognitive tests, patients with MCI and depression scored lower than those with MCI [108]. In addition, MCI participants with depression showed greater deficits in immediate and delayed memory than MCI participants without depression [109].

Depression increases the risk of conversion of MCI to dementia, while causing severe impairment of functioning and quality of life and placing a significant burden on caregivers [102]. The meta-analysis found that the group of MCI participants with depressive symptoms was prone to progression to dementia compared to MCI participants without depressive symptoms (OR = 1.28) [110]. This may be related to the fact that depressed patients have more amyloid abnormalities and an increased risk of neuropsychiatric symptoms due to Aβ load in the brain [111, 112]. In addition, people with MCI are more likely to suffer from depression [113].

Therapeutically, exercise interventions such as aerobic exercise [114], dance [115], and Baduanjin [116] can improve the level of cognitive function in elderly patients with MCI. Adding cognitive behavioral therapy to routine care may slightly reduce depressive symptoms in people with dementia and MCI and may increase remission rates of depression [117]. There is little research on the psychological effects of game training in older adults with MCI, which is based on cortical stimulation designed to improve patients' cognitive function and reduce the risk of MCI and depression [118]. Xue *et al*. [119] found that 8 weeks of game training for people with MCI and depression significantly improved participants' cognitive and depression scores. However, the potential treatment with antidepressants remains uncertain at this time [120, 121].

Anxiety

Current research has determined that anxiety can increase the incidence of MCI [122, 123]. Smith *et al*. [122] investigated 32,715 individuals aged ≥ 50 years from six countries and found a positive correlation between anxiety and MCI in all of them (OR 1.35-14.33), which suggests a high incidence of MCI in older people with anxiety disorders. The reason for this may be that anxiety may reduce intellectually stimulating activities, increase sleep problems, and increase the risk of cognitive decline with the use of benzodiazepines. Anna *et al*. [123] found that Aβ deposition and anxiety synergistically increased the risk of MCI (joint effect HR 6.77). The co-occurrence of MCI and anxiety increases the likelihood that MCI will turn into dementia, especially AD [124, 125]. A systematic review and meta-analysis determined that the group of MCI patients with anxiety were more likely to progress to dementia (OR=1.18) [126]. At the same time, people with MCI can also promote anxiety symptoms, and the two influence each other [127, 128]. One longitudinal study showed a significant bidirectional longitudinal association between anxiety and MCI, with a total effect of 37.1% for anxiety and 27.1% for MCI [129]. Healthy lifestyle habits such as physical activity [130], healthy diet [131], psychological interventions [132], as well as arts-based interventions (dance, theater, music, *etc*.) [133] can reduce anxiety and decrease the incidence of MCI.

Conclusions

The cardiovascular and respiratory systems, endocrine metabolism, social life factors, and psychological factors contribute to the development of MCI in the elderly. It is not difficult to find out that by targeting the mechanism of action of these factors, their effects on cognitive function can be mitigated and the progression of MCI to dementia can be reduced by appropriate pharmacological or non-pharmacological treatments. The interventions we reviewed are not too difficult to implement, implying a high degree of practical practicability, low requirements for medical conditions, and low investment in medical resources. However, there may be more variable risk factors than those mentioned above, which need to be further identified and effective interventions.

Declarations

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