Vascular basis for brain degeneration: faltering controls and risk factors for dementia

Raj N Kalaria

The integrity of the vascular system is essential for the efficient functioning of the brain. Aging-related structural and functional disturbances in the macro- or microcirculation of the brain make it vulnerable to cognitive dysfunction, leading to brain degeneration and dementing illness. Several faltering controls, including impairment in autoregulation, neurovascular coupling, blood-brain barrier leakage, decreased cerebrospinal fluid, and reduced vascular tone, appear to be responsible for varying degrees of neurodegeneration in old age. There is ample evidence to indicate vascular risk factors are also linked to neurodegenerative processes preceding cognitive decline and dementia. The strongest risk factor for brain degeneration, whether it results from vascular or neurodegenerative mechanisms or both, is age. However, several modifiable risks such as cardiovascular disease, hypertension, dyslipidemia, diabetes, and obesity enhance the rate of cognitive decline and increase the risk of Alzheimer's disease in particular. The ultimate accumulation of brain pathological lesions may be modified by genetic influences, such as the apolipoprotein E ε4 allele and the environment. Lifestyle measures that maintain or improve cardiovascular health, including consumption of healthy diets, moderate use of alcohol, and implementation of regular physical exercise are important factors for brain protection.

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INTRODUCTION

The brain comprises only 2% of the body weight yet consumes a critical 20% of the body's oxygen and other nutrients supplied via the vascular system. The integrity of the vasculature is therefore essential for the optimal functioning of the brain. In addition to the cardiovascular system, brain vascular control mechanisms are vital for the maintenance of the neurovascular milieu, created by nerve terminals, astrocytic endfeet, and the microvasculature. Numerous molecular signals, including vasoactive peptides, gaseous transmitters, and growth factors, mediate the tight regulation of cerebral blood flow (CBF) in tandem with neural activity. Structural, chemical, or functional disturbances in the macro- or microcirculation of the brain would ultimately affect cognitive function and behavior. Increasing age is the strongest risk factor for brain degeneration and age-related cognitive disorders (Table 1). However, none of the protective mechanisms is immune to the selective or general cumulative effects of aging, and malfunction in one could impact on the other with respect to both time and space (Figure 1).

Various factors may influence the nature and severity of brain degeneration. The degree of cerebral grey matter damage, neuronal death, and survival will be dictated by the multiplicity, size, and laterality of the tissue injury or the extent of vascular disease. Anatomical features of the circulation, including the size of vessels and vascular wall cellular elements, e.g., arterioles versus capillaries, are

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important factors in defining the pathology.\textsuperscript{1} The distribution territories of the anterior, posterior, and middle cerebral and the lenticulostriate arteries affect different structures, including the angular gyrus, the caudate nucleus and medial thalamus in the dominant hemisphere, the amygdala, and the hippocampus, all structures implicated in forms of cognitive impairment.\textsuperscript{3} The origin and degree of vascular occlusion or injury and whether this results in ischemic or hemorrhagic lesions are further factors that define the extent and severity of damage. Alterations in specific genes associated with systemic disease or brain-specific proteins and environmental or lifestyle factors may further modify the course of degeneration. This review will consider aging-related changes at the fluid-tissue surfaces of the brain and various factors that put vascular health at risk to cause brain degeneration and dementia in old age.

Historical aspects

Both cerebrovascular and neurodegenerative diseases increase significantly after 60 years of age in almost all populations worldwide.\textsuperscript{4} Alzheimer’s disease (AD) is widely recognized as the most common cause of dementia, predominantly resulting from neurodegenerative changes.\textsuperscript{5} Cerebrovascular disease causes the second most common form of brain degenerative disorder leading to dementia. Just over 100 years ago, Alois Alzheimer and

![Table 1 Risk factors for brain degeneration during aging.](image)

\begin{table}
\centering
\caption{Risk factors for brain degeneration during aging.}
\begin{tabular}{|l|l|}
\hline
Factor\textsuperscript{1} & Degree of risk \\
\hline
Increasing age & Strongest \\
Family history of dementia or depressive illness & High \\
Down’s syndrome & High \\
Head trauma & Moderate \\
Vascular disease & Moderate \\
Apolipoprotein E ε4 allele & High \\
Smoking & Moderate \\
Illiteracy & High \\
Sedentary lifestyle & Moderate \\
Female gender & Low \\
\hline
\end{tabular}
\end{table}

\textsuperscript{1} Collective evidence indicates these are the most widely accepted degrees of risk for AD as the most common cause of dementia. Other less recognized risk factors include lower head circumference and shorter leg length.\textsuperscript{4} Majority of evidence suggests more women develop Alzheimer’s disease, whereas vascular dementia is more prominent in men.

![Figure 1 Schematic diagram showing various interfaces/barriers between blood or fluid and brain.](image)

\textbf{Figure 1} Schematic diagram showing various interfaces/barriers between blood or fluid and brain. Each of the sites can be affected to a variable degree by aging and, more selectively, as a consequence of neurodegeneration.

Abbreviations: AE, astrocytic endfoot; BM, basement membrane; EC, endothelial cell; P, pericyte; VSMC, vascular smooth muscle cell; FB, fibroblast; CSF, cerebrospinal fluid; Arach, arachnoid; PIA, pia matter; SAS, subarachnoid space. Modified after Nils-Olof Hagnellus, 2009 (RNK, personal communication).
Emil Kraeplin were among the first neuropsychiatrists who had reasoned that gradual strangulation of the blood supply to the brain was the main cause of organic brain degeneration. They surmised aging-related progressive hardening of the arteries leads to arteriosclerotic dementia. Even until the late 1960s arteriosclerotic dementia, attributed to cerebral softening with loss of a relatively large volume (>50 mL) of tissue, was described as a major cause of dementia, which was reported to be over-diagnosed clinically. In recent years, vascular dementia (VaD) or, more precisely, vascular cognitive impairment has been described that takes into account the consequence of a variety of cerebrovascular lesions or impaired brain perfusion. Subcortical ischemic VaD appears the most significant subtype of VaD, which involves small vessel disease and longer survival. The original recognition of subclasses of VaD should probably be credited to Otto Binswanger, who described subcortical arteriosclerotic encephalopathy upon pathological verification of cerebral white matter (WM) lesions in patients with hypertensive disease. Clinical, neuroimaging, and pathological features have facilitated the definition of VaD or vascular cognitive impairment subtypes and allowed the appreciation of specific risk factors and the evaluation of treatment or prevention strategies.

Distinguishing between neurodegenerative and vascular processes that result in dementia is pertinent to identifying the causes and treatment options. However, unselected community-based studies show brains of demented subjects often exhibit more than one type of pathology. Vascular lesions are frequently found to coexist with AD-type of lesions in older subjects. Even in prospectively assessed AD subjects, entirely pure neurodegenerative pathology appears to be an exception, particularly among the oldest old (>85 years). Autopsied brains of AD subjects frequently bear cerebrovascular pathology consisting of degenerative microangiopathy, cerebral amyloid angiopathy, cerebral infarcts, and, to a small extent, intracerebral hemorrhages. The coexistence of two or more pathologies is not novel to dementia. This was apparent from the description of Alzheimer’s first case, Auguste D. In his original report, he had written that, besides “one or several fibrils in otherwise normal cells, and numerous small miliary foci . . . and . . . storage of peculiar material in the cortex, one sees endothelial proliferation and also occasionally neovascularization”. While it is unlikely to be known whether the vascular changes represented angiogenesis as a result of ischemic injury or microvascular degeneration per se, the important question is whether the described microvascular pathology was coincident with or causal in the neurodegenerative changes leading to AD. However, it is now apparent vascular and neurodegenerative pathologies are additive in influencing the clinical presentation of dementia. Cerebrovascular disease or strokes appear to not only hasten the pathological processes leading to dementia but also increase the possibility that individuals with AD lesions in their brains will exhibit dementia. Although cerebrovascular disease may be the main cause of degeneration and dementia, it is likely a cerebrovascular event overcomes the brain’s reserves in individuals being compromised by neurodegenerative changes related to AD pathology.

**CONTROL AND REGULATION OF CEREBRAL PERFUSION**

**Cerebral microvasculature and blood-brain barrier**

Several clinical studies suggest blood-brain barrier (BBB) dysfunction is involved in the progression and pathogenesis of AD. The cerebrospinal fluid (CSF)/serum albumin ratio (commonly used indicators of BBB integrity) is increased in AD patients with particularly comorbid vascular disease. In 85-year-old AD patients, higher CSF/serum albumin ratios were reported, but the indications of disturbed BBB function were evident even before the onset of disease. The positive correlations between CSF-albumin index and measures of disease progression over 1 year in a subgroup of AD patients also suggest BBB impairment could modify disease progression. The relative dysfunction of the BBB may increase the possibility of substances penetrating the BBB more rapidly to interact with neurons, and initiating a cascade of events involving amyloid accumulation and Alzheimer encephalopathy (Figure 2).

Prior biochemical and morphological studies (Table 2) have reported a variety of age-related alterations in the intracranial vessels, including the perforating arteries, arterioles, and capillaries in animals and man. Cerebral arteriosclerosis, focal constrictions, and stiffening of the vessel wall resulting from increased collagen fibers and extracellular matrix components result in loss of distensibility or elasticity that would affect brain perfusion. The terminal type arterioles of the deep WM are particularly vulnerable targets in the elderly. Thus, age-related increases in both the prevalence and severity of tortuosity of vessels in the WM may contribute to a chronic hypoxic state that is attributed to the increasing long-term disability in the elderly. In addition, cerebral amyloid angiopathy, microbleeds, and atherosclerosis affecting the neocortical perfusing surfaces would make not only the circumscribed neuronal populations behind them vulnerable but also the distal fields of the end arteries. When the vascular changes are compounded by neurodegenerative processes, the outcomes are predicted to be worse.

Age-related changes in cellular elements of the neurovascular unit (Table 2), which consist of focal necrosis
of the cerebral endothelium, accumulation of extracellular matrix components within the vascular basement membrane, decreased endothelial mitochondrial density, increased pinocytotic vesicles, loosening of tight junctions, loss of the perivascular nerve plexus, changes in the astrocytic endfeet, and selective degeneration of the microvascular tree, have also been described. These changes are more intense in brains from AD subjects, which also exhibit convolutional abnormalities and “collapsed” or attenuated capillaries in cortical lobes. This vascular phenomenon, associated with amyloid β deposits in all cortical lobes, is also evident in Down’s syndrome. The microvascular changes imply abnormalities in the patency of the brain microvasculature and breach of the BBB. These descriptions support previous conclusions on disturbances in local perfusion and decreased

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**Table 2** Features of the cerebral microvasculature and blood-brain barrier in aging and neurodegenerative dementia.

<table>
<thead>
<tr>
<th>Cellular feature or type/source of cells</th>
<th>Morphological changes</th>
<th>Biochemical markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral endothelium loss of glucose transporter, Na+/K+ ATPase</td>
<td>Loss of cytoplasm and endoplasmic reticulum; increased pinocytosis</td>
<td>↓ glucose transporter-type 1, Na+/K+ ATPase, CD31, CD34</td>
</tr>
<tr>
<td>Vascular basement membranes increase in collagen proteins and perlecan</td>
<td>Thickening of the extracellular matrix, collagen fibers</td>
<td>↑ collagens, perlecan, fibrinogen, matrix metalloproteinases</td>
</tr>
<tr>
<td>Perivascular cells</td>
<td>Increased astrocytic feet</td>
<td>↑ GFAP reactivity</td>
</tr>
<tr>
<td>Arteries/arterioles</td>
<td>Loss of vascular smooth muscle cells; increased microthrombi</td>
<td>↑ CD68, macrophage markers</td>
</tr>
<tr>
<td>Cerebral microvessels</td>
<td>Changes in cerebral endothelium and perivascular cellular elements</td>
<td>↑ α-smooth muscle actin; accumulation of amyloid β</td>
</tr>
</tbody>
</table>

† Results derived from previously published reviews and studies and unpublished data (Kalaria et al.).

‡ Arrows indicates decrease or increase.

Abbreviations: CD, clusters of differentiation markers; GFAP, glial fibrillary acid protein; GGT, γ-glutamyl transpeptidase.
oxygen tension within the neuropil as a consequence, so that neurons farthest away from the capillary surface are divested. Changes in the dynamics of supporting cells within the neurovascular unit, such as astrocytes, microglia and pericytes, may bear additional consequences in reactive or compensatory mechanisms. Conversely, evidence from elegant studies by Zlokovic has indicated microvascular abnormalities lead to faulty BBB clearance of amyloid β through the deregulated low-density lipoprotein-related protein 1 and receptor for advanced glycation endproducts (RAGE)-mediated transport. These impaired clearances of amyloid β and glycation endproducts then lead to aberrant angiogenesis, remodeling of the cerebral microvasculature, and eventual arterial dysfunction, which in turn initiates neurovascular uncoupling.

Vascular functional proteins in brain degeneration

Selective changes in key BBB proteins, including the glucose and nutrient transporters and the neurotransmitter receptors and degrading enzymes (Table 2), have been recorded in the cerebral microvasculature of demented subjects. The glucose transporter (type I), a protein integral to the cerebral endothelium, is reduced in the microvasculature of AD subjects compared to aging controls. Whether amyloid β deposition in brain microvessels in AD directly impairs synthesis or enhances degradation of the protein remains unknown, but profound effects on the permeability and function of the brain endothelium would be expected. These in vitro observations are corroborated by positron emission tomography studies showing the transport of glucose (kinetic parameter k1) into the brains of AD subjects is diminished. Moreover, uptake of 2-deoxy-D-glucose is also decreased, further implying impairment of hexokinase activity in the cerebral microvasculature. The decreased activity directly relates to the reduced glucose transporter protein findings and suggests microvessels deprived of glucose may be using other sources of metabolic fuel. Impairment in glucose transport or metabolism may also induce overactivation of glycogen synthase kinase-3beta, and this, together with downregulation of the O-GlcNAcylation process, promotes abnormal hyperphosphorylation of tau, leading to neurofibrillary pathology.

Biochemical approaches demonstrate selective changes in markers of the BBB or in cerebral microvessels in AD. Specific proteins, including the cholinesterases and amyloid precursor protein (APP)-cleaving proteases, may promote or deregulate amyloid β deposition in the vasculature to affect the cerebral microcirculation, which is considered a source of neurotoxic and inflammatory mediators. It is not unlikely that breakdown of the BBB occurs focally and transiently over a protracted period in association with reactive mechanisms that direct repair and growth. For example, vascular endothelial growth factor reactivity is substantially increased in astrocytes and perivascular deposits in brains of subjects with AD, indicating angiogenic signals are induced to counter insufficient vascularity or reduced perfusion (oligemia). However, the ensuing pathology probably overwhelms the compensatory mechanisms, so that the angiogenic or growth response is stunted.

Cerebrospinal fluid-blood barrier

The choroid plexus CSF system ensures not only CSF secretion and clearance but also the constant scrutiny of nutrients and harmful substances to maintain homeostasis. Both the quantity (by 50%) and the quality of the CSF decline with age and in neurodegenerative disease. The choroidal epithelium undergoes atrophy, thickening of the basement membrane, and stromal fibrosis and accumulates Biondi ring tangles and lipofuscin with age, even more so in AD. These changes together with activation of inflammatory mechanisms are responsible for an estimated 50% reduction in turnover and alteration of CSF contents. The impaired ability of the choroid plexus to clear molecules from the CSF in older age has potentially serious implications for brain clearance of key proteins, including amyloid β in AD subjects. This is analogous to the early vascular changes in APP in overexpressing transgenic (Tg) mice, which show regional specific microvascular anomalies may precede the more profound pathologies that characterize neurodegeneration and AD.

Cerebral autoregulation

Autoregulation of CBF is the first-order mechanism that ensures the flow and supply of oxygen, glucose, and nutrients through the vascular beds remain within the upper and lower limits of the autoregulatory range (50–160 mm Hg) during fluctuations in systemic arterial pressure. Cerebral resistance arteries dilate or constrict during changes in arterial pressure. Aging-related changes in the systemic circulation and degenerative changes in the extracerebral resistance arteries may shift the lower and upper limits of the autoregulatory plateau to cause hypertensive encephalopathy or cerebral hypoperfusion, which may not necessarily cause ischemic injury as obvious as in stroke but oligemia or hypovolemia that overwhelms the compensatory mechanisms, leading to disruption of the microcirculation, damage to the cerebral endothelium, breach of the BBB, and edema. Neurogenic responses via the brainstem autonomic nuclei, which degenerate in age-related brain disorders, may also cause disruptions in CBF autoregulation that may increasingly cause orthostatic hypotension.
and syncope. In addition, pathological changes in vascular wall smooth muscle (myogenic effect) and altered release of metabolic factors could profoundly influence autoregulatory responses, which would have a high impact in the oldest old (>85 years of age). Animal studies reveal autoregulation fails in Tg mice overexpressing APP and accumulating amyloid β deposits. In the APP-expressing Tg mice, vascular alterations are observed at 3 months of age, much in advance of amyloid β deposition and cognitive decline.2

**Neurovascular coupling**

Functional hyperemia or neural activity coupling with CBF is another vital mechanism to protect the tight dynamic relationship between the cellular elements of the neurovascular unit and homeostasis of the cerebral microenvironment.2 Sensitive neuroimaging methods confirm aging-related regression in global and regional measures of CBF (~4 mL/min/year), cerebral metabolic rate for oxygen, glucose oxidation, cerebral blood volume, and, not surprisingly, CSF secretion and flow.49 In AD, more pronounced regional effects are apparent.2 Under certain pathological and pharmacological conditions, CBF and metabolism are uncoupled, likely resulting from weaker muscle tone, failure of angiogenesis, or breakdown in the molecular communication between neurons and microvessels.38 The microvessels undergo several changes, including loss of pericytes,1 that indicate the BBB in the elderly is less likely to compensate for leaks.17 The characteristic deposition of amyloid in cerebral vessels in AD exacerbates vascular dysfunction and promotes hypoperfusion. APP-expressing Tg mice also show impaired reactivity of the cerebral circulation to endothelium-dependent vasodilators, a major vasoregulatory mechanism. This is consistent with the diminished vasodilator responses attributed to altered modulatory function of the endothelium rather than to impairments in vascular smooth muscle per se during aging.49

**VASCULAR RISK FACTORS IN NEURODEGENERATION AND DEMENTIA**

Recent advances indicate dementia risk is modified by perinatal events, education status, nutritional intake, degree of physical activity, and cognitive and social engagement.49 Several of these factors impact adult-onset vascular disorders such as strokes, hypertension, atherosclerotic disease, atrial fibrillation, diabetes mellitus, dyslipidemia, hyperinsulinemia, hyperglycemia, hyperhomocysteinemia, and obesity (Table 3).50 It is increasingly recognized that factors that increase cardiovascular disease or brain vascular pathology exacerbate the onset or progression of late-onset dementias (Figure 2). While data from individual studies that may relate to the clinical diagnosis of dementia vary, carriers of the apolipoprotein E ε4 allele in general appear at greater risk for the presence of vascular disease. However, the evidence for single clinically defined cardiovascular risk factors associated with incident AD is inconsistent.51 Some genetic influences or environmental factors may modify the progressive changes that define the final phenotype and burden of brain pathology.11 While randomized or controlled trials of risk factor modification (with multiple simultaneous interventions) are lacking, it is encouraging that interventions of cognitive and physical activity were shown to improve cognitive performance and slow cognitive decline.52

**Strokes, silent infarction, and mixed pathologies**

In the elderly, stroke episode or history of transient ischemic attack increases the risk of AD up to threefold.53–55 Cerebral infarcts appear to accelerate AD progression and account for a large proportion of cases of mixed pathologies in older age groups.34,56–58 Silent brain infarction (without overt neurological sequelae) occurs with high prevalence in the healthy elderly, estimated at −5% in those 60 years of age in both genders.59,60 Almost 90% of these occur subcortically (and appear as lacunae in the basal ganglia), with the rest occurring in the neocortex. Silent infarcts double the risk of dementia, cause steeper cognitive decline (memory performance), and impact executive dysfunction.61,62

Patients with cerebrovascular disease who survive long may progress to develop dementia characterized by Alzheimer-type changes.55,64 Conversely, Henon et al.65 have shown severe cognitive impairment or low cognitive ability, which could represent AD, is also a risk for cerebrovascular disease or strokes.66 Stroke incidence was highest in those with severe impairment, and the association between cognitive impairment and incident stroke appears not to be mediated by systemic vascular disease. The elevated risk of subsequent strokes in older persons with cognitive impairment suggests cerebrovascular disease may play a direct role in cognitive impairment. Therapeutic monitoring or treatment of the vascular component should ameliorate or prevent worsening of dementia symptoms in individuals with a diagnosis of AD or other insidious neurodegenerative disease.7

Neuropathological studies provide further evidence for considerable overlap between AD and cerebrovascular disease.53 High proportions of individuals fulfilling the neuropathological diagnosis of AD have significant cerebrovascular lesions,11–13,67–69 while VaD patients frequently show extensive AD-type changes.70,71 Thus, in one prospective study70 in clinically diagnosed VaD patients, at autopsy nearly 60% were found to have AD pathology.
alone, and 40% had AD pathology in combination with cerebrovascular disease. Older patients diagnosed with VaD may accumulate some Alzheimer pathological features, e.g., cerebrall Amyloid β levels comparable to those seen in AD.72 The concomitant vascular pathology in terms of lacunae, microinfarcts, and arteriosclerosis appears to coexist by more than chance alone.73 For example, studies have emphasized the existence of a significant association between cortical microinfarcts and AD (32% cases versus 3% controls).57,74 The microinfarcts were restricted to watershed cortical zones, indicating disturbed hemodynamic factors were involved in the genesis of these vascular lesions that may precede Alzheimer’s symptoms.75 When both neurodegenerative, e.g., amyloid β deposits and neurofibrillary tangles, and vascular pathologies are present, the burden of dementia tends to be associated with small or microischemic lesions76,77 rather than large infarctions. These findings corroborate the importance of microvascular disease rather than macroscopic infarction as the critical substrate in dementia.78

Further clinical importance of the combined neurodegenerative and vascular pathologies is emphasized by the finding that dementia was worse and was compounded by the coexistence of both neuropathological features of AD and VaD in elderly nuns.13 In this prospectively assessed cohort with low vascular disease risk and in which there was no association between cerebral infarcts and AD type of pathology, it was estimated an eightfold greater burden of neocortical neurofibrillary tangles would be necessary to develop dementia in the absence of strategic cerebral infarction.13,79 Similarly, the Religious Orders Study found, although there was no interaction between infarctions and AD pathology,13 the presence of one or more infarctions independently increased the odds of dementia by nearly threefold.80 The Honolulu Aging in Asians Study provides additional support for the independence of AD and vascular neuropathology.81 These reports do not show whether ischemic cerebrovascular disease contributes directly to the development of Alzheimer’s pathology, but they indicate vascular changes have an additive effect and reduce the threshold for dementia diagnosis in patients with an otherwise asymptomatic low-grade Alzheimer’s pathology.82

### Table 3  Vascular risk factors for neurodegeneration, cognitive impairment, and dementia.

<table>
<thead>
<tr>
<th>Vascular risk factor*</th>
<th>Individual features</th>
<th>Methods of diagnosis</th>
<th>Degree of risk†</th>
<th>Genetic influence‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke(s)</td>
<td>Silent infarcts</td>
<td>Clinical, imaging</td>
<td>+++</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Transient ischemic attacks</td>
<td>Clinical, imaging</td>
<td>+++</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Lacunar infarcts</td>
<td>Clinical, imaging</td>
<td>++</td>
<td>ApoE e4</td>
</tr>
<tr>
<td></td>
<td>Microinfarcts</td>
<td>Pathological</td>
<td>+++</td>
<td></td>
</tr>
<tr>
<td>Vascular pathology:</td>
<td>Carotid arteries</td>
<td>Clinical, imaging</td>
<td>++</td>
<td>ApoE e4</td>
</tr>
<tr>
<td>Atherosclerosis</td>
<td>Aortic arch</td>
<td>Pathological</td>
<td>++</td>
<td>ApoE e4</td>
</tr>
<tr>
<td></td>
<td>Circle of Willis</td>
<td>Pathological</td>
<td>+++</td>
<td>ApoE e4</td>
</tr>
<tr>
<td>Abnormal blood pressure</td>
<td>Hypertension: systolic BP &gt;130 mm Hg; diastolic BP &gt;95 mm Hg</td>
<td>Clinical, imaging</td>
<td>+++</td>
<td>ApoE e4</td>
</tr>
<tr>
<td></td>
<td>Hypotension</td>
<td>Clinical, imaging</td>
<td>++</td>
<td>–</td>
</tr>
<tr>
<td>Heart disease</td>
<td>Coronary artery disease</td>
<td>Pathological</td>
<td>+++</td>
<td>–</td>
</tr>
<tr>
<td></td>
<td>Atrial fibrillation</td>
<td>Clinical, imaging</td>
<td>++</td>
<td>–</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>High cholesterol</td>
<td>Clinical</td>
<td>++</td>
<td>ApoE e4</td>
</tr>
<tr>
<td></td>
<td>High triglycerides</td>
<td>Clinical</td>
<td>++</td>
<td>–</td>
</tr>
<tr>
<td>Homocysteine/folate</td>
<td>Hyperhomocysteinemia (&gt;13 mM)</td>
<td>Clinical</td>
<td>++</td>
<td>ApoE e4</td>
</tr>
<tr>
<td>metabolism</td>
<td>Diabetes mellitus</td>
<td>Diabetes type 2</td>
<td>+</td>
<td>ApoE e4</td>
</tr>
<tr>
<td>Metabolic syndrome</td>
<td>Insulin dysregulation</td>
<td>Clinical, imaging, pathological</td>
<td>+</td>
<td>ApoE e4</td>
</tr>
<tr>
<td></td>
<td>Several factors</td>
<td>Clinical</td>
<td>+++</td>
<td>–</td>
</tr>
<tr>
<td>Obesity</td>
<td>Body mass index</td>
<td>Clinical, imaging</td>
<td>++</td>
<td>–</td>
</tr>
<tr>
<td>Overweight</td>
<td>Skin-fold thickness</td>
<td>Clinical</td>
<td>+</td>
<td>–</td>
</tr>
</tbody>
</table>

* Factors that may directly or indirectly affect vascular tone, resilience, and reactivity are listed. Results are summarized from several population-based observational and longitudinal cohort studies.72
† Degree of risk (+++, high, >3-fold relative risk or hazard ratio; ++, moderate, 2–3-fold relative risk or hazard ratio; +, low, <2-fold relative risk or hazard ratio) was derived from published relative risk and hazard ratio values.
‡ The only consistent allelic influence identified.

Abbreviations: ApoE, apolipoprotein E.

### White matter hyperintensities

Progressive age-related changes in intracerebral vessels or presence of infarcts may result in WM abnormalities in as many as 96% of those over 65 years of age.83 WM abnormalities are seen as WM74,84 hypersignals in
T2-weighted or fluid-attenuated inversion recovery sequences on magnetic resonance imaging. Significant risk factors for more severe white matter hyperintensities (WMH) include older age, history of hypertension, prior stroke, presence of diabetes, smoking habit, and clinically silent strokes. The pathological correlates of WMH comprise regions of deep WM pallor or myelin loss, axonal disruption, and arteriosclerosis within small-to-medium sized arteries with perivascular spaces. These changes are worsened by edema and diffuse damage of the BBB, with chronic leakage of fluid and macromolecules. Multidisciplinary correlalory studies show both deep WM and periventricular hyperintensities represent primarily oligemic tissue damage, which may be accompanied by a Wallerian type of axonal degeneration secondary to neurodegenerative processes and lead to dementia (Figure 2).

Past studies have attempted to assess correlations between the degree of WMH from magnetic resonance imaging and cognitive function or disability in the elderly. Although distinctions between periventricular and deep WM may be arbitrary, it appears the total WMH volume is a critical measure. Most studies with cohorts of variable size reveal declines in frontal lobe functions that include executive tasks, attention, and motor and processing speed rather than memory per se and appear to be associated with increased WMH volume. In the Leukoaraiosis and Disability cohort, executive dysfunction was attributed to WM lesion severity in the nondisabled elderly. On the other hand, volume of periventricular WMH rather than deep WMH at baseline and progression was longitudinally associated with decline in processing speed. Severe WMH has likewise been reported to increase the risk of disability and death in community-dwelling elderly without stroke or other neurological disease. Increased WMH and the presence of lacunar infarcts, indicative of subcortical vascular disease, are associated with greater global atrophy. An association between WMH severity and medial temporal atrophy was reported in one study of siblings affected and at risk for AD, consistent with demyelination secondary to AD neuronal damage.

Hypertension

Alterations in arterial pressure during aging have been strongly implicated in brain degeneration and dementia. Many studies have confirmed a history of hypertension during midlife may increase the risk of dementia, particularly AD. In the first longitudinal study, Skoog et al showed increased systolic (>160 mm Hg) and diastolic (>95 mm Hg) blood pressure 10–15 years before they were factors in the onset of AD. The risk of developing dementia between the ages of 80 and 85 years increased with increasing blood pressure at the age of 70 years, even when the increase was within the lower ranges of blood pressure values obtained. A long-standing increase in blood pressure may increase the risk of dementia and AD by inducing small-vessel disease, WM changes, and cerebral hypoperfusion by disrupting vaso-regulatory functions. However, atherosclerotic disease leading to cerebral hypoperfusion has also been implicated. In later life and after the onset of dementia, blood pressure actually decreases, suggesting cerebral atrophy or intrinsic neuropathological changes are responsible for lowering pressure.

Pathological studies have revealed hypertensive individuals with elevated systolic and diastolic pressures in midlife exhibit an increased burden of AD-type neurodegenerative lesions that include neuritic plaques and neurofibrillary tangles, which are also linked to low brain weight. A few trials also show the use of antihypertensive drugs offers some protection from the risk of dementia. However, there is no convincing evidence from the currently published trials indicating that lowering blood pressure in late life prevents the development of dementia or cognitive impairment in hypertensive patients with no apparent prior cerebrovascular disease.

Atherosclerosis and dyslipidemia

In comparison with the risk associated with hypertension, the risk of developing dementia after hypercholesterolemia is less robust. This may relate to how studies are conducted and the age at which cholesterol concentrations are determined. However, using Doppler scanning, the Rotterdam investigators concluded atherosclerosis, when exhibited as carotid artery thickening or accumulation of wall plaques in the elderly, is a strong risk factor for late-onset AD and VaD. On the other hand, cholesterol levels measured in midlife were associated with higher risk of AD but not VaD. Total cholesterol and low-density lipoprotein concentrations and a history of diabetes have also been shown to be associated with more rapid cognitive decline in individuals with AD. Consistent with the increased risk of AD, subjects with coronary heart disease also exhibit an increased amount of brain amyloidosis. It is clear that high cholesterol and other lipids play a role in increasing risk, but the course of the converging pathways and how this occurs are debated.

Diabetes and metabolic syndrome

Several epidemiological studies show that a history of adult-onset diabetes mellitus increases the risk of cognitive impairment and dementia in the elderly. The
The risk is even higher in individuals expressing taenioic acids, flavonoids, and the B vitamins—especially omega-3 fatty acids, docosahexaenoic and eicosapentaenoic acids. Diets that emphasize polyphenols, including resveratrol, enhancing vascular tone, and countering atherosclerosis may offer protection by countering inflammation, dementia. This suggests a faster decline in body mass declining body mass in late life appear to reduce risk of diabetes or other cardiovascular-related morbidities. Conversely, higher baseline body mass index and slower rate of cognitive decline. Fish suggests regular consumption of fish is related to lower risk of AD and VaD, independent of the development of diabetes or other cardiovascular-related morbidities. Accumulating evidence suggests changes in lifestyle factors, such as increasing physical activity, will decrease the risk of developing dementia in later life. Most studies show a reduced rate of age-related cognitive decline and a decreased risk of incident dementia or AD in individuals who exercise regularly. In a prospective cohort study, higher physical activity was identified to reduce the risk of dementia in community-dwelling elderly people. In the largest clinical trial of its kind, physically active volunteers with memory...
problems exhibited significant improvement in cognition after a 24-week intervention.

The effects of physical exercise on vascular health may be obvious, but neuroimaging studies\(^{40}\) suggest the more aerobically fit older adults lose less grey matter. Likewise, whole-brain volume was found to be positively associated with aerobic fitness levels among patients with early-stage AD.\(^{141}\) Higher aerobic fitness levels also have been associated with larger hippocampus, increased blood flow, oxygen delivery, and better spatial memory.\(^{142}\) In related studies on prevention, increased physical activity in midlife\(^{138}\) has been found to be associated with less neocortical atrophy in the elderly. The latter association was independent of atherosclerosis and brain infarcts. The likely mechanisms through which exercise induces brain growth and improves cognition include upregulation of brain-derived neurotrophic factor and preservation of synapses.\(^{143}\)

**CONCLUSION**

Several lines of evidence suggest a strong role for vascular factors in the etiology and pathogenesis of brain degeneration. Aging-associated cerebral microangiopathy inflicted at several control levels may explain deficits in autoregulation and neurovascular coupling and can be predicted to occur in subjects developing AD, the most common cause of dementia. Prevailing evidence from population- and community-based studies suggests pre-existing features of cardiovascular disease are strongly linked to late-onset dementia. These may lead to cerebral hypoperfusion, which involves key pathological substrates, mainly WM changes, axonal damage, and microinfarction. Unlike age and genetic background, vascular risk factors are modifiable through management and lifestyle changes that then help to protect the brain.

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