

Special Section: Vascular Contributions to Alzheimer's Disease

## Pathophysiologic relationship between Alzheimer's disease, cerebrovascular disease, and cardiovascular risk: A review and synthesis

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### Abstract

As the population ages due to demographic trends and gains in life expectancy, the incidence and prevalence of dementia increases, and the need to understand the etiology and pathogenesis of dementia becomes ever more urgent. Alzheimer's disease (AD), the most common form of dementia, is a complex disease, the mechanisms of which are poorly understood. The more we learn about AD, the more questions are raised about our current conceptual models of disease. In the absence of a cure or the means by which to slow disease progress, it may be prudent to apply our current knowledge of the intersection between AD, cardiovascular disease, and cerebrovascular disease to foster efforts to delay or slow the onset of AD. This review discusses our current understanding of the epidemiology, genetics, and pathophysiology of AD, the intersection between AD and vascular causes of dementia, and proposes future directions for research and prevention.

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### Keywords:

Alzheimer's disease; Cardiovascular disease; Cerebrovascular disease; Vascular contributions to cognitive impairment and dementia; VCID; Dementia; Risk factors

## 1. Introduction

One of the greatest advancements of health in the 20th century was an increase in average life expectancy by 30 years [1]. Today, people aged 85 years and older are the fastest growing segment of the population, and this has led to a new set of problems for modern health care as the elderly are the most susceptible to disease and disability. One in three adults over 85 years old suffer from Alzheimer's disease (AD) or other forms of dementia [2], the prevalence of which

is estimated to increase dramatically over the next 40 years unless preventive measures are developed [3]. AD is currently the sixth leading cause of death in the United States and the cost of the disease is high. Approximately \$236 billion will be spent on AD during 2016 calendar year overall, including patient care and caregivers' lost wages [4].

Despite the global increase of both incidence and prevalence of AD, it is the only leading cause of death that we are currently unable to prevent or cure [5]. The remarkable heterogeneity of risk factors, etiologies, and neuropathologic processes associated with AD makes it especially challenging for development of new treatments to slow disease progression [4,6]. Fortunately, a number of experimental therapies are currently in development. These are aimed

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at mechanisms including neurotransmission regulators, tau-based therapies, amyloid- $\beta$ -based strategies, intracellular signaling cascade modulators, oxidative stress reducers, mitochondrial target therapy, cellular calcium homeostasis modulators, and anti-inflammatory therapies [7–11]. It is possible that the heterogeneity of behavioral presentations, cognitive impairments, and functional statuses observed in AD is due to its potentially varied etiology [12]. Adding to this complexity, older adults with AD typically present with comorbid medical conditions that further complicate accurate disease monitoring [13]. The current dominant AD models are insufficient to account for the complexity of biologic processes, polygenic, and epigenetic factors at work [14]. As a result, key opinion leaders have suggested that the field would benefit from the development of new conceptual models of AD [14]. The purpose of this review is to explore the complex relationship between AD, cardiovascular disease (CVD), and cerebrovascular disease (CBVD). Recent reports that question the strength of the association between these disease entities will be reviewed and recommendations will be made for additional research questions to more precisely characterize causal links between AD, CVD, and CBVD.

## 2. Shared genetic contributions to AD and cardiovascular disease

The genetic contribution to AD risk is complex. Three familial autosomal-dominant genes associated with early-onset disease have been discovered (*PSEN1*, *PSEN2* and *APP*) [15–20], and these genes may also be associated with some later onset cases, although together they likely account for less than 10% of all AD cases [21]. The most predominant type of AD is late-onset Alzheimer's disease (LOAD, referred to herein as AD), which affects adults in their sixth to eighth decade of life. Although many genetic risk factors for AD have been studied, a definitive genotype that causes (late onset) AD has not yet been identified [22]. Thus far, few genetic markers have been linked to both risk of AD and CVD or CBVD risk. The  $\epsilon 4$  allele of the apolipoprotein E (*APOE*) gene is a risk factor for both AD and CVD. Over the past two decades, numerous studies have shown that individuals who carry at least one copy of the  $\epsilon 4$  allele have an increased risk for AD compared to those without the  $\epsilon 4$  allele [23–26] and  $\epsilon 4$  carriers with AD have lower blood levels of apoE [27]. Low plasma levels of apoE protein have been found to increase the risk of AD, independently of *APOE* genotype [28].

Two polymorphisms (rs1801133, rs1801131) in the methylenetetrahydrofolate reductase (*MTHFR*) gene correlate with elevated levels of plasma homocysteine and appear to be associated with AD and vascular contributions to cognitive impairment and dementia (VCID) [29,30]. High plasma homocysteine levels have been identified as a risk factor for VCID in a Northern Irish population [29]. Mutations in the

*MTHFR* gene were found to increase the risk of AD by 2.5 fold and VCID by 3.7 fold in an Asian population [30].

Beyond *APOE* and *MTHFR*, few other genes have been identified to significantly increase the risk of both AD and CVD. Genetic associations with smaller effects have been found, but a detailed discussion of these is beyond the scope of this review. Recently, new approaches to evaluating genetic pleiotropy in complex diseases have been developed [31]. These methods are now being applied to AD [32], and one recent study demonstrated genetic overlap between AD and CVD by conditioning on CVD phenotypes including C-reactive protein and plasma lipids [33].

## 3. Shared risk factors for AD and CVD

AD and CVD share important cardiometabolic and lifestyle risk factors that occur in middle-aged to elderly populations. Both AD and CVD are associated with increasing age, and both are among the leading causes of death. The primary causes of CVD are coronary heart disease (CHD), hypertension, stroke, and heart failure. These diseases are frequently interconnected and share an underlying pathology of atherosclerosis. All known risk factors for atherosclerosis have been the focus of studies to identify modifiable risk factors for AD. Researchers from the Framingham Heart Study [34,35] developed a composite measure of general cardiovascular risk, the Framingham Cardiovascular Risk Profile (FCRP), derived by evaluating one's age, gender, diabetes, smoking, treated and untreated systolic blood pressure (SBP), total cholesterol, and high-density lipoprotein (HDL) cholesterol [36]. In addition to increased risk of CVD, an elevated FCRP score on has been related to markers of abnormal brain aging, such as smaller brain volume and increased white-matter hyperintensities in brain imaging examinations [37]. High FCRP scores are associated with worsening of cognitive abilities, both in cognitively intact subjects and in mild cognitive impairment (MCI) patients [38] and are a reliable predictor of progression from MCI to AD [39]. Other scores developed from Framingham, the Framingham Stroke Risk Profile, and the Framingham Coronary Heart Disease Risk Score, have been similarly associated with cognitive change over time, incident cognitive impairment, and dementia [35,39–43]. These risk models are similar to one developed specifically to assess dementia risk, the Cardiovascular Risk Factors Aging and Dementia (CAIDE) risk score [44–46]. Common elements across scores are blood pressure, cholesterol, and diabetes. In the following, we review elements of these risk scores as they relate to both CVD and AD.

### 3.1. Hypertension/hypotension

Chronic hypertension, a common risk factor for CVD, causes a thickening of vessel walls, reduced vessel elasticity, and the narrowing of the lumen, especially in small vessels [47,48]. These sequelae result in reduced cerebral blood

flow, a prominent step in the pathophysiology of both AD and CVD. Chronic hypertension also compromises blood–brain barrier (BBB) integrity, leading to both cerebral edema and the introduction of systemic elements into the brain parenchyma [49]. Hypertension recorded 15 years prior has been associated with smaller brain volumes in areas typically affected by AD such as the hippocampus [50]. Our group has observed that an increased resting-state cardiac rate pressure product as a surrogate of myocardial oxygen use has a small to moderate correlation with neocortical amyloidosis in midlife adults with preclinical AD [51].

Epidemiological studies have shown that hypertension is a risk factor for dementia [52–56], but the association is complex [57]. Studies have found that the risk of dementia and AD may vary in strength and direction according to the age of onset [54,55,58,59]. Further complicating these findings, several studies have demonstrated that antihypertensive drugs can reduce the risk of AD [60–64]. Diuretic, angiotensin receptor-1 blocker, or angiotensin-converting enzyme inhibitor use in the Ginkgo Evaluation of Memory Study, was associated with a reduced risk for MCI and AD [61]. Among 2197 participants from the Honolulu-Asia Aging Study who were dementia free at baseline, beta-blocker users experienced a 31% lower risk of developing new cognitive impairments of any cause, compared to those with other antihypertensive or no antihypertensive use [62]. Taken together, these findings suggest that methods to effectively lower BP in midlife, for example, lifestyle changes or medications, should help to retain or improve cognitive function by reducing the risk of AD and/or VCID.

Conversely, there is evidence demonstrating that hypotension in late life is closely associated with a higher risk of AD. The Bronx Aging Study [65] followed a healthy cohort of older adults aged  $\geq 75$  years over a median follow-up of 6.7 years. Participants with diastolic blood pressure (DBP)  $< 70$  mm Hg were twice as likely to develop AD as those with DBP  $> 90$  mm Hg, and this risk was even higher for subjects with persistently low DBP. Interestingly, there was no such relationship for SBP, and the association between diastolic hypotension and AD was specific; no such association existed for VCID. A pooled analyses of data from the Rotterdam Study ( $N = 6668$ ) and the Gothenburg H-70 Study ( $N = 317$ ) found baseline diastolic hypotension was associated with higher risk of AD and/or VCID over an average of 2.1 years of follow-up, and that the risk was more pronounced in antihypertensive medication users [56]. Another population-based study ( $N = 599$ , mean age 83.5 years) similarly revealed that lower DBP and SBP were associated with a higher incidence of AD [66]. Extremely low DBP ( $\leq 65$  mm Hg) produced an adjusted relative risk of 1.7 (95% CI 1.1–2.4) for AD in a prospective study of 1270 individuals aged 75–101 years [67]. Finally, a meta-analysis of 20 population-based studies revealed that a decline in DBP in later life may contribute to

diminished cerebral perfusion, and the subsequent ischemic state may lead to increased cerebral A $\beta$  accumulation [68].

### 3.2. High cholesterol

Cholesterol metabolism plays an important role in the central nervous system (CNS), as the brain is a cholesterol rich organ, comprising 25% of the body's cholesterol [69]. Studies have indicated that lipoprotein lipase, an enzyme that hydrolyzes triglycerides, may be involved in the biological basis of both AD and CVD (e.g., essential hypertension, CHD) [70–72] through its interaction with brain lipoproteins and modulation of cholesterol homeostasis in neuronal cells [73]. Apolipoprotein E is crucial for the catabolism of triglyceride-rich lipoprotein components and for cholesterol transport [74]. Cholesterol supplied as a lipoprotein complex, such as HDL, is critical for the maturation of synapses and the maintenance of synaptic plasticity [75,76]. Cholesterol levels influence the clearance of A $\beta$  and the formation of neurofibrillary tangles through action at the lipid rafts located in neuronal membranes.

Outside the brain, atherosclerosis is a frequent consequence of high cholesterol and is an important risk factor for ischemic cerebrovascular disease [77]. The contribution of atherosclerosis, a frequent consequence of high cholesterol, is an important risk factor for ischemic cerebrovascular disease [77]. *APOE*  $\epsilon 4$  carrier status is both a risk marker for AD and CVD. In the Rotterdam Study, *APOE*  $\epsilon 4$  carriers with atherosclerosis frequently had comorbid AD and more frequent comorbid VCID [78,79].

Elevated total serum cholesterol levels have been associated with MCI and AD risk in some studies [55,80]. Others have found that the association between cholesterol and AD is complex [81,82]. Similar to hypertension, the risk of dementia associated with high cholesterol may be influenced by the timing and duration of the condition, as well as its treatment. One reason for this complexity is that plasma cholesterol levels do not reflect cholesterol concentrations inside the BBB. The association between high cholesterol and increased risk of AD has resulted in a number of studies testing the hypothesis that statins, which play a role in cholesterol reduction, might prevent the onset or progression of AD. Early epidemiological studies in this area predicted that statins could reduce the incidence of AD by as much as 70% [83–85]. However, whether statins and resultant reduction of cholesterol cause a significant reduction in AD pathology is still unclear. More recent results of large-scale randomized controlled trials suggest no significant clinical benefit of statins in participants at risk for AD [86,87].

### 3.3. Diabetes mellitus

Diabetes mellitus (DM) is a complex metabolic disorder that is closely associated with changes in cognition as well as other risk factors for accelerated cognitive decline and

dementia, such as hypertension and atherosclerosis [88]. DM occurs when there is a prolonged period of high blood glucose levels or hyperglycemia. There are two types of DM. Type 1 is congenital and caused by insulin deficiency, and type 2 is acquired and caused by insulin resistance.

Although there are points of intersection between the molecular mechanisms underlying diabetes and AD, the exact mechanism of how insulin inefficiency increases the risk of AD remains unknown. The literature is currently separated into two different schools of thought [89]. One follows from Rotterdam study findings, suggesting that the excess of insulin or glucose from type-2 diabetes mellitus (T2DM) leads to AD. This is based on studies demonstrating that AD patients have significantly higher levels of insulin and glucose than healthy controls [90–92]. A second school of thought suggests that insulin deficiency, either due to the relative deficiency that results from insulin resistance in early stages of T2DM, or absolute deficiency that occurs when beta cell dysfunction occurs in full-blown T2DM, causes AD by impairing insulin's ability to perform its roles in the brain [93–96].

In addition to these two theoretical approaches in the literature, some have suggested the term “type 3 diabetes” was coined to account specifically for the underlying abnormalities associated with concurrent AD-type neurodegeneration and diabetes [97]. These researchers maintain that AD and diabetes share common pathophysiology, and therefore therapeutic regimes aimed at diabetes treatment and amelioration could be effective for treatment of AD [98].

A recent meta-analysis demonstrated a strong link between diabetes and VCID [99]. Findings from the Rotterdam study demonstrated a nearly two-fold risk of AD and suggest that DM increases the risk of dementia by 1.9 fold and that DM patients treated with insulin were at even greater risk (4.3 fold) [100]. Multiple population-based studies have shown that patients with DM exhibit an increased risk of developing AD [97,101–103]. The authors of one such study concluded that 39% of AD in a large sample of elderly subjects was attributable to hyperinsulinemia or DM [104].

As with other CVD risk factors, treatment for diabetes has been shown to alter the risk of AD. Metformin has been shown to reduce the risk of AD and is currently being studied in clinical trials with promising preliminary results in MCI patients [105]. A large clinical trial is currently underway to evaluate the efficacy of low-dose pioglitazone as a preventive treatment for MCI due to AD [106]. Other studies have considered the use of intranasal insulin, which has been shown to exert a modest effect on memory performance in AD patients [94,107–109].

#### 4. Lifestyle, behavioral, and environmental risk factors

High-fat diets and sedentary lifestyles have led to a growing incidence of obesity, dyslipidemia, high blood pressure, and metabolic syndromes [110–112]. These conditions are precursors to, or develop along with, atherosclerosis, diabetes, CVD, and an increased risk for AD [113]. Major depression has also been linked to both AD and CVD, and more recently,

environmental exposures such as fungal pathogens and pollution have been under investigation for ties to both AD and CVD. In the following, we review the literature that explores obesity, aerobic exercise, smoking, major depression, and exposures such as fungal pathogens and air pollution, each as shared risk factors for both CVD/CBVD and AD.

##### 4.1. Obesity

The mechanism by which obesity influences cognition and AD risk remains under active investigation. One mechanism may be through vascular pathologies, or there may be hormonal, genetic, or inflammatory processes at work [114]. The Framingham Heart Study reported a marked impairment of cognitive function in patients with obesity compared with non-obese counterparts [115]. Epidemiological studies have shown associations between obesity and increased AD risk in females [116,117] although other studies have found increased risk of dementia for both genders [58]. Pooled results from 11 studies [118] demonstrated that the strength and direction of the association vary over the life course. The association between body mass index (BMI) and later onset of AD appears to be stronger when BMI is measured at midlife [119] than when BMI is measured in later life [116,120]. Although they frequently co-occur, DM and obesity are widely accepted as important independent risk factors for AD [121].

##### 4.2. Aerobic exercise and physical fitness

In contrast to metabolic syndromes, aerobic exercise and healthy lifestyles have been shown to reduce the incidence of both CVD and AD in observational studies. Cardiovascular diseases have become very common as communities and individuals attain more wealth and pursue more sedentary lifestyles [121]. Aerobic exercise promotes brain vascularization and may reduce vascular risk factors and improve cognitive function [122–125]. Randomized controlled trials with as little as six months of exercise training lead to increased hippocampal volume and improved performance on spatial memory and executive function tasks [126,127]. Aerobic exercise also upregulates brain-derived neurotrophic factor, which augments plasticity in the hippocampus [128,129].

Epidemiological studies have demonstrated reduced risk of cognitive decline and dementia as a function of activity levels [130–132], and studies have shown increased gray- and white-matter volume in the brains of participants assigned to aerobic training [133] or those with higher levels of self-reported exercise [134]. Recent meta-analysis of clinical trials of exercise interventions in dementia patients demonstrated positive effects [135]. A recent prevention trial of an exercise intervention in sedentary older adults failed to find a significant effect on cognitive function [136]; however, secondary analyses found significant improvement in cognitive function among the subset of participants who were diabetic [137].

A related measure of physical fitness is heart rate variability (HRV) on continuous electrocardiography

recordings. HRV is usually relatively high for those who exercise frequently [138], as well as for young and healthy individuals. Aging and poor physical fitness are associated with an impairment of cardiac vagal function [139], and HRV is lower for those with relatively diminished parasympathetic tone [140], including those with CVD [141]. Vagal tone, the ability of the vagus nerve to rapidly regulate cardiac output, accounts for a substantial portion of HRV. Vagal tone can be quantified via respiratory sinus arrhythmia (RSA), which measures the slight ebb and flow in heart rate that occurs during the respiratory cycle. RSA is higher in older adults who demonstrate better performance on tasks of verbal episodic memory, a cognitive domain that is typically impaired with the onset of AD [142].

In Table 1, we provide a listing of evidence-based interventions for the treatment of CVD, discussed in the sections previously, and how these specific interventions have been explored in the treatment of AD.

#### 4.3. Smoking

There is some evidence to suggest that long-term cigarette smoking is an independent risk factor for AD, CVD, and CBVD [159–161]. Smoking increases total plasma

homocysteine, an independent risk factor for stroke, cognitive impairment, AD, and other dementias [162–165]. Smoking accelerates atherosclerosis [140] and can cause oxidative stress, which is associated with excitotoxicity, leading to neural death [166]. A dose–response relationship between smoking and dementia risk has been documented [167], and AD risk among smokers is increased in *APOE*  $\epsilon$ 4 carriers [100,168]. A meta-analysis of studies performed in the 1990s and early 2000s revealed that relative to nonsmokers, current smokers had increased risks of 1.79 fold (95% CI 1.43–2.23) for AD and 1.78 fold (95% CI 1.28–2.47) for VCID [169]. A more recent systematic review confirmed the previous findings with increased risks of 1.59 fold (95% CI 1.15–2.20) for AD and 1.35 fold (95% CI 0.90–2.02) for VCID [170].

#### 4.4. Major depression

A history of major depression is another shared risk factor for AD and CVD. Late-onset depression is often associated with AD, and AD patients with episodes of major depression over their lifetimes show greater hippocampal pathology at autopsy [171]. Evidence exists to suggest that the two disorders may share common etiological substrates [172,173].

Table 1  
Shared evidence-based treatments for cardiovascular disease (CVD) and Alzheimer's disease (AD)

Treatment	Clinical effects in treatment of CVD	Clinical effects in treatment of AD
Specific medication interventions		
Diuretics	Thiazide diuretics lead to lowering of blood pressure [143,144].	Long-term use of diuretics may be associated with decreased incidence of AD [60,61].
Angiotensin receptor-1 blocker (ARB) or angiotensin-converting enzyme (ACE) inhibitor	Reduce risk of cardiovascular events [145,146].	ARB and ACE inhibitors may slow progression of symptoms in mild–moderate AD [61,63].
$\beta$ blockers	$\beta$ blockers can prevent cardiovascular events in patients at increased cardiovascular risk [147,148].	$\beta$ -blocker use is associated with a lowered risk of developing cognitive impairment in older adults without dementia [62,64].
Statins	Reduce risk of cardiovascular events [149,150].	Mixed literature, with no consistent evidence that statins reduce the incidence of AD or slow cognitive decline [86,87].
Anti-inflammatory drugs	Mixed literature on use of nonaspirin anti-inflammatory drugs to reduce cardiovascular risk [151,152]. Low-dose aspirin is commonly used as an anti-platelet agent for secondary CVD prevention.	Mixed literature, suggesting that NSAIDs may confer modest protective effects [10,11]. Low-dose aspirin is commonly used as an anti-platelet agent for stroke prevention.
Insulin treatment	Effective diabetes treatment confers long-term beneficial effects on risk of CVD [153,154].	Intranasal insulin appears to improve cognition and modulates A $\beta$ aggregation in early AD [93,94].
Specific behavioral interventions		
Aerobic exercise and physical fitness	Long-term protective effects on risk of cardiovascular disorders [155,156].	Aerobic exercise promotes brain vascularization and may reduce vascular risk factors as well as to improve cognitive function [123,125].
Healthy diets (e.g., MIND diet)	Healthy diets may protect against CVD [157,158].	High-fat diets have shown an increased risk for AD [110,113]. Conversely, carefully designed diets have been shown to confer protective effects [111,112].

Abbreviation: NSAIDs, nonsteroidal anti-inflammatory drugs.

NOTE. Given the breadth of this literature, all cited references are exemplars published within the past 10 years, and all are empirical reports.

Chronic, untreated major depressive disorder is associated with the selective loss of noradrenergic cells in the locus coeruleus [174,175] and the loss of dorsal raphe serotonergic nuclei [176], both of which have been demonstrated in AD. Major depression is now widely acknowledged to be a CHD risk factor, based on work demonstrating that psychosocial factors such as chronic dysphoria, anxiety, perceived loss of locus of control, and perceived stress are strongly predictive of incident myocardial infarction [177]. Nearly one of five patients with CVD suffers from major depressive disorder [178]. Depression may be directly linked to cerebral ischemia secondary to reduced cerebral blood flow [178] and is associated with an increased risk of recurrent stroke in patients with VCID [179]. CVD has been proposed as a mediator of the relationship between major depression and AD [180]. Hyperhomocysteinemia has been demonstrated in both AD and major depression [181,182]. Adding to this already complex picture, heightened homocysteine levels are found in CVD [163], indicating a potential shared mechanism in AD, CVD, and major depression. The exact nature of the downstream effects of this mechanism requires further research.

#### 4.5. Fungal pathogens

More recently, fungal macromolecules have been identified as a potential pathophysiological substrate of both AD and CVD. The presence of fungal cells in different sizes and hyphae inside capillaries and other blood vessels in some AD patients suggests that fungal infections can be detected in the neurovascular system and may, in some cases, explain the vascular pathology frequently detected in AD patients [183,184]. One study showed that A $\beta$  peptide, a cardinal feature of AD pathology, could exert antimicrobial activity for at least eight different microorganisms, suggesting a brain with AD could specifically induce A $\beta$ -mediated inflammatory activity against *Candida albicans* [185]. Unfortunately, many macromolecules with antimicrobial activity have been shown to be cytotoxic toward vascular smooth muscle cells [186], and A $\beta$  is no exception [187]. There is also association of AD with various types of spirochetes, and *C pneumonia* [188]. However, thus far, to our knowledge, the only documented common fungal or microbial pathogenic link between AD and CVD is *Candida albicans*. The pathophysiological link between pneumonia and acute cardiovascular events has been explained via the long-lasting infection hypothesis, which implicates microorganisms in atherosclerosis [189].

#### 4.6. Air pollution

Chronic exposure to air pollution, which is associated with reduced HRV, is another environmental factor that is associated with both CVD and AD. Specifically, long-term exposure to high ozone and high particulate matter in the air leads to increased risk for obesity, metabolic syndromes

[190], and a host of CVDs [191] including myocardial ischemia and infarction, heart failure, arrhythmias, stroke, and increased cardiovascular mortality [192]. Recently, a dose-response relationship was found between longitudinal exposure to high concentrations of atmospheric particulate matter <10  $\mu$ m in diameter and significantly increased risk of AD and VCID in industrial regions of Taiwan [193].

### 5. Co-occurrence of AD and cerebrovascular diseases

CBVD is a generic term from a heterogeneous set of insults to the cerebral vasculature, and such insults often lead to various cognitive impairment(s). CBVD insults include, but are not limited to, microvascular degeneration (with looping, twining, and braiding vessels) [194], periventricular venous collagenases, and vascular tortuosity [195]. These microvascular changes all cause impaired cerebral perfusion [196]. Some studies have shown a correlation between capillary length per brain volume and reduction of glucose utilization [197]. Intracerebral hemorrhages due to A $\beta$  accumulation within vessel walls can contribute to AD pathology [198]. This leads to increased incidence of infarcts in the brain tissue innervated by this system [199]. Collectively, these conditions are considered among the causes for VCID (vascular contributions to cognitive impairment and dementia). VCID refers to a progressive worsening of cognitive functions and memory. VCID is due exclusively to vascular disease within the brain [200]. It is often very difficult to distinguish AD from VCID as they appear very similar on clinical examination. VCID patients often present with episodic memory impairments, word-finding difficulties, disorientation to time, and subtle executive deficits [201]. Thus, a differential diagnosis is aided by careful neuropsychological examination in conjunction with appropriate biomarker studies [202].

In the United States, CBVD is the leading cause of disability in adults and the third leading cause of death [203]. CVD often plays a direct causal role in cerebrovascular events, as CBVD often results from a lack of blood flow to the brain. Various CBVD pathologies are observed in 60%–90% of AD patients, including white-matter lesions, microinfarcts, hemorrhages, microvascular degeneration, and cerebral amyloid angiopathy (CAA) [74]. CAA is the abnormal deposition of a congophilic material in meningeal and cerebral arterioles. The prevalence of CAA is high in AD and CAA often progresses in severity causing vessel rupture [204]. Atherosclerosis, a common cause of CBVD, can lead to cerebral infarction or stroke, and disabling cognitive impairments in late life [205]. Many large population-based epidemiologic studies have provided strong support for the relationship between AD and cerebrovascular changes. One such study examining two large cohorts of AD patients found a strong relationship between AD and cerebral atherosclerosis, such that the presence of atherosclerosis was associated with worse cognitive performance in AD [206]. The Framingham Heart Study found that a lower cardiac index was

associated with increased risk of AD [207]. These findings suggest that age-related changes in systemic hemodynamics may contribute to the pathogenesis or exacerbation of amyloid deposition, subsequent neuronal injury, and vascular pathology [207]. Similar findings have been reported for other large epidemiologic studies, including the Pittsburgh Cardiovascular Health Study [208] and the Prospective Population Study of Women in Gothenburg, Sweden [209]. Likewise, the Atherosclerosis Risk in Communities study found a high prevalence of magnetic resonance imaging (MRI)-detected cerebral abnormalities, related to cognitive functioning, that might reflect preclinical AD [210].

As described previously and across a large body of published literature, VCID can manifest solely as a result of CBVD events, such as hemorrhagic or ischemic strokes, or by the accumulation of multiple ischemic events. However, it remains unclear whether AD occurs in the absence of any vascular pathology, or whether CVD and CBVD changes are mechanistically related to the fundamental pathology of AD. Two separate imaging studies have recently cast doubt on the interdependence of AD and vascular pathologies [211,212]. The studies suggest that AD-related amyloid burden and CBVD independently affect cognitive impairment, as there was no correlation between the images comparing specific neuroanatomic coordinates of both amyloidosis (positron emission tomography [PET] PIB ligand binding) and white-matter hyperintensities (WMHs) with structural MRI. In a study of 251 cognitively impaired subjects, Ye et al. found that PIB retention ratios were associated with both hippocampal atrophy and memory impairments and, conversely, the WMH imaging was more strongly associated with frontal cortex thinning and executive dysfunction. The authors concluded that the effect on cognition for individuals with both pathologies was additive and not synergistic; thus, the impact of AD and CVD pathologies on cognition is mediated through independent mechanisms [212]. Vemuri et al. (2015) evaluated MRI and PET images from 393 cognitively normal participants, aged 70–90 years from the Mayo Clinic Study of Aging and showed that for subjects with both vascular and amyloid pathologies, the effect of both pathologies on cognition was additive and not synergistic [211]. Both Ye and Vemuri et al. have put forward similar arguments, but they are based on a single MRI imaging marker of CBVD. However, as we outline in the following, cardiovascular and cerebrovascular pathologies are highly complex clusters of biological processes that share many points of mechanistic links to AD. These two recent imaging studies stand as outliers within a large body of literature suggesting that although VCID may frequently occur in the absence of AD, the converse is not necessarily true.

## 6. AD, CVD, and CBVD: shared pathophysiology and neuropathological substrates

AD, CVD, and CBVD primarily affect the same at-risk population who share many common risk factors. All three

diseases may independently and/or interdependently lead to debilitating, unremitting, and progressive changes in cognition. The direct causal relationship between vascular and cerebrovascular insults, and dementia or apoplexia, was described over three centuries ago by Thomas Willis [213]. Medical practitioners generally considered dementia to result from vascular insults. As early as 1833, Lobstein used the term “dementia arteriosclerotica” attributing the nature of the disease to vascular origins [214]. A causal link between other nonvascular brain disease states and dementia was not well described until the latter half of the 19th century. In 1871, Charles Darwin received a letter from the director of England’s largest lunatic asylum, Dr. James Crichton-Browne, who observed that senile decay was the result of central nervous system disease that was linked to emotional liability [173]. Thirty-six years later, the initial case report of Alois Alzheimer’s; described the finding of senile plaques and neurofibrillary tangles found on postmortem histopathology examination of a patient who had “ordinary dementia” and neuropsychiatric symptoms [215].

Prof. Alzheimer presaged the complexity and multicausality of dementia by reporting atherosclerosis in the cerebral blood vessels of his 55-year-old patient, for which he coined the term Alzheimer’s sclerosis [216]. The term AD was reserved for the diagnosis of dementia with onset between ages 40 and 90 years, if the other causal explanations (e.g., vascular causes) of dementia were absent [217]. The National Institute of Aging (NIA) and the Alzheimer’s Association (AA) revised the diagnostic and research criteria for AD in 2011, and this reformulation of the diagnostic nosology were detailed in three publications that year [218–220]. According to the new NIA-AA criteria, a diagnosis of “preclinical AD” is based on the presence of relevant positive biomarkers (e.g., PET amyloid imaging) in conjunction with known risk factors for the disease (e.g., *APOE*  $\epsilon$ 4 allele). The identification of individuals in this stage of prodromal AD is made essentially for research purposes only [218]. MCI due to AD includes patients with mild cognitive symptoms (impaired performance on measures of episodic memory function) with positive evidence of the disease from appropriate biomarker studies [219]. Ultimately, a diagnosis of AD is now based on criteria that account for recent developments in disease-specific biomarkers, which allow for confirmation of AD without the need to rely on postmortem histopathology [220–222].

In the following, we briefly review the major overlapping pathophysiology between CVD, CBVD, and AD, all of which is briefly summarized in Table 2.

### 6.1. Reduced cerebral blood flow

Normal brain function is dependent on receiving 20% of the cardiac output of oxygenated blood, and both higher and lower blood pressure may reduce this cerebral blood flow [227]. Hence, impaired cardiac function may subsequently lead to both reduced intracranial blood flow (e.g., as

Table 2  
Domains of shared patient characteristics and pathophysiology between cardiovascular and cerebrovascular diseases and Alzheimer's disease

	AD	CVD/CBVD	Key reference citations
<b>Patient characteristics</b>			
Age range	Yes	Yes	[2,34,35,203]
Genetic risk factor	Yes	Yes	[23–33,223–225]
Hypertension/hypotension	Yes	Yes	[34,35,38–43,50–68,226]
High cholesterol	Yes	Yes	[36,70–85]
Diabetes mellitus	Yes	Yes	[34,35,38–43,88–109,226]
Obesity	Yes	Yes	[94,110–119]
Poor physical fitness	Yes	Yes	[122–135]
Smoking	Yes	Yes	[34,35,39–44,141,142,159–168,226]
History of depression	Yes	Yes	[171–182]
Pathogens (e.g., fungal)	Yes	Yes	[183,184]
Air pollution	Yes	Yes	[190–193]
<b>Pathophysiology</b>			
Reduced cerebral blood flow	Yes	Yes	[196,227–235]
A $\beta$ deposition	Yes	No	[198,236–243]
Morphological changes in vasculature	Yes	Yes	[48,194,195,244–252]
Alterations in BBB permeability	Yes	Yes	[253–265]
Cholinergic neurodegeneration	Yes	Yes	[266–281]

Abbreviations: AD, Alzheimer's disease; CVD, cardiovascular disease; CBVD, cerebrovascular disease; BBB, blood–brain barrier.

measured within the Circle of Willis) and ischemia, and this is readily observed in AD patients [228]. Reduced cerebrovascular reactivity was observed in a study of 18 young adult (mean age 24 years) carriers of at least one *APOE*  $\epsilon$ 4 allele [229]. Suri et al. surmise that this lifelong relative decrease in cerebral blood flow will lead to areas of hypoperfusion and microvascular damage; thereby, contributing to aggregation of blood products, endothelial dysfunction, and impaired A $\beta$  clearance [229]. It is of note that the sample size in this study was small, and further investigation is required to elucidate the nature of the interaction between cerebral blood flow, *APOE* status, and AD. A meta-analysis was conducted to investigate whether the changes in cerebral blood flow velocity and pulsatility index by Doppler ultrasonography in AD and VCID follow similar patterns. Both disease states were found to be associated with pronounced disturbances in cerebrovascular hemodynamics, with VCID patients showing significantly lower cerebral blood flow [230].

Another factor that may contribute to reduced regional cerebral blood flow is the observed decrease of endothelial nitric oxide (NO) synthesis in AD [231]. The enzyme endothelial nitric oxide synthase (eNOS) is responsible for NO generation, which is important for cardiovascular homeostasis and acts as a vasodilator involved in the control of vasomotor function and local blood flow [232]. Endothelial production of NO is important for the prevention of CBVD, as it mediates protection from stroke by preserving cerebral blood flow and preventing inflammation, thrombosis, and apoptosis [233]. Besides the CBVD contributions, it can also increase expression of APP and BACE1, consequently increasing A $\beta$  levels [234]. The evolving opinion is that cerebrovascular dysfunction is not only present in CBVD but also a prominent component of neurodegenerative pathologies such as AD [235].

## 6.2. A $\beta$ deposition

The amyloid cascade hypothesis postulates that neurodegeneration in AD is due to an abnormal accumulation of A $\beta$  plaques in various areas of the brain [236], and the neurodegenerative processes in AD are the consequence of the imbalance between A $\beta$  peptide production and clearance [237]. Recently, Yau et al. provided clear support for targeting A $\beta$  clearance in early AD based on their longitudinal study of 16 patients with an autosomal-dominant mutation for early-onset AD. In their study, they demonstrated that amyloidosis is one of the earliest events in the neuropathological cascade leading to AD, with the majority of A $\beta$  aggregation occurring before the progressive structural neurodegeneration and cognitive decline [238].

The abnormal aggregation of A $\beta$  protein in the brain neuropil may lead to either diffuse plaques and/or concentrated neuritic plaques, with the latter form of deposits often present in the vicinity of the cerebral microvasculature [239]. The A $\beta$  protein, with its crystalline molecular structure, infiltrates the vessel walls and compromises the BBB [239]. Deposition of A $\beta$  protein within the walls of cerebral blood vessels also leads to CAA, increasing the risk of cerebral hemorrhage [74], which is the most common clinical presentation of CAA [240]. In an APP/PS1 transgenic mice study with induced hyperhomocysteinemia, Sudduth et al. showed that congophilic amyloid deposition was decreased in the parenchyma and significantly increased in the vasculature in CAA. This suggests that CBVD can significantly impact A $\beta$  distribution in the brain by vascular deposition and that such deposition can induce microhemorrhages and activate neuroinflammation [241]. In an in vivo study of Sprague–Dawley rats, infusion of solubilized A $\beta$  peptides enhanced constriction of cerebral and peripheral vessels, contributing to cerebral hypoperfusion and leading to decreased blood flow and increased vascular resistance [242].



The risk of both repeated hemorrhagic strokes, as well as ischemic events due to vessel wall stenosis and oligemia, increases with continued A $\beta$  accumulation for both CAA and AD patients. This pathologic cascade leads to medial temporal lobe atrophy, cognitive decline, and progressive brain atrophy [74]. Finally, vascular A $\beta$  deposits observed in AD have been shown in vitro to induce degeneration of human and murine cerebrovascular smooth muscle and endothelial cells, resulting in vasoconstriction, intraluminal thickening, inhibiting angiogenesis, impairing vascular tone, and decreasing total cerebral blood flow [243].

### 6.3. Morphological changes in the vasculature

Arterial stiffness can be caused by structural or cellular change within vessel walls, and amyloid deposition in the vessels leads directly to this pathophysiological process [244]. The fragmentation of elastin alters the hemodynamics of vessel walls, resulting in increased systolic pressure by increasing the speed of the arterial wave that arrives prematurely during systole rather than during diastole [245]. Atherosclerosis also accelerates arterial stiffness [246], a frequent finding in patients with CVD. Arterial stiffness is a clear risk factor for cognitive impairment in later life, as it can cause structural changes in the brain, such as white matter or cortical infarcts and cortical brain atrophy [247,248]. A recent systematic review of this association concludes that arterial stiffness is related to cerebral small vessel disease and decreased cognitive function [249].

The deposition of A $\beta$  in arterial vessel walls, and subsequent impediment of perivascular drainage of A $\beta$  due to AD pathology, can lead to intracerebral hemorrhage and an increase of A $\beta$  peptides [74]. These morphological and architectural changes of the cerebral vasculature, studied in APP23 tg mice, start early in life. Along with the increase in observable amyloid plaques, there is also increased atrophy and altered blood flow, suggesting that disrupted microvasculature integrity can contribute to the progression of AD [250]. However, subtle changes in cerebral microcirculation are difficult to measure with high precision for the exploration of longitudinal changes within subjects associated with increased disease burden. These subtle morphological changes may be more easily observed in the microvasculature of the retina. Patients with AD have sparser retinal microvascular networks and other structural alterations that may mirror pathophysiological events found in the cerebral microvasculature [251]. Patients with AD show changes in retinal microvasculature, such as more tortuous retinal vessels and a narrowing of retinal venules [252]. These retinal vascular changes have been posited to precede the majority of neurodegeneration that characterizes AD progression [48].

### 6.4. Alterations in BBB permeability

The brain vasculature has cellular elements forming a developmental, structural, and functional relationship with

the brain tissue termed the neurovascular unit [244]. The neurovascular unit has a fundamental role in the broad spectrum of pathologies underlying cognitive impairment. Neural activity requires continuous and regulated blood flow to activate neurons, astrocytes, and vascular cells through a wide variety of molecular signals (ions, arachidonic acid, metabolites, NO, adenosine, neurotransmitters, and neuropeptides) [253]. Specific neuroimaging techniques to visualize deleterious changes to the BBB are still under exploration. Several studies have shown that plasma proteins like prothrombin, which are typically excluded from the CNS, can be found within the microvessel walls and surrounding neuropil in AD patients, showing that the leakage of the BBB may be frequent in AD [254]. The vascular abnormalities found in the AD brain, such as alteration in smooth muscle cells and pericytes, endothelial cell thinning, loss of endothelial mitochondria, and thickening of the vascular basement membrane, all contribute to alterations in BBB permeability [255]. The end result is a continuous cycle of reduced cerebral perfusion leading to acceleration of the neurodegenerative process, which further reduces perfusion.

The changes in BBB permeability lead to an ionic imbalance and accumulation of toxic metabolic products. As a consequence, synaptic, neuronal, and oligodendrocyte dysfunction occurs [256] because an intact BBB is crucial for limiting the entry of toxic products and cells into the brain. Glucose transport across the BBB is also impaired, and PET studies show reduced regional metabolic rate in the AD brain [257]. Alterations on the (Na<sup>+</sup>/K<sup>+</sup>)-pump function of the BBB can result in fluid balance impairment, leading to deregulation of regional cerebral blood flow [258].

A $\beta$  accumulation can contribute to the leakage of the BBB [259]. These peptides, spread across a defective BBB, contribute to higher oxidative and nitrosative damage, as well as increased protease activity [74]. A $\beta$  deposition leads to microglial activation, reactive astrogliosis and a multiprotein inflammatory response [260]. Studies of WT and *APOE* deficient mice show that BBB permeability increases with age and a defect in the BBB is exacerbated in *APOE* deficient mice [261,262]. Additionally, arterial stiffness results in an uncoupling of the neurovascular unit, and this disruption of the cerebral microenvironment is likely to contribute to brain dysfunction [263]. The resulting accumulation of A $\beta$  in the neuropil and vessel walls leads to the activation of neuroinflammatory response, which plays an important role in BBB disruption [264]. Anatomically, neuroinflammation may lead to transient increases in thickness of various cortical tissues, as well as at least one neuronal cell layer of the retina in preclinical stage disease. Snyder et al. (2016) have provided initial evidence to suggest an increase in the thickness of the retinal inner plexiform layer, in preclinical AD, and they postulate this volume increase may be partly due to a localized neuroinflammatory process and/or deposition of amyloid-containing inclusion

bodies within the cell layer. They suggest that this observation may precede a gradual thinning of neuronal cell layers (e.g., the ganglion cell layer) and the retinal nerve fiber layer with continued disease progression [265].

### 6.5. Cholinergic neurodegeneration

Postmortem studies have shown reduced activity of choline acetyltransferase, decreased numbers of nicotinic acetylcholine receptors, and reduced basal forebrain cholinergic neurons (particularly in the nucleus basalis of Meynert), contribute to the oldest model of neurobiologic dysfunction in AD—the “cholinergic hypothesis” [266,267].

This reduction in cholinergic innervation and activity may result, in part, from a reduction in noradrenaline release due to locus coeruleus (LC) neuron loss [268]. There is a strong reciprocal connection between the LC and the prefrontal cortex, and this area is involved in the mediation of executive functioning, memory, and vigilance [269]. The LC is responsible for exerting an excitatory influence on wakefulness-promoting nuclei, such as the cholinergic nuclei of the septal area, medial preoptic area and substantia innominata [270]. Pathological changes in the LC occur early in AD [271], and this reduction in LC activity likely leads to the common finding of reduced levels of arousal and alertness in AD patients. The number of LC neurons projecting to areas such as the hippocampus and the frontal cortex declines slowly with normal aging, and this may result in some modest age-related changes in spatial learning and memory [272].

This structural and functional loss in the LC affects both efferent and afferent pathways. The LC exerts both direct (via a descending excitatory noradrenergic pathway) and indirect effects (via modulation of the activity of other premotor sympathetic nuclei) on preganglionic sympathetic neurons in the intermediolateral cell column [273]. The LC sends efferent inputs to the nucleus tractus solitarius, which is critical for the modulation of the vasomotor response to changes in blood pressure through vagal nerve stimulation and autonomic inputs to the heart. The vagal nerve provides cholinergic input to increase parasympathetic activity, which decreases heart rate and lowers blood pressure when needed [274].

The earliest stages of AD are marked, in part, by altered function of the basal forebrain cholinergic system, with eventual degenerative changes including neuronal loss [275,276]. We have recently reported that a down-regulation of central cholinergic neurotransmission appears to be one of the earliest neuropathological changes in preclinical AD [277], and we have also found that individuals with evidence of both decreased central cholinergic tone and amyloid aggregation within the anterior cingulate region show evidence of increased resting cardiac workload at rest [51]. The aggregation of A $\beta$  plaques in the neocortex, within this specific region of interest that is part of the central cholinergic system, appears to be directly associated with

increasing cognitive impairment as well as the higher myocardial oxygen consumption at resting state [51]. In fact, there is a growing body of literature to suggest a direct link between A $\beta$  aggregation, basal forebrain cholinergic damage, and diminished cholinergic innervation of cortical blood vessels, leading to the microvascular pathology that has been documented in the majority of AD cases [278–281]. We are currently exploring whether indices of phasic vagal cardiac control, such as RSA and HRV, are also related to cortical amyloidosis in preclinical AD because both RSA and HRV are directly modulated by muscarinic cholinergic and nicotinic autonomic neurotransmission.

## 7. Discussion

This review is intended to tie together several lines of research on the shared mechanistic relationships between AD, CVD, and CBVD. The literature that binds these diseases is both large and confusing. Why is AD so tightly connected to disruption of the cerebrovasculature and to cardiologic disease? Why do these broad disease entities share so many risk factors and mechanistic relationships? One compelling answer to these larger questions may come from the field of medical anthropology and attempts to study the global distribution of *APOE* gene alleles across the human species. The  $\epsilon 4$  allele is the ancestral form of *APOE* [223,224] and is associated with both higher absorption of cholesterol at the intestinal level and higher plasma cholesterol levels in carriers. The phenotypic expression of this allele would likely confer a survival benefit to humans that evolved with limited food supplies and in harsh weather conditions. Expression of the  $\epsilon 4$  allele under contemporary/modern diet, exercise, and environmental conditions, together with the relatively recent and dramatic increase in human longevity, may have now led to the identification of the  $\epsilon 4$  allele as pleiotropic, showing susceptibilities for both CVD and AD [224]. Although this anthropological viewpoint is not universally accepted, nor the focus of the current review, it affords us an overarching heuristic model to explain the strong relationship between CVD, CBVD, and AD.

Another question that arises from the frequent coincidence of AD, CVD, and CBVD is whether or not they are the end result of shared etiologic mechanisms. If one supposes a direct, bidirectional causal link between these disease clusters, then all cases of CVD and/or CBVD would also demonstrate AD pathology, and we know this is not the case. Rather, we have reviewed a large literature indicating that vascular/cerebrovascular pathology is present for most individuals with AD but not all of them. In support of this notion, an autopsy study with the largest cohort to date ( $N = 5715$ ) showed increased prevalence of CBVD and vascular pathology in AD compared to healthy controls and patients with dementias of non-AD etiologies [225]. Additionally, a recent autopsy study combining two well-known longitudinal cohorts (the Religious Orders Study

and the Rush Memory and Aging Project,  $N = 1143$ ) revealed an increased risk of incident AD dementia with the presence of CBVD pathology. There was a stepwise increase in the odds ratio for AD development with the severity of CBVD pathology, suggesting that this pathology is a risk factor for AD development [206].

So what, then, is the causal nature of the relationships between these diseases? To answer this question, it is important to determine whether the cognitive effects of AD and CVD/CBVD are additive or synergistic. This is a topic that continues to elicit considerable scientific exploration. It is possible that AD and CVD/CBVD contribute independently to dementia, such that the severity of the dementia is a cumulative result of two separate pathologies [210]. Alternatively, these disease processes could be synergistic, such that the pathology of one accelerates the progress of the other. The majority of the literature reviewed herein supports the model of a synergistic interaction between vascular/cerebrovascular and neurodegenerative processes early in disease pathogenesis. This theory is further supported by a reciprocal relationship between A $\beta$  accumulation and cerebrovascular insult such that A $\beta$  deposition provokes vascular/cerebrovascular changes [74] and vice versa [282,283]. Clinical studies demonstrate that even mild cerebrovascular pathology results in reduced cognitive performance in very early AD [77,284]. It is possible that both additive and synergistic processes are affecting cognitive decline at different stages of these disease processes. This theory is congruous with variability in observational findings based on timing, severity, and duration of CVD risk factors. In fact, it has been suggested that later disease stages could demonstrate a more additive relationship [285].

There is evidence that vascular/cerebrovascular pathology can accelerate the progression of preclinical AD and speed disease evolution [286,287]. The relationships between AD and CVD/CBVD are complex, and further investigation is required to discern the exact nature of these relationships at different stages of disease progression. We suggest that, because AD is so frequently accompanied by comorbid vascular and/or cerebrovascular symptoms, it is both clinically and scientifically relevant to consider these pathologies concurrently, regardless of whether their respective underlying pathologic mechanisms are independent and additive, or functionally related and synergistic.

We support the widely studied hypothesis that effectively controlling vascular risk factors serves to delay onset of AD. In fact, a recent statement by the World Dementia Council suggested that “Regular physical activity and management of cardiovascular risk factors (e.g., diabetes, obesity, smoking, and hypertension) are associated with a reduced risk of cognitive decline and may reduce the risk of dementia” [288,289]. A recent cross-sectional study concluded that the use of certain medications to treat vascular disease, especially angiotensin receptor blockers and diuretics, may decrease A $\beta$  accumulation [290]. In a recent review, Deckers

et al. (2015) [291] found that the most common modifiable risk factors for AD development included hypertension, diabetes, midlife obesity, physical inactivity, hyperlipidemia, and smoking. Simple, inexpensive interventions involving diet and exercise in midlife could be very useful tools to prevent CVD, CBVD, and AD. These interventions are currently under evaluation by several large prospective clinical trials, including the CAIDE [292] and the Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER [293]). Nonetheless, preliminary results indicate that the complex multifactorial nature of AD requires interventions that simultaneously target multiple risk factors and disease mechanisms during the preclinical stage of the disease [292,293]. The CAIDE screening tool has been developed based on vascular and metabolic factors shown to increase dementia risk to identify individuals who are at risk for dementia and who require preventive intervention [44], and this has recently been developed into a freely available smartphone application [292].

The validation of sensitive and reliable measures of dementia risk that account for CVD susceptibility (e.g., CAIDE), paired with lifestyle intervention techniques to control or reduce these same risk markers, will ultimately lead to a better understanding of the relationship between these two disease clusters. The exploration of the dynamic pathogenic relationships between AD and CVD/CBVD has the potential to lead to a reduction and/or delay in AD incidence. In accordance with earlier work revealing that interactions between mechanistic, genetic, and lifestyle factors influence vascular disease, we expect that these multifactorial interventions targeting common mechanistic and lifestyle factors in AD and CVD/CBVD will confirm that the adoption of a heart-healthy lifestyle has the potential to contribute to a future decline in all three disease processes.

### 7.1. Future directions

Despite the rapid advancement of medical technology, we are still developing a suite of reliable and sensitive diagnostic markers to identify individuals at risk for AD before onset of clinical symptoms. This is an area of research that needs to be urgently addressed to enable the study of early interventions to maintain quality of life in premonitory AD and to reduce the individual and societal burden of the disease. There are currently several secondary prevention trials aimed at pharmacologically slowing or reducing the A $\beta$  accumulation that occurs in preclinical AD, but as of this writing, these secondary prevention trials are still in progress and we do not yet have successful therapies to prevent or slow/reduce disease progression. It is typically the case that such large prospective studies seek to exclude participants with significant cardiovascular or cerebrovascular comorbidities. Given the evidence supporting a substantial overlap of epidemiology, genetics, risk factors, and mechanistic factors in vascular and AD pathology, we argue that future secondary prevention

trials should focus on a more heterogeneous and phenotypically representative population.

Aside from clinical trials and recruitment science, there continues to be an outpouring of literature aimed at untangling the mechanistic relationships between CVD, CBVD, and AD. Recently, the National Institutes of Health launched the Molecular Mechanisms of the Vascular Etiology of Alzheimer's Disease Consortium, the primary aim of which is to construct a comprehensive model of Alzheimer's disease that more accurately reflects its complex underpinnings, and the multiple pathways of disease development. The main objectives of this initiative are to elucidate the complex mechanisms by which cardiovascular risk factors influence the development and progression of AD and to identify new targets for treatment and prevention. Thus far, the consortium supports five project areas addressing a wide range of topics, including the following: the contribution of Alzheimer's risk genes (*APOE*  $\epsilon$ 4) to AD and CVD; the contribution of DM to AD, CVD, and CBVD; the contribution of hypertension to AD development and progression; identifying metabolic signatures underlying risk factors for both AD and CVD; and investigating the mechanism of A $\beta$  accumulation and clearance at the molecular, single-blood vessel, and whole-brain level and the relationship of A $\beta$  accumulation at all three levels in AD and CBVD. Moving forward, studies such as these that investigate the interaction of vascular biology with genetic, cardiometabolic, and lifestyle risk factors and AD pathology will be crucial to the development of therapeutic agents.

There are many questions about the relationships between AD, CBVD, and CVD that remain unanswered. One important public health question is how these diseases intersect in the oldest-old. The World Health Organization has reported a worldwide dementia incidence of 47.5 million in 2015, and a projected incidence of 75.6 million in 2030. The largest risk factor for AD, CVD, and CBVD is increasing age. In the United States, the population of adults aged  $\geq 90$  years is expected to grow over six-fold by 2050 [285]. As the average lifespan increases, the social and economic consequences of AD, CVD, and CBVD are expected to expand accordingly. Because of difficulties in finding, recruiting, and diagnosing the oldest-old, very little literature exists examining the relationships between AD, CBVD, and CVD in this population. Future population-based studies should aim to include this cohort to further understand the nature of disease interactions over time and to identify prevention targets to reduce cardiovascular risk (i.e., blood pressure, glycemic index, and cholesterol levels) in these specific populations. More accurate models are required for assessing prognosis and life expectancy in older adults with AD, CVD, and/or CBVD in the context of multiple chronic conditions.

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### RESEARCH IN CONTEXT

1. Systematic review: The authors conducted online searches for all the relevant literature describing the relationship between Alzheimer's disease (AD), cardiovascular disease (CVD), and cerebrovascular disease (CBVD). A thorough review of common epidemiology, risk factors, and possible mechanistic pathways that might link these three entities is provided.
2. Interpretation: There is a substantial overlap in epidemiologic, genetic, and clinical literature of shared risk factors for AD and cardiovascular and cerebrovascular comorbidities. There is also very substantial overlap in shared mechanistic relationships between AD and both CVD and CBVD. We suggest that vascular/cerebrovascular pathology is present for most individuals with AD, although the converse is not necessarily true.
3. Future directions: Further investigation is required to understand the mechanistic pathways for shared pathology between these two constellations of diseases. Our group and others are tracking vascular changes in preclinical AD patients. Epidemiological studies of CVD progression promise new insights on the effects of subclinical CVD on the brain. Currently ongoing cardiovascular prevention trials impacting dementia risk will provide substantial insight into the possibility of delaying the onset of AD.

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