

# Microvascular Contribution to Late-Onset Depression: Mechanisms, Current Evidence, Association With Other Brain Diseases, and Therapeutic Perspectives

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## ABSTRACT

Depression is common in older individuals and is associated with high disability and mortality. A major problem is treatment resistance: >50% of older patients do not respond to current antidepressants. Therefore, new effective interventions for prevention and treatment of depression in older individuals need to be developed, which requires a better understanding of the mechanisms underlying depression. The pathophysiology of depression is multifactorial and complex. Microvascular dysfunction may be an early and targetable mechanism in the development of depression, notably depression that initiates in late life (late-onset depression). Late-onset depression commonly co-occurs with other diseases or syndromes that may share a microvascular origin, including apathy, cognitive impairment, dementia, and stroke. Together, these disabilities may all be part of one large phenotype resulting from global cerebral microvascular dysfunction. In this review, we discuss the pathophysiology of microvascular dysfunction-related late-onset depression, summarize recent epidemiological evidence on the association between cerebral microvascular dysfunction and depression, and indicate potential drivers of cerebral microvascular dysfunction. We also propose the hypothesis that depression may be a manifestation of a larger phenotype of cerebral microvascular dysfunction, highlight potential therapeutic targets and interventions, and give directions for future research.

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Depression is a large contributor to global disability in older individuals. Major depression occurs in 2% of adults aged 65 years or older, and its prevalence rises with increasing age. In addition, 10% to 15% of older adults have clinically significant depressive symptoms, even in the absence of major depression (1). Major depression and depressive symptoms in older adults are associated with frailty (2), lower quality of life (3), and 1.5- to 2-fold higher mortality risk (4,5). However, current antidepressant medications targeting neurotransmitters are less effective (6,7) and have more side effects (8) in older patients than in younger patients. More than 50% of older patients do not respond to such treatment (9). Given the aging society, better understanding of the underlying mechanisms of depression in older individuals is required so that more effective prevention and treatment strategies can be developed.

The pathophysiology of late-life depression is multifactorial and complex. Patients with late-life depression are a heterogeneous group, including individuals with late-onset depression, in whom the initial depressive episode occurs after age 60 years, and individuals with early-onset depression who already had a first depressive episode earlier in life (10). Several years ago, it was postulated that cerebrovascular damage may contribute to depression via disruption of brain regions

involved in mood regulation (11), notably, damage to subcortical regions (12,13). This mechanism may be particularly relevant in older individuals without a history of depression (i.e., late-onset depression). Subsequent studies have identified evidence for this vascular depression hypothesis (10,14,15) and suggest that vascular depression may be a specific subtype of depression (Table 1). However, these studies mostly focused on late stages of cerebrovascular disease when irreversible brain damage was already evident. For effective interventions, it is crucial to identify mechanisms that can be targeted in an early stage of the disease before irreversible damage occurs.

We propose that microvascular dysfunction is an early and targetable mechanism in the development of late-onset depression. Late-life depression commonly co-occurs with other syndromes or diseases that may share a microvascular origin, including apathy, cognitive impairment, dementia, and stroke. Together, these disabilities may all be part of one large phenotype resulting from global cerebral microvascular dysfunction.

In this review, we discuss the functions of the cerebral microvasculature and how microvascular dysfunction may contribute to the development of late-onset depression.

Cerebral microvascular dysfunction is the overlying construct that includes (or can be defined by) blood-brain barrier leakage, impaired cerebral autoregulation, impaired neurovascular coupling, and disturbed capillary flow patterns (16,17) (Table 1). We review emerging evidence that cerebral microvascular dysfunction and damage are present in older individuals with depression and are associated with apathy, cognitive dysfunction, and stroke in these individuals. We will also indicate which factors may contribute to cerebral microvascular dysfunction in depression, highlight potential interventions, and give directions for future research.

In discussing these issues, we rely to an important extent on data obtained in humans, because currently, no experimental model exists that approximates the complex underlying mechanisms and heterogeneous manifestations of late-onset depression in patients. However, experimental studies are crucial to understand the individual causative pathways by which impairment of the different functions of the microvasculature can contribute to depressive symptoms. For example, recent basic studies have provided important insights into the role of stress susceptibility and blood-brain barrier leakage in the development of depressive symptoms. These studies suggest that maintenance of blood-brain barrier integrity could represent an approach to develop therapeutic strategies to treat depression. This has been discussed in recent reviews (18–20).

### FUNCTIONS OF THE CEREBRAL MICROVASCULATURE

Optimal function of the brain depends on a healthy microvasculature (21,22). The cerebral microcirculation represents the site of resistance to flow and the surface of exchanges. It is the major component of the blood-brain barrier and has a crucial role in the regulation of cerebral perfusion via control of neurovascular coupling and cerebral autoregulation (Table 1) (16,17,23).

### CONTRIBUTION OF MICROVASCULAR DYSFUNCTION TO DEPRESSION

The mechanistic pathways by which microvascular dysfunction may contribute to depression are shown in Figures 1 and 2. Microvascular dysfunction includes increased blood-brain permeability and impaired blood perfusion regulation, with disturbed neurovascular coupling and cerebral autoregulation (17). These impairments can each lead to focal brain injury, which may damage neuronal circuits involved in mood regulation and contribute to clinical depressive symptoms and negatively influence the effect of antidepressants (10,15).

### EVIDENCE OF CEREBRAL MICROVASCULAR DYSFUNCTION IN DEPRESSION

A summary of studies in adults on the association between cerebral microvascular function and structure and depression is shown in Table 2, and these studies are discussed in the sections below. Most studies found an association between microvascular dysfunction and depression, although not all results are consistent. Most studies had a case-control design and included relatively small ( $N < 100$ ) clinical samples of individuals with a current depressive episode.

### Blood-Brain Barrier Permeability

Evidence for the presence of increased blood-brain barrier permeability in depression in humans comes mostly from biochemical studies that assessed the ratio of cerebrospinal fluid albumin to serum albumin level, which is known as the albumin quotient (for explanation of albumin quotient, see Table 1). One case-control study (24) found a higher albumin quotient among older patients with depression than among older individuals without depression. Other studies among patients with depression found a higher albumin quotient in a subset of these patients than previously reported reference values in the general population (25,26), and a higher albumin quotient was associated with suicidality (27). Additionally, postmortem studies have found evidence of structural alterations of the blood-brain barrier in depression. This includes an increased endothelial expression of intercellular adhesion molecule-1 (28–30), a marker of microvascular endothelial dysfunction, and reduced coverage of the endothelium by astrocyte end feet in the prefrontal cortex (31). Other studies found an increased expression of endothelial protein claudin-5, a key tight-junction protein in the nucleus accumbens (32,33). The prefrontal cortex and nucleus accumbens are crucial regions within the brain's reward circuitry, and their function is impaired in individuals with major depression (34). Reduced expression of claudin-5 has also been found in an animal model of depression, and this was related to greater blood-brain permeability in this model (32).

### Cerebrovascular Reactivity, Cerebral Autoregulation, and Resting Cerebral Blood Flow

Microvascular dysfunction may manifest as disrupted cerebrovascular reactivity (for explanation of cerebrovascular reactivity, see Table 1). One prospective, population-based study showed that lower cerebrovascular reactivity was associated with higher risk of depression in older individuals (35). Additionally, most cross-sectional studies (36–41), but not all (42), found lower cerebrovascular reactivity in individuals with depression than in individuals without depression. However, most of these studies measured cerebrovascular reactivity at the level of a large artery with use of Doppler ultrasound, and only some studies (38,42) measured cerebrovascular reactivity at the tissue level with use of magnetic resonance imaging or single-photon emission computed tomography. The interpretation of vasoreactivity measured in a large artery is difficult because it may reflect the function not only of arterioles and capillaries but also of larger cerebral arteries (43).

Microvascular dysfunction might also contribute to altered cerebral autoregulation (for explanation of cerebral autoregulation, see Table 1). However, data on cerebral autoregulation in depression are scarce. Altered cerebral autoregulation was identified in a recent small cross-sectional study (44), but replication of this finding is needed.

Altered resting cerebral blood flow or blood flow velocity may be another manifestation of cerebral microvascular dysfunction. However, the interpretation of resting cerebral blood flow is complex, because reduced resting cerebral blood flow might be a cause of tissue damage or a consequence (i.e., reflect loss of viable tissue), or both. Lower cerebral blood flow

**Table 1. Selected Key Terms and Definitions**

Terms	Definition and Comments
Depression Heterogeneity	Depression is a highly heterogeneous syndrome driven by varying genetic and neurophysiological mechanisms, which give rise to varying symptom profiles, clinical trajectories, and treatment outcomes. This heterogeneity may be more apparent in late-life depression, because aging-related changes across multiple organ systems may contribute to depression (10).
Vascular Depression	A subtype of depression characterized by a distinct clinical presentation and an association with cerebrovascular damage. A recent consensus report (14) suggested the following criteria for vascular depression: 1) evidence of vascular pathology in elderly subjects with or without cognitive impairment, 2) absence of previous depressive episodes preceding obvious cerebrovascular disease, 3) presence of cerebrovascular risk factors, 4) coincidence of depression with cerebrovascular risk factors, 5) clinical symptoms characteristic of vascular depression (executive dysfunction, decrease in processing speed, and lethargy), and 6) neuroimaging data confirming cerebrovascular disease. However, these diagnostic criteria for vascular depression are, until now, not widely accepted, and vascular depression has not been included in formal psychiatric manuals.
Cerebral Microvascular Function and Dysfunction	Core functions of the cerebral microcirculation, defined as cerebral vessels with a diameter <150 μm (arterioles, capillaries, and venules), are to 1) optimize the delivery of nutrients and removal of waste products in response to variations in neuronal activity, 2) maintain the cerebral interstitial milieu for proper cell function, and 3) decrease and stabilize pulsatile hydrostatic pressure at the level of capillaries (16,17). Cerebral microvascular dysfunction is defined as an impairment in any of these functions.
Blood-Brain Barrier	A tightly linked monolayer of endothelial cells, together with a basement membrane, astrocyte end feet, and mural cells (pericytes in capillaries and vascular smooth muscle cells in arterioles). The blood-brain barrier separates the circulating blood and brain compartments and strictly regulates blood-to-brain and brain-to-blood transport of solutes to maintain the highly controlled internal milieu of the central nervous system (16,135).
Neurovascular Coupling	Mechanism by which the brain can rapidly increase local blood flow to activated neurons (132). Upon an increase in neuronal activity, astrocytes signal to endothelial cells the paracrine release of vasoactive agents. These signals engage smooth muscle cells and, possibly, pericytes to induce vasodilatation, reduce cerebrovascular resistance, and increase local cerebral blood flow (22).
Cerebral Autoregulation	Ability of the cerebrovasculature to maintain a constant level of global brain perfusion despite varying arterial blood pressure (22). This ensures a relatively constant level of blood flow to meet the high metabolic demand of the brain (137). Arterioles together with larger cerebral arteries regulate this response by varying cerebrovascular resistance mediated by myogenic responses (22).
Albumin Quotient	Ratio of cerebrospinal fluid albumin to serum albumin level. Albumin originate solely from the systemic circulation and cannot cross an intact blood-brain barrier. An increase in the albumin quotient can, thus, be used as an indirect measure of blood-brain permeability.
Cerebrovascular Reactivity	Change in flow in response to increased neuronal activity (i.e., neurovascular coupling) or a metabolic or vasodilatory stimulus, e.g., increase in partial pressure of carbon dioxide (138). This response reflects the ability of the cerebrovasculature, notably, arterioles and capillaries, to dilate in response to increased neuronal metabolic demand and is endothelium-dependent (22,139).

velocity assessed at the level of large cerebral arteries with Doppler ultrasound, which may be related to lower global cerebral perfusion (45), was associated with higher risk of incident depressive symptoms in individuals with heart failure (46) and with incident depression in a large population-based study (35). In addition, cross-sectional studies in older individuals with depression have found altered global (measured at the level of large arteries) or regional (at the tissue level) cerebral perfusion, independent of cerebral atrophy (47–49). In one study, regional cerebral perfusion was altered to a greater extent in individuals with late-onset depression (defined in that study as the first onset of the episode after the age of 60 years), compared with individuals with early-onset depression and individuals without any depression, and altered cerebral perfusion was associated with worse cognitive performance in these individuals (48).

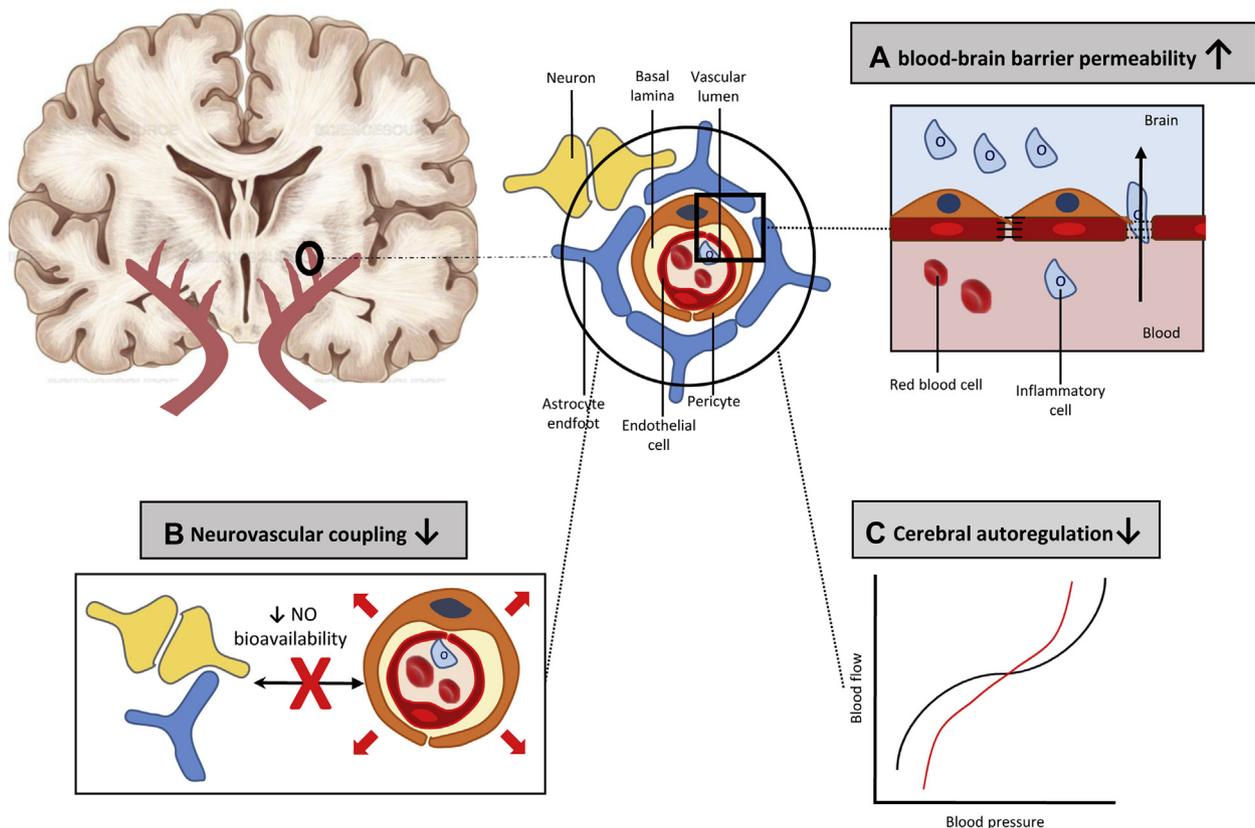
### Retinal Microvascular Changes

The retina offers a unique opportunity to study microvascular changes in the brain because it allows direct and reproducible visualization of a microvascular bed that shares anatomical and physiological similarities with the cerebral microvasculature

(50,51). To date, only two studies (52,53), both population based, evaluated the association between measures of the retinal microvasculature and incident depressive symptoms, but they had inconsistent findings. One study found that a reduced flicker light-induced retinal arteriolar dilatation response, indicating worse microvascular function, was associated with a higher incidence of depressive symptoms (52). Another study evaluated the association between retinal arteriolar and venular diameters and incident depression but did not find a statistically significant association (53).

### Features of Cerebral Small Vessel Disease

Cerebral microvascular dysfunction can also manifest itself as features of cerebral small vessel disease, which include white matter hyperintensities and lacunes of presumed vascular origin, cerebral microbleeds, perivascular spaces, total cerebral atrophy, and microinfarcts (54). These features are indirect or late-stage markers of small vessel abnormalities because they reflect brain parenchymal damage potentially related to various small vessel changes. Recent meta-analyses (55–57) have consistently shown that cerebral small vessel disease features are associated with a higher risk of depression.



**Figure 1.** Detrimental effects of cerebral microvascular dysfunction on the brain. Microvascular dysfunction may include increased blood-brain permeability (A) and impaired blood perfusion regulation, with disturbed neurovascular coupling (B) and impaired cerebral autoregulation (C) (17). Increased blood-brain permeability (A) leads to leakage of inflammatory proteins and cells and other plasma constituents into the perivascular space (16). Neurovascular coupling (B) involves a complex interaction between various cells (i.e., neuronal cells, astrocytes, endothelial cells, pericytes, and smooth muscle cells) and various mediators (16). Dysfunction of each of these components may contribute to disturbed neurovascular coupling. For instance, both endothelial and neuronal dysfunction may lead to lower release of endothelial- or neuronal-derived nitric oxide, leading to impaired vasodilatation (132). Cerebral autoregulation (C) is the ability of the cerebrovasculature to maintain a constant level of global brain perfusion despite varying arterial blood pressure (22). With impaired autoregulation, the normal autoregulation curve that expresses the relationship between cerebral blood flow and mean blood pressure (black curve) in panel (C) may become more linear and steeper, and perfusion may become pressure-dependent (red curve) in panel (C) (133).

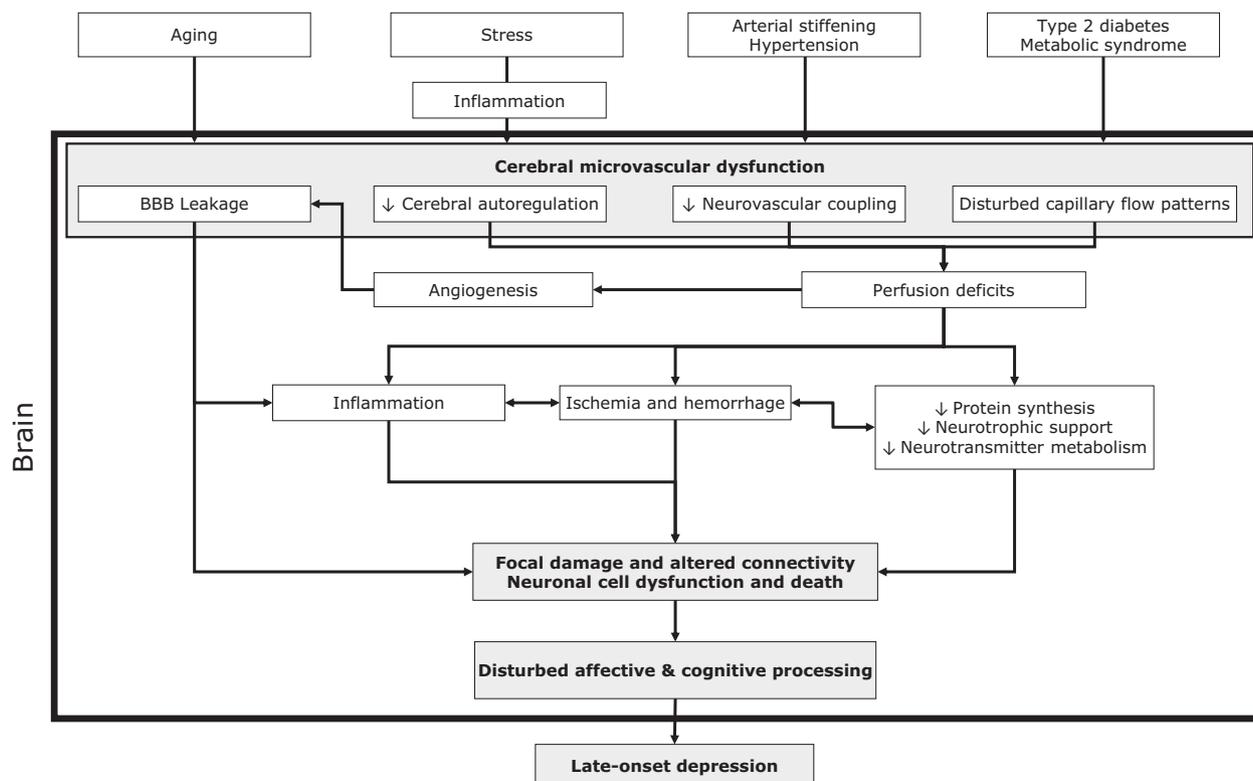
Strongest associations were found for features located in regions involved in mood regulation, i.e., frontal and subcortical brain regions, compared with features in other brain regions (56,58). In contrast, results of neuropathology studies (59–65) on the presence of cerebral small vessel disease in depression have been inconsistent. The results of these studies are, however, difficult to compare because of differences in patient populations, brain regions of interest, and the definitions used of cerebral small vessel disease features.

### CONTRIBUTION OF MICROVASCULAR DYSFUNCTION TO APATHY, COGNITIVE DYSFUNCTION, AND STROKE IN DEPRESSION

Depression, apathy, cognitive dysfunction, and stroke commonly occur together. Apathy, or diminished motivation, is a common symptom in late-life depression but may also exist independently of depression (66). In addition, late-life depression and apathy increase the risk of decline in any and multiple cognitive domains but most commonly in executive function

and processing speed (15). Furthermore, late-life depression and apathy are associated with a 1.5- to 2-fold higher risk of dementia (15,67) and stroke (68,69).

Increasing data suggest that the link between late-life depression, apathy, cognitive dysfunction, and stroke can be explained, at least in part, by microvascular dysfunction as a shared underlying mechanism. These disabilities may therefore be manifestations of a larger phenotype of global cerebral microvascular dysfunction. For example, the clustering of depression and executive dysfunction, also described as the depression-executive dysfunction syndrome (15), has been related to higher white matter hyperintensity volume in the frontal and subcortical brain regions (70) and is associated with a lower response to current antidepressant medications (15). Recent longitudinal data showed that only individuals with depressive symptoms that increased in late life and no other trajectories of depressive symptoms across the life course had higher white matter hyperintensity volumes (71). In addition, only this trajectory has been associated with greater decline in executive function (71) and higher risk of dementia (72,73).



**Figure 2.** Mechanistic pathway by which cerebral microvascular dysfunction may contribute to late-onset depression. Microvascular dysfunction-related increased blood-brain permeability leads to leakage of proteins and other plasma constituents into the perivascular space. This may directly damage neurons and is related to inflammatory and immune responses (16,17). Cerebral microvascular dysfunction also includes impaired blood flow regulation with impaired cerebral autoregulation and neurovascular coupling and disturbed capillary flow patterns (134). This can result in perfusion deficits, reduced oxygen extraction, and hypoxia. Hypoxia leads to activation of hypoxia-inducible transcription factors, which, in turn, triggers inflammation and expression of matrix metalloproteinases and proangiogenic factors (135). Matrix metalloproteinases damage endothelial tight junctions, contributing to increased blood-brain barrier permeability. Proangiogenic factors, including vascular endothelial growth factor, also increase the permeability of the blood-brain barrier and stimulate angiogenesis. Angiogenesis is associated with formation of capillaries that are leaky and poorly perfused and that lack pericyte support (21). Via these mechanisms, microvascular dysfunction can lead to local ischemia and hemorrhage and focal brain injury, ultimately leading to disturbed affective and cognitive processing and depression. BBB, blood-brain barrier.

Also, various measures of microvascular dysfunction (e.g., retinal microvascular changes and blood biomarkers) have been associated with apathy (74) and cognitive dysfunction (55,75,76) in individuals without depression. In addition, presence and progression of cerebral small vessel disease over time, notably, increase in white matter hyperintensity volume and incident lacunar infarcts, have been associated with a higher risk of dementia (55,77). Microvascular dysfunction has also been reported to be associated with an increased risk of stroke, notably lacunar ischemic stroke and deep hemorrhagic stroke (16), and with worse outcomes after stroke (78,79).

### **DRIVERS OF MICROVASCULAR DYSFUNCTION IN DEPRESSION: AGING, PSYCHOLOGICAL STRESS, ARTERIAL STIFFNESS AND HYPERTENSION, AND TYPE 2 DIABETES AND THE METABOLIC SYNDROME**

#### **Aging**

Aging of the vasculature is an important contributor to cerebral microvascular dysfunction. Aging has been associated with

increased blood-brain barrier permeability, lower cerebrovascular reactivity, altered cerebral autoregulation, and reduced cerebral microvascular perfusion (80). The factors involved in vascular aging are complex and include various cellular and molecular mechanisms, as reviewed previously (81).

#### **Psychological Stress and Inflammation**

Chronic stress is major risk factor for depression. For example, the association between objective stress-related environmental risk factors (e.g., neighborhood quality) and increased risk of depressive symptoms in adulthood is well established (82,83). Stress has multiple and complex effects on brain function and structure [as reviewed previously, e.g., (84,85)]. Emerging experimental data suggest that chronic stress also has detrimental effects on the microvasculature, mediated via inflammatory mechanisms, which may contribute to the development of depression (32,33,86). Chronic stress mobilizes the innate immune system and stimulates enhanced proliferation and release of inflammatory monocytes and neutrophils into the bloodstream (87). Animal studies have shown that this stress-induced inflammation can alter blood

**Table 2. Altered Cerebral Microvascular Function and Structure in Individuals With Incident or Prevalent Depression as Compared With Individuals Without Depression: Summary of Findings in Humans<sup>a</sup>**

Manifestation of Altered Cerebral Microvascular Function and Structure	Technique(s)	Findings in Individuals With Depression as Compared to Those Without
Increased Blood-Brain Barrier Permeability	Qalb; neuropathology	Increased blood-brain barrier permeability in cross-sectional studies (24–27). No prospective data available.
Reduced Cerebral Vasoreactivity	TCD; ASL; SPECT	One prospective study (35) found that cerebral vasoreactivity increased the risk of depression. Most cross-sectional studies (36–41), but not all (42), also found reduced cerebral vasoreactivity. Most of these studies determined vasoreactivity at the level of a large cerebral artery.
Impaired Cerebral Autoregulation	TCD	One cross-sectional study (44) found impaired cerebral autoregulation. No prospective data available.
Altered Resting Cerebral Blood Flow	TCD; SPECT; ASL; PC-MRA	In two prospective studies (35,46), lower cerebral blood flow velocity, an indirect measure of blood flow, was associated with incident depression. No prospective data available on direct measures of cerebral blood flow. Cross-sectional studies (47–49) found altered regional or global cerebral perfusion independently of cerebral atrophy.
Retinal Microvascular Changes	DVA; funduscopy	One prospective study (52) showed that lower flicker light-induced vasodilatation is associated with increased risk of depression, but another prospective study (53) did not find associations between microvascular diameters and depression.
Cerebral Small Vessel Disease	MRI: T1W, T2W, T2*W, FLAIR; neuropathology	Meta-analyses (55–57) found that cerebral small vessel disease features increase the risk of depression. Results are stronger for features in frontal and subcortical regions. Neuropathology studies (59–65) have found inconsistent results.

ASL, arterial spin labeling; DVA, dynamic vessel analysis; FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging; PC-MRA, phase-contrast magnetic resonance angiography; Qalb, cerebrospinal fluid/plasma albumin ratio; SPECT, single-photon emission computed tomography; TCD, transcranial doppler; T1W/T2W/T2\*W, T<sub>1</sub>-weighted/T<sub>2</sub>-weighted/T<sub>2</sub>\*-weighted MR images.

<sup>a</sup>Studies evaluated major depressive disorder according to DSM criteria (24–27,35–42,47–49,53,60–62,64,65), or presence of depressive symptoms based on questionnaires (35,40,44,46,52,53,59). The sample sizes of studies (*N*) were <50 (26,38,41,42,49,60,61,64,65), 50–100 (24,25,36,37,39,44,62), 100–500 (27,46–48,59), or >500 (35,40,52,53). Study designs included case-control (25–27,36–39,41,42,44,48,49,59–62,64,65) and cross-sectional (24,40) or longitudinal (35,46,52,53) cohorts. Population sources were clinical sample-based (25–27,36–39,41,42,44,46–49,60–62,64,65) and population-based (24,35,40,52,53,59). Studies included older adults (>60 years or older) only (24,35,38,40,42,47–49,53,59–62,64) or also included younger individuals (25–27,36,37,39,41,44,46,52). Of the studies investigating older individuals only, some excluded individuals with a depressive disorder before late life (38,47,48,62,65), whereas others did not (24,35,40,42,49,52,53,59–61,64).

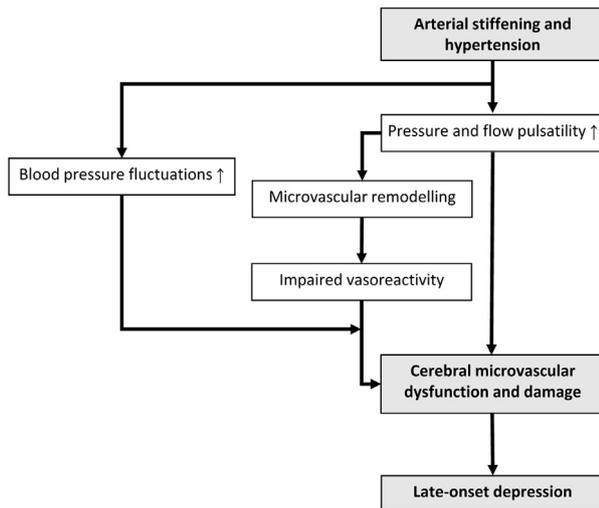
vessel morphology in the brain with discontinuous tight junctions, leading to greater blood-brain permeability (32,33,86). Greater blood-brain permeability was associated with depression-like behaviors in these models. For example, in a study of mice undergoing social defeat, a mouse model of chronic stress, it was shown that expression of the tight-junction protein claudin-5 in the blood-brain barrier was reduced in stress-susceptible animals (32). This promoted the passage of interleukin 6 across the blood-brain barrier and induced depressive-like behaviors in these animals. Furthermore, other studies showed that anti-inflammatory therapy was able to reduce stress-induced increases in blood-brain barrier permeability and lower depressive symptoms (88). Whether these findings can be translated to humans remains to be investigated.

### Arterial Stiffness, Hypertension, and Blood Pressure Fluctuations

Large artery stiffness and hypertension may lead to cerebral microvascular dysfunction (89). Stiffening of large arteries impairs their cushioning function and increases blood pressure and flow pulsatility (Figure 3). This increased pulsatile load may

transmit distally into the cerebral circulation and thereby contribute to cerebral microvascular damage (89). The microvasculature of the brain is particularly vulnerable because it is characterized by high flow and low impedance, allowing the pulsatile load to penetrate deeply into its microvascular bed (90). Consistently, recent population-based data (91) showed that greater stiffness of the carotid artery is associated with a higher risk of depressive symptoms. In addition, cross-sectional data from another large study (92) showed that the association between greater arterial stiffness and presence of depressive symptoms was in part explained, or mediated, by features of cerebral small vessel disease. In addition, some studies (93,94), but not all (95,96), have shown that hypertension is associated with a higher risk of depression in older individuals.

Arterial stiffening may also contribute to substantial fluctuations in blood pressure, including orthostatic hypotension and exercise-induced hypertension (89). Greater blood pressure fluctuations may further sensitize the brain to the harmful effects of impaired microvascular-related cerebral autoregulation and vasoreactivity, with cerebral hypoperfusion during hypotension and overexposure to high pulsatility at high pressure (Figure 3). In accordance, studies have shown



**Figure 3.** Presumed pathway by which arterial stiffness contributes to cerebral microvascular dysfunction and late-onset depression. Stiffening of large arteries impairs their cushioning function and increases pressure and flow pulsatility. This increased load may cause direct microvascular damage and may induce a microvascular remodeling response (89). This response initially serves to limit the penetration of the pulsatile load into the microvascular system by raising cerebrovascular resistance (136). However, this protective response may ultimately become unfavorable, leading to impaired vasoreactivity and hypoperfusion. In addition, arterial stiffening may cause excessive blood pressure fluctuations that may further sensitize organs to the harmful effects of impaired microvascular vasoreactivity (89).

that orthostatic hypotension (97) and exercise-induced hypertension (98) are associated with higher risk of depressive symptoms.

### Type 2 Diabetes and Metabolic Syndrome

Type 2 diabetes and late-life depression commonly co-occur; individuals with type 2 diabetes have a doubled risk for depression as compared with individuals without type 2 diabetes. Furthermore, individuals with depression have a 1.5 times higher risk of type 2 diabetes (99). The mechanisms underlying the relationship between type 2 diabetes and late-life depression are likely multifactorial and may include psychosocial factors, e.g., diabetes burden and distress, and biological factors, including central insulin resistance (100) and microvascular dysfunction (17).

Microvascular dysfunction is present in many organs in individuals with diabetes or the metabolic syndrome, including the brain (17). Some evidence also suggests that depression in diabetes may be associated with microvascular dysfunction. One cross-sectional study found that individuals with type 2 diabetes and depression had wider retinal arterioles than individuals with type 2 diabetes but without depression (101), consistent with an association between depression and early microvascular changes in diabetes. Moreover, a recent, population-based large study found that individuals with type 2 diabetes had greater increase in depressive symptoms over time, and cerebral small vessel disease partly explained this association (102). Type 2 diabetes and the metabolic syndrome are also associated with accelerated stiffening of large

arteries (89), and this may contribute to depression in these individuals (103). Importantly, cerebral microvascular blood flow may be increased in early type 2 diabetes, possibly to compensate for reduced oxygen extraction efficacy related to subtle, or early, microvascular dysfunction, whereas in more advanced stages of the disease, blood flow may be reduced (17). Because of this high flow state in early diabetes, the increased pulsatile load associated with arterial stiffening may penetrate more deeply into the cerebral microvascular bed and contribute to cerebral damage (89). This suggests that individuals with type 2 diabetes may be more vulnerable for the detrimental effects of arterial stiffening on the brain, but this requires further study.

### POTENTIAL THERAPEUTIC TARGETS AND INTERVENTIONS

Vascular-related depression is associated with poor response to current antidepressant treatments (104). In addition, there are no current evidence-based primary prevention pharmacotherapies for late-onset depression. The identification of cerebral microvascular dysfunction as a potential contributor to depression could allow for the development of more effective prevention and treatment strategies. In this context, targeting cerebral microvascular function as a complementary treatment strategy of late-onset depression would represent a paradigm shift in the management of late-onset depression.

Currently, no therapeutic agents are available that specifically enhance microvascular function in the brain. Yet, some established therapies that are approved for diseases other than depression have been linked to improved cerebral microvascular function and might also be beneficial in depression as discussed below. It has been hypothesized that some currently used antidepressant medications targeting neurotransmitters may also have vasoprotective effects. However, data in humans are scarce, and results have been inconsistent (105).

### Lifestyle Factors

Microvascular dysfunction might be at least partly reversible through weight loss and exercise (23). Recent meta-analyses suggest that exercise and weight loss interventions have a beneficial effect on depressive symptoms across a wide age range, including older individuals (106,107). To what extent any effects of these interventions are mediated by improvement of microvascular function remains to be elucidated.

### Pharmacological Interventions

Various drugs may improve microvascular function, including renin-angiotensin system (RAS) inhibitors, calcium antagonists, glucose-lowering drugs, statins, anti-inflammatory therapies, and drugs that enhance signaling of nitric oxide or prostacyclin.

RAS inhibitors, i.e., angiotensin converting enzyme inhibitors and angiotensin receptor 2 blockers, are commonly prescribed antihypertensive drugs. Experimental studies suggest that these drugs may improve the function of small vessels beyond their blood-lowering effects via upregulation of endothelial nitric oxide synthetase (108–110) and via their anti-inflammatory effects (111). There are no randomized clinical

trials of RAS inhibitors and depression. However, experimental data suggest that RAS inhibitors may have mood-elevating effects (111). Moreover, some (112–114), but not all (115,116), explorative observational studies have suggested that RAS inhibitors may protect against depression.

Calcium channel blockers are other commonly prescribed antihypertensive drugs. Animal studies suggest that these drugs might have beneficial effects on the microcirculation (117). In addition, one clinical trial ( $N = 101$ ) showed that older individuals treated with fluoxetine combined with nimodipine reduced depressive symptoms more than treatment with fluoxetine alone (118). Further study is needed to elucidate the effects of calcium channel blockers on the microvasculature in humans and to confirm the findings of the clinical trial.

Statins and glucose-lowering drugs, including metformin, peroxisome proliferator-activated receptor- $\gamma$  agonists, and incretin-based therapies (i.e., glucagon-like peptide 1 receptor agonists and dipeptidyl peptidase 4 inhibitors), might also improve cerebral microvascular function and have neuroprotective effects through nonlipid and nonglucose pathways. Small trials and observational studies (119–122) suggest that these drugs may lower depressive symptoms. In addition, several trials are being done to evaluate the effect of statins (e.g., NCT03435744 and NCT04301271) and incretin-based therapies (e.g., NCT04466345 and NCT04410341) as add-on treatment to standard antidepressant therapy in patients with major depression. Additionally, anti-inflammatory interventions may be beneficial in depression in part via improvement of microvascular dysfunction (123). Therapeutic approaches aimed at reducing inflammation are currently investigated [as reviewed elsewhere (124)].

RAS inhibitors, statins, and glucose-lowering and anti-inflammatory interventions may also improve microvascular function in part via their beneficial effects on large arteries. Experimental studies have shown that these drugs may improve large artery elasticity, possibly beyond their blood pressure-, glucose-, or lipid-lowering effects (92,125).

Other potentially interesting interventions are drugs that enhance signaling of nitric oxide or prostacyclin (also known as prostaglandin I<sub>2</sub> or related prostaglandins), such as nitric oxide donors (e.g., isosorbide mononitrate), phosphodiesterase 3 inhibitors (e.g., cilostazol), and phosphodiesterase 5 inhibitors (e.g., dipyridamole). Experimental studies have shown that these drugs can improve blood-brain barrier integrity and vasoreactivity (126), but their effect on depression remains to be investigated. Trials testing some of these drugs in depression are ongoing (e.g., NCT03736538, NCT04199143, NCT04344678, and NCT04069819).

## DIRECTIONS FOR FUTURE RESEARCH

Emerging evidence suggests that microvascular dysfunction may contribute to depression, but many questions are unanswered. Further research is needed to fully characterize the association between microvascular dysfunction and specific depressive symptoms, specific depressive symptoms trajectories, and its comorbidities. This will help to further define microvascular depression as a specific subtype of depression, to better understand the larger phenotype of microvascular dysfunction-related brain diseases, and to establish the

clinical value of this phenotype. Based on this information, the recent consensus criteria for vascular depression (Table 1) may be adapted to include a definition of a microvascular dysfunction-related depression phenotype.

Although experimental studies are crucial to understand the individual causative pathways by which impairment of the different functions of the microvasculature can contribute to depressive symptoms, these studies cannot evaluate the effect of microvascular dysfunction in the context of the heterogeneous manifestations of depression and the other morbidities with which they co-occur in patients. Studies in humans are therefore needed. To distinguish different clusters and trajectories of depressive symptoms and to identify the clinical phenotype that is related to microvascular dysfunction, longitudinal population-based studies are needed with multiple measures of a large set of individual depressive symptoms across the life course, ideally from adulthood or earlier onward. Rigorous methods to control for depressive symptoms at baseline and other potential confounders will limit the risk of reverse causality and bias due to residual confounding. In addition, high-quality measurements of microvascular function should be used to minimize measurement-error bias. Retinal microvascular parameters, which can be readily assessed noninvasively at large scale, may be a good proxy for microvascular changes in the brain. These include static (e.g., calibers, fractals, and tortuosity) and dynamic (e.g., vasodilatation response to flicker light) parameters. The static parameters are measures of the efficiency of retinal blood distribution (127), and flicker light-induced vasodilatation is a key functional measure of neurovascular coupling (128). In addition, advanced neuroimaging methods now enable direct measurement of blood-brain barrier permeability, cerebrovascular reactivity at the tissue level, and microvascular blood flow perfusion and pulsatility in humans (129–131). These techniques may not be easily applied at a large scale but may provide crucial information about cerebral microvascular pathophysiology even in small samples. In addition, clinical studies are needed to evaluate whether stratification of patients according to the presence of microvascular dysfunction could identify subgroups more likely to respond to specific clinical therapies, including agents that improve microvascular function.

## CONCLUSIONS

A growing body of evidence from human studies suggests that microvascular dysfunction may contribute to the development of late-onset depression and may also underly apathy, cognitive dysfunction, and stroke, which are common in depression. Further research is needed to fully characterize the association between microvascular dysfunction and specific depressive symptoms, specific depressive symptoms trajectories, its comorbidities, and response to specific therapies. This will help to understand the clinical value of microvascular dysfunction-related depression.

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## ARTICLE INFORMATION

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