

Cerebral small vessel disease and Alzheimer's disease

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Abstract: Cerebral small vessel disease (CSVD) is a group of pathological processes with multifarious etiology and pathogenesis that are involved into the small arteries, arterioles, venules, and capillaries of the brain. CSVD mainly contains lacunar infarct or lacunar stroke, leukoaraiosis, Binswanger's disease, and cerebral microbleeds. CSVD is an important cerebral microvascular pathogenesis as it is the cause of 20% of strokes worldwide and the most common cause of cognitive impairment and dementia, including vascular dementia and Alzheimer's disease (AD). It has been well identified that CSVD contributes to the occurrence of AD. It seems that the treatment and prevention for cerebrovascular diseases with statins have such a role in the same function for AD. So far, there is no strong evidence-based medicine to support the idea, although increasing basic studies supported the fact that the treatment and prevention for cerebrovascular diseases will benefit AD. Furthermore, there is still lack of evidence in clinical application involved in specific drugs to benefit both AD and CSVD.

Keywords: dementia, cerebrovascular diseases, lacunar infarct, leukoaraiosis, cerebral microbleeds

Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disease of the brain. AD is clinically characterized by cognitive impairment at first and dementia eventually, which gradually worsen over a number of years.¹ Increasing research indicates that AD results from the destruction and death of nerve cells triggered by amyloid plaques and neurofibrillary tangles,¹⁻³ both of which are thought to contribute to the neurodegenerative death of the neurons in the brain and the subsequent symptoms of AD. The main risk factor for AD is advanced age, while the incidence of AD increases with the progress of aging.⁴ Substantial clinical research implicates the involvement of vascular risk factors in AD, such as hypertension,⁵ coronary artery disease,⁶ diabetes,^{7,8} and hyperlipidemia.^{9,10} These vascular factors increase the risk of AD occurrence.^{5,11}

Cerebral small vessel disease (CSVD) is considered as an important pathological process of subcortical structures such as lacunar infarcts, white matter lesions, and microbleeds.¹² CSVD is responsible for the pathogenesis of ischemic strokes, cerebral hemorrhages, and encephalopathy, which are associated with advanced age, and deteriorated by hypertension and diabetes mellitus.¹³ CSVD mainly contains lacunar infarct or lacunar stroke, leukoaraiosis, Binswanger's disease, and cerebral microbleeds.¹¹ With the development of imaging examination and its clinical usage, it has been well identified that cerebral vascular diseases, especially CSVD, contribute to the occurrence of AD (Figure 1).^{9,14}

This work focused on the relationship between AD and CSVD. An overview was provided for the association between AD and lacunar infarct, leukoaraiosis,

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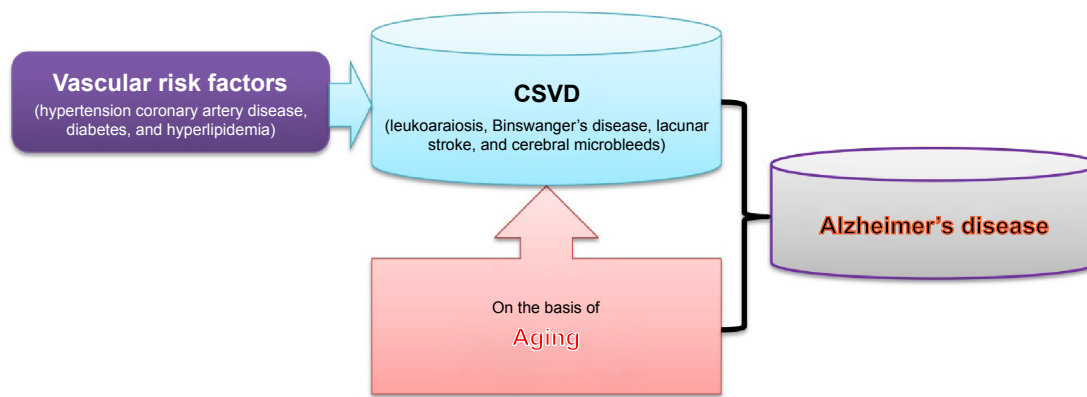


Figure 1 CSVD and Alzheimer's disease.

Notes: Both CSVD and aging contribute to the occurrence of Alzheimer's disease. On the basis of aging, CSVD can accelerate the development of Alzheimer's disease.

Abbreviation: CSVD, cerebral small vessel disease.

Binswanger's disease, and cerebral microbleeds, respectively. It was reviewed that CSVD plays an important role in the development of cognitive impairment and dementia. It was also discussed that it is possibly an effective measure to prevent cerebrovascular disorders as an attractive target for AD.

Cerebral small vessel disease

CSVD, microangiopathy of the cerebral white and gray matter, indicates a group of pathological process with multifarious etiology and pathogenesis that involve the small vessels, including arterioles, venules, and capillaries of the brain.^{15,16} CSVD is responsible for 20%–30% cases of ischemic strokes, as well as for a considerable proportion of cerebral hemorrhages and encephalopathy.¹⁷ CSVD is regarded as an important pathological process of subcortical structures such as lacunar infarcts, white matter lesions, and microbleeds.¹² Despite atherosclerotic plaque biology has not been considered into being suitable to small cerebral vessels, a lesion by fibrinoid necrosis causing lacunar infarcts and primary intracerebral bleeds has been identified as an important pathology in the CSVD.¹⁸ CSVD is a common aging phenomenon that is exacerbated by hypertension and diabetes mellitus,¹³ including leukoaraiosis, Binswanger's disease, lacunar stroke, and cerebral microbleeds.¹⁹ Leukoaraiosis refers to white matter changes (WMC) in the brain, often occurring after 65 years of age. Leukoaraiosis pathogenesis includes breakdown of axons, an unnatural paleness of myelin, gliosis, loss of ependymal cells, and enlarged perivascular spaces. Binswanger's disease is also known as subcortical leukoencephalopathy caused by arteriosclerosis and thromboembolism influencing the blood vessels on the blood supply of white matter. Lacunar stroke or lacunar infarct is a little

stroke that is caused from occlusion of the penetrating small arteries that supply blood into the brain's deep distributions. Cerebral microbleeds result from impaired small vessel integrity, mainly being attributed to either hypertensive vasculopathy or cerebral amyloid angiopathy. Microbleeds are commonly combined with Alzheimer's dementia and stroke.²⁰ Research findings demonstrate that vascular factors play a pathogenic role in the early stages of AD because these cerebrovascular alterations impair the delicate balance between the brain's energy requirements and cerebral blood supply,^{21–23} resulting in the upregulation of beta-amyloid (A β) production and impaired A β drainage.^{24,25}

Age-related and hypertension-related small vessel diseases are the most common forms of CSVD (Figure 1).¹⁵ CSVD is often recognized as the most common etiology of vascular cognitive impairment and dementia, acting as the same role of large vessel disease and other forms of cerebrovascular disease (CVD) in vascular cognitive impairment and dementia. CSVD gradually develops into decline of cognition, vascular dementia (VaD), impairment of gait and balance, mood depression, and urinary incontinence and often results in great social and economic burdens.¹⁷ Increasing evidences suggest that there are decreased vascular density and cerebral microvascular pathology in the process of aging and neurodegeneration and cerebrovascular dysfunction, and CSVD precedes or accompanies cognitive dysfunction and neurodegeneration.²⁶ Several investigations indicate that cerebrovascular atherosclerosis, especially atherosclerosis of the Willis circle, is more severe in AD and correlates with the severity of AD pathology,^{27,28} implicating that atherosclerosis-induced cerebrovascular hypoperfusion correlates with AD pathology and the clinical manifestations of AD. CSVD on the basis of atherosclerosis will accelerate the development of

AD since cerebral hypoperfusion and reduced glucose uptake have been found very early in AD,^{28,29} in consideration that the regulation of cerebral blood flow plays an important role in the coordinated interaction of neurons, glia, and vascular cells. Many studies show that CSVD increases the risk of AD occurrence, while signs of AD pathology can often coexist with both VaD and CSVD.³⁰

Lacunar infarct and AD

Lacunar infarct or lacunar stroke is a small (0.2–15 mm in diameter) noncortical infarct, which is generally believed to be the cause of occlusion of the penetrating arteries. Lacunar infarct onsets when one of the penetrating arteries that provide blood to the brain's deep distributions is obstructed. It is assessed that lacunar infarcts make up 25% of all ischemic strokes, with an annual incidence of approximately 15 per 100,000 people.^{31,32} The clinical manifestations of lacunar stroke vary, such as the disorders of sensation, movement, sight, speech, balance, and coordination, because different functions are determined by different areas of the brain involved in lacunar stroke.⁸ Diagnosis of lacunar stroke is mainly according to the setting of clinical representations and neuroimaging results.³³ In many cases, a lacunar infarct manifests a silent stroke, which does not have any outside symptoms. Patients are not aware of it at all when they suffer a lacunar stroke. Lacunar infarct induces a significant impairment to the cells in small parts of the brain and leads to death of corresponding parts of the brain tissue. In spite of no symptoms, lacunar stroke still gradually destroys the brain function and acts as an existing risk of major stroke attacks therein.^{34,35} The onset of multiple lacunar strokes occur and get accumulated with the progress of aging and role of risk factors. This ultimately results in a state of cognitive impairment and development of dementia.^{36–38}

It is well accepted that lacunar infarct is an age-related cerebral ischemia disorder,^{39,40} and the different location of lacunar infarct within subcortical gray matter is a determinant of different cognitive impairment.^{40,41} The greatest known risk factor of AD is the advancing age, and the majority of patients with AD are >60 years old.⁴² Accordingly, aging is a common contributor to the occurrence of lacunar infarct and the development of AD. Furthermore, AD and lacunar infarct have a considerable degree of overlap in risk factors,^{43–45} such as hypertension, diabetes, hyperlipidemia, adiposity, smoking, and drinking, as well as unhealthy lifestyle.

A number of clinical and basic findings indicate that CVD is closely associated with both the presence and the severity of the clinical symptoms of AD.⁴⁶ As the progress of

cerebrovascular lesions was inextricably linked with vascular risk factors and age, the involvement of vascular risk factors will fully aid in clinical presentation of elderly patients with AD.^{42,47} It has been found that AD is highly prevalent in the elderly and often coexists with multimicroinfarcts; the number of microinfarcts is roughly in proportion to the degree of cognitive impairment, and the presence of microinfarcts was intimately linked with AD rather than cerebral amyloid angiopathy.⁴⁸ Lacunar infarct, one of the cerebrovascular disorders, is also known to play important roles in the pathogenesis underlying AD, especially in the elderly patients with AD.⁴² Additionally, several studies implicate the associations between lacunar infarct and Alzheimer's pathology, including A β and tau pathology.^{49–51} A cross-sectional study showed that the presence of lacunar infarct was associated with higher A β 42 in VaD and lower tau in AD in cerebrospinal fluid (CSF).⁴⁹ Another cross-sectional study demonstrated that the presence of lacunar infarctions could be tightly coupled to increased plasma A β 40 and plasma A β 40 concentration in the patients with AD.⁵¹

However, the relationship between AD and lacunar infarct remains largely unclear. Although it appears that there are several shares in risk factors and related pathogenesis in AD and lacunar infarct, how these neglected silent infarcts develop multiple domain cognitive deficits and AD? It seems that cerebral atherosclerosis plays a strong role in the occurrence of cystic infarcts and microinfarcts but not Alzheimer's pathogenesis.⁹

Cerebral microbleeds and AD

Currently, cerebral microbleeds have been well identified as an important imaging marker of CSVD. Cerebral microbleeds are small hypointense imaging appearances according to T2* gradient-recall echo and susceptibility-weighted magnetic resonance imaging (MRI) sequences.^{20,52,53} With the development of MRI techniques, cerebral microbleeds have been found in the patients of stroke and cognitive impairment, as well as in healthy people and in people with other disorders.^{54,55} A confirmed diagnosis of cerebral microbleeds indicates the acceptance of the underlying small vessel disease, the safety of antithrombotic use, the risk of symptomatic intracerebral hemorrhage, and the cause of cognitive impairment and dementia.^{56,57} Substantial literature to date has indicated that cerebral microbleeds contribute to the clinical manifestation and are linked with the occurrence of biochemical hallmarks of AD, suggesting the involvement of cerebral microbleeds in the pathogenesis of AD.⁵⁸

Multiple cerebral microbleeds have been shown to occur in AD and are linked with cerebral network breakdowns in the patients with AD,⁵⁹ affecting approximately one-third of subjects who are present with the clinical manifestations of AD dementia.⁶⁰ Furthermore, cerebral microbleeds in AD are more closely linked with cerebral amyloid angiopathy than CVD.⁶¹ Atypical AD subjects seem to be at a particular risk for developing large numbers of microbleeds and for developing microbleeds in the frontal lobe under T2*-weighted MRI.^{60,62} In a review literature, it has been proved that the neuropathology of AD results in the breakdown of the silent microbleeds, caused by pulse-induced damage to the cerebral vessels underlying the age-related stiffening of the aorta and great arteries, which increases the intensity of the pressure pulse.⁶³ It has been reported that the incidence of multiple lobar microbleeds that have occurred in the preclinical AD and microbleeds in AD are particularly linked with additional A β burden.⁶⁴ Cerebral microbleeds were also related to the alterations of A β metabolism in AD.⁶⁵ Concomitantly, older age, higher A β burden, and CVD may all facilitate the occurrence of lobar microbleeds.⁶⁶ A cross-sectional study, investigating the prevalence, locations, and risk factors for cerebral microbleeds in neurodegenerative disorders identified that cerebral microbleeds are linked with vascular burden and AD diagnosis.⁶⁷ It has been reported that there was a high prevalence of cerebral microbleeds in patients with early AD according to 7 T MRI tests.⁶⁸

A growing body of research studies has proved that sortilin-related receptor 1 gene (*SORL1*) is genetically linked to AD pathological changes.^{69–73} The *SORL1* was downregulated in the AD brain and positively contributed to A β accumulation. Emerging data suggest that *SORL1* acts as a central regulating role of the trafficking and processing of amyloid precursor protein and interacts with ApoE and tau protein.⁷¹ A recent study found that *SORL1* single nucleotide polymorphism (SNP) rs2070045-G allele was linked to CSF-tau and hippocampal atrophy, two endophenotype markers of AD.⁷⁴ In addition, haplotype-based analyses discovered an association between haplotype rs11218340-A/rs3824966-G/rs3824968-A and higher CSF-tau and CSF-tau phosphorylated at threonine 181, implicating that *SORL1* may be the tau pathology in AD.⁷⁴ The association of *SORL1* with cerebral microbleeds indicates that the amyloid cascade sweeps into microbleeds into the etiology of AD.⁷⁵

Cerebral microbleeds have been highlighted as a potential key risk factor in the pathogenesis of AD, linking the main pathological contributors of A β accumulation with cerebrovascular damage.⁷⁶ However, it seems that cerebral microbleeds are likely to unfavorably affect cognitive functioning.⁷⁷ There is a

debate concerning the relationship between microangiopathy and the clinical course of AD or the conversion of mild cognitive impairment to AD.^{78,79} Cerebral microbleeds did not affect disease course in terms of progression to AD.^{77,80} Hence, the role of cerebral microbleeds in AD remains to be identified.

Leukoaraiosis and AD

Leukoaraiosis describes a diffuse, aberrant appearance of white matter on imaging, often presented in the normal elderly and in the patients with vascular risk factors or those suffering with cognitive impairment.^{81,82} The most common imaging to find leukoaraiosis is hyperintensity on T2-weighted MR in cerebral white matter. Age, hypertension, diabetes mellitus, and cardiovascular diseases are the major risk factors for leukoaraiosis.⁸³ Leukoaraiosis was characterized by reduced cerebral blood flow and cerebrovascular reactivity and a leakage in the blood–brain barrier.⁸⁴ It is gradually becoming clearer that leukoaraiosis is associated with CVD,⁸⁵ AD, and other diseases.⁸³

It has been reported that in compelling neuroimaging data, similar white matter abnormalities of leukoaraiosis appear in the patients with AD and in elderly healthy people.^{85–88} Coffman et al confirmed that the presence of leukoaraiosis might be of important significance in understanding changes in the white matter among populations at increased risk for AD.⁸⁹ A longitudinal study indicated that leukoaraiosis is associated with a greater degree of cognitive impairment in patients with AD.⁹⁰ A cross-sectional, descriptive, multicenter study involving 109 patients with AD and 59 with mild cognitive impairment identified that AD had a higher prevalence of leukoaraiosis and apathy.⁹¹ A recent pilot study suggests that jugular venous reflux is associated with cerebral WMC in individuals with AD, implying that cerebral venous outflow impairment might play a role in the dynamics of WMC in patients with AD, particularly in the periventricular regions.⁹² It is well accepted that white matter hyperintensities (WMH) in imaging are linked with aging and AD.⁹³ Makedonov et al reported that WMH perfusion was lower than normal-appearing white matter perfusion in both age-matched elderly controls and AD groups. WMH tended to have a lower perfusion in AD compared with age-matched elderly.⁹⁴ This imaging study suggests a common WMH etiology in AD and healthy aging. This finding is also suggestive of susceptible WMH hypoperfusion in AD compared with healthy aging, implicating that AD pathology decreases the perfusion at anatomic locations susceptible to the formation of WMH through either the neurodegenerative process or AD-related vasculopathy or both.⁹⁴ The leukoaraiosis and disability prospective multinational European study evaluated

the influence of WMC on the transition of independent elderly subjects, disclosing that self-perceived memory complaints predicted AD.⁹⁵

Binswanger's disease and AD

In 1894, Dr Otto Binswanger, professor of psychiatry in Switzerland, first described a new clinical and neuropathological phenomenon that he termed "encephalitis subcorticalis chronica progressive" and Binswanger's disease is named after him.^{96,97} Other names for Binswanger's disease are also known as subcortical leukoencephalopathy, subcortical arteriosclerotic encephalopathy, ischemic periventricular leukoencephalopathy, or subcortical dementia.^{98–101} Binswanger's disease is featured by damage to small penetrating blood vessels in the subcortical regions of the brain. Binswanger's disease is often associated with advanced age, chronic hypertension, stroke, disease of the large blood vessels in the neck, alcohol and smoking, and cardiovascular diseases. Signs and symptoms of Binswanger's disease usually start after the age of 60 years. The onset of this disease is often between 54 years and 66 years of age, and the first symptoms are usually mental disorders or little stroke. A slow progressive dementia is identified as an important clinical feature of the disease. Binswanger's disease sometimes presents a rare form of dementia and often referred to as subcortical dementia.

Like other CSVD, Binswanger's disease shares some backgrounds with AD,^{102,103} including aging and vascular risk factors, such as hypertension, diabetes, cardiovascular diseases, metabolic syndrome, obesity, hyperlipidemia, smoking, and drinking. Binswanger's disease seems to be a risk factor for AD.¹⁰⁴ However, there are no biomolecular reports concerning the relationship between Binswanger's disease and AD until now.

Cerebral atrophy: a common morphological feature in both AD and CSVD

Cerebral atrophy, a common feature of brain disorders, is a condition in which brain cells are lost, or the connections between them are damaged, resulting in the decrease of normal brain volume.^{105,106} A number of conditions can lead to brain atrophy, including epilepsy,¹⁰⁷ traumatic brain injuries,^{108,109} strokes,¹¹⁰ AD,¹⁰⁵ multiple sclerosis,¹¹¹ cerebral palsy,¹¹² and Huntington's disease.¹¹³ Like other atrophies, cerebral atrophy involves loss of tissue. Loss of brain tissue can lead to sinister consequences, including a variety of neurological and cognitive problems. Focal cerebral atrophy, the corresponding damage concerned with a particular area of the brain, manifests the corresponding function impairment

of concerned area of brain. Generalized cerebral atrophy will be linked with a range of clinical problems because of the involvement of the whole brain.

Cerebral atrophy can usually be identified in medical imaging such as Computed Tomography (CT) and/or MRI, which can demonstrate structural changes in the brain. Increasing imaging results have evidenced that CSVD has a close association with cerebral atrophy.^{114,115} A prospective follow-up research conducted by Nitkunan et al showed that brain volume is decreased in the patients with CSVD with respect to normal aging subjects, and this decrease was correlated with cognition decline during 1-year prospective follow-up.¹¹⁶ The leukoaraiosis and disability study further proved that brain atrophy facilitates cognitive decline, and brain atrophy is independently related to longitudinal cognitive decline in CSVD.¹¹⁷ According to MRI measurement, the severity of brain atrophy was correlated with the number of lacunar infarcts and the size of subcortical and periventricular white matter lesions, while shorter telomere length is associated with brain atrophy and WMH.^{114,118–120}

A large number of imaging studies have confirmed that cerebral atrophy is the most significant morphological characteristic of AD,^{121–125} which has the widening grooves and fissures of the cerebral cortex, indicating progressively severe brain atrophy and loss of brain mass. It has been found that the acceleration of hippocampal atrophy in mild cognitive impairment subjects enhances the progress to clinical AD within 3 years of baseline,¹⁰⁵ and regional measures of hippocampal atrophy are the strongest predictors of progression to AD.¹²⁶

On the basis of the above information, it can be suggested that cerebral atrophy is a common morphologic feature in both AD and CSVD. On the background of cerebral atrophy, what is the relationship between AD and CSVD? The problem is still pending. Thus, it is important to reveal the exact role of CSVD in AD underlying cerebral atrophy.

Dementia: a common clinical result of both AD and CSVD

CSVD is common in the elderly and enhances the process of cognitive impairment and dementia.^{127,128} Clinical studies implicate the link between cognitive disorders with white matter lesions (a marker of small vessel disease in the brain) caused by aging, hypertension, systemic circulatory disturbances, or other processes (cerebral amyloid angiopathy, cerebral autosomal dominant arteriopathy with subcortical infarcts, and leukoencephalopathy).^{129–131} Genetic predispositions and environmental exposures may promote the development of CSVD and interact with normal aging to impact cognitive function.^{132,133} It has been demonstrated that

the increasing severity of white matter lesions was associated with a steeper decline in cognitive function, accompanying with generalized brain atrophy and the presence of brain infarcts.^{127,134} White matter diffuse lesion could directly influence the recall processes controlled by the frontal lobe.¹³⁵ The cognitive impairment is specifically focused on information processing speed and executive function in older people, implicating that CSVD may lead to cognitive impairment by blemishing information processing speed and executive function.¹²⁷ The epidemiology of dementia in Singapore study showed that cerebral microbleeds were, independent of other concomitant markers of CSVD, helpful in poorer cognitive function.¹³⁶

Available evidence demonstrates that cognitive impairment and dementia are the clinical manifestation for both AD and CSVD.^{137,138} Increasing evidence of a complex relationship between AD and cognitive impairment and VaD has been reported while CVD and stroke are related to high risk of both cognitive impairment and AD.^{139,140} The manifestation of CVD in imaging is extremely similar to AD in the elderly, whereas imaging markers of subcortical vascular diseases (leukoaraiosis, lacunar infarcts, microbleeds, ventricular enlargement, cortical, and hippocampal atrophy).^{141–143} Leukoaraiosis is linked with functional impairment in older patients with AD but not VaD, while leukoaraiosis might play a synergistic effect with cognitive and behavioral disturbances to the onset and progression of cognitive disability of AD.¹⁴⁴ The Sunnybrook Dementia Study demonstrated that Visible Virchow–Robin spaces in the white matter, markers for small vessel diseases, may be more related to AD-related vascular pathology since AD had significantly greater volumes of WMH, lacunes, and Virchow–Robin spaces in the white matter,¹⁴⁵ and WMH may be related to regional neurodegeneration.^{146,147} It has been described and illustrated that WMH volume, particularly in parietal regions, is elevated among individuals with risk for AD, predicts future diagnosis of AD, predicts the rate of progression of cognitive symptoms among individuals with AD, and increases over time among individuals destined to develop AD.¹⁴⁸ The vascular pathology of CSVD in AD may interact with neurodegenerative process and deteriorate cognitive decline. Thus, the progress of disorders from cognitive impairment to dementia can be attributed to cerebrovascular causes.^{149–151}

Conclusion and perspective

CSVD has been readily identified on CT and/or MRI scans. CSVD, a leading cause of cognitive impairment, ultimately

leads to dementia and contributes to neurodegenerative progress, including Alzheimer's onset. Up to now, a number of studies have confirmed that CSVD can co-occur with AD, and signs of AD pathology have been found in CSVD, indicating that the pathology of CSVD and AD are interconnected. It seems that CSVD could stimulate amyloid pathology, while AD-associated cerebral amyloid pathology may enhance auxiliary vascular damage. The association between CSVD and incident dementia and Alzheimer's onset has never been well clarified. CSVD has been highlighted as a potential key risk factor for AD, linking the main pathological contributors of A β accumulation with cerebrovascular damage. However, there are no biomolecular reports concerning the relationship Binswanger's disease and AD until now. The role of cerebral microbleeds in AD remains to be identified. Furthermore, it remains unclear if and how associations between CSVD and Alzheimer's pathology result in cognitive impairment and dementia.

According to the above information, it can be suggested that CSVD may play a crucial role in AD. Based on the theory of CVD, the treatment and prevention for CVDs will benefit AD. It seems that statins have such a role in the treatment and prevention of Alzheimer's neurodegeneration since they can benefit CVDs. In spite of this, there is no strong evidence-based medicine to support the idea. So far, increasing basic molecular biology findings report that the treatment and prevention for CVDs will benefit AD. However, there is still lack of evidence in clinical application involved in specific drugs to benefit both AD and CSVD.

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Disclosure

The authors report no conflicts of interest in this work.

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