



**HAL**  
open science

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

Jean-Philippe Empana, Pierre Boutouyrie, Cédric Lemogne, Xavier Jouven,  
Thomas van Sloten

## ► To cite this version:

Jean-Philippe Empana, Pierre Boutouyrie, Cédric Lemogne, Xavier Jouven, Thomas van Sloten. Microvascular Contribution to Late-Onset Depression: Mechanisms, Current Evidence, Association With Other Brain Diseases, and Therapeutic Perspectives. *Biological Psychiatry*, 2021, 90 (4), pp.214-225. <10.1016/j.biopsych.2021.04.012>. <hal-04244494>

**HAL Id: hal-04244494**

**<https://hal.science/hal-04244494v1>**

Submitted on 22 Jul 2024

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire HAL, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



Distributed under a Creative Commons CC BY-NC 4.0 - Attribution - Non-commercial use - International License

<LRH>Biological Psychiatry •••• •, 2021; XX:•••–•••

<RRH>Microvascular Late-Onset Depression Hypothesis

<DOC>Review

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

<AU>Jean-Philippe Empana, Pierre Boutouyrie, Cédric Lemogne, Xavier Jouven, and  
Thomas T. van Sloten\*

<BEGIN ABSTRACT>

## 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.

<END ABSTRACT>

<KW>Keywords: Diabetes, Human studies, Hypertension, Late-onset depression,

Microvasculature, Vascular depression

<https://doi.org/10.1016/j.biopsych.2021.04.012>

<BEGIN ARTICLE>

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-fold to twofold 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).

### <H1>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).

### <H2>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).

### <H1>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.

## <H2>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 (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 intracellular 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).

## <H2>Cerebrovascular Reactivity, Cerebral Autoregulation, and Resting Cerebral Blood Flow

Microvascular dysfunction may manifest as disrupted cerebrovascular reactivity (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 (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 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).

## <H2>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).

## <H2>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. 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.

## <H1>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-fold to twofold 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). 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).

# <H1>Drivers of Microvascular Dysfunction in Depression: Aging, Psychological Stress, Arterial Stiffness and Hypertension, and Type 2 Diabetes and the Metabolic Syndrome

## <H2>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).

## <H2>Psychological Stress and Inflammation

Chronic stress is a 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 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.

## <H2>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 that orthostatic hypotension (97) and exercise-induced hypertension (98) are associated with higher risk of depressive symptoms.

## <H2>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.

## <H1>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).

## <H2>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.

## <H2>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).

## <H1>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.

## <H1>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.

## <ACK> Acknowledgments and Disclosures

This work was supported by a VENI research grant (Grant No. 916.19.074 [to TTvS]) from the Netherlands Organization for Scientific Research and the Netherlands Organization for Health Research and Development, and a Dutch Heart Foundation research grant (Grant No. 2018T025 [to TTvS]).

The authors report no biomedical financial interests or potential conflicts of interest.

## Article Information

<AFN> From the Université de Paris (J-PE, PB, XJ, TTvS), INSERM, UMR-S970, Paris Cardiovascular Research Center; Université de Paris (CL), AP-HP, Hôpital Hôtel-Dieu, DMU Psychiatrie et Addictologie, Service de Psychiatrie de l'adulte, INSERM, Institut de Psychiatrie et Neurosciences de Paris, UMR\_S1266, Paris, France; and Cardiovascular Research Institute Maastricht and Department of Internal Medicine (TTvS), Maastricht University Medical Centre, Maastricht, the Netherlands.

<COR>\* Address correspondence to Thomas T. van Sloten, M.D., Ph.D., at [t.vansloten@maastrichtuniversity.nl](mailto:t.vansloten@maastrichtuniversity.nl).

Received Dec 9, 2020; revised Apr 20, 2021; accepted Apr 21, 2021.

## References

1. Kok RM, Reynolds CF, 3rd (2017): Management of depression in older adults: A review. *JAMA* 317:2114–2122.
2. Lyness JM, Heo M, Datto CJ, Ten Have TR, Katz IR, Drayer R, *et al.* (2006): Outcomes of minor and subsyndromal depression among elderly patients in primary care settings. *Ann Intern Med* 144:496–504.
3. Chachamovich E, Fleck M, Laidlaw K, Power M (2008): Impact of major depression and subsyndromal symptoms on quality of life and attitudes toward aging in an international sample of older adults. *Gerontologist* 48:593–602.
4. Barefoot JC, Schroll M (1996): Symptoms of depression, acute myocardial infarction, and total mortality in a community sample. *Circulation* 93:1976–1980.
5. Penninx BW, Geerlings SW, Deeg DJ, van Eijk JT, van Tilburg W, Beekman AT (1999): Minor and major depression and the risk of death in older persons. *Arch Gen Psychiatry* 56:889–895.
6. Tedeschini E, Levkovitz Y, Iovieno N, Ameral VE, Nelson JC, Papakostas GI (2011): Efficacy of antidepressants for late-life depression: A meta-analysis and meta-regression of placebo-controlled randomized trials. *J Clin Psychiatry* 72:1660–1668.
7. Calati R, Salvina Signorelli M, Balestri M, Marsano A, De Ronchi D, Aguglia E, Serretti A (2013): Antidepressants in elderly: Metaregression of double-blind, randomized clinical trials. *J Affect Disord* 147:1–8.
8. Coupland C, Dhiman P, Morriss R, Arthur A, Barton G, Hippisley-Cox J (2011): Antidepressant use and risk of adverse outcomes in older people: Population based cohort study. *BMJ* 343:d4551.
9. Thomas A, O'Brien JT (2015): Management of late-life depression: A major leap forward. *Lancet* 386:2374–2375.

10. Taylor WD, Aizenstein HJ, Alexopoulos GS (2013): The vascular depression hypothesis: Mechanisms linking vascular disease with depression. *Mol Psychiatry* 18:963–974.
11. Alexopoulos GS, Meyers BS, Young RC, Campbell S, Silbersweig D, Charlson M (1997): ‘Vascular depression’ hypothesis. *Arch Gen Psychiatry* 54:915–922.
12. Taylor WD, Steffens DC, Krishnan KR (2006): Psychiatric disease in the twenty-first century: The case for subcortical ischemic depression. *Biol Psychiatry* 60:1299–1303.
13. Krishnan KR, Taylor WD, McQuoid DR, MacFall JR, Payne ME, Provenzale JM, Steffens DC (2004): Clinical characteristics of magnetic resonance imaging-defined subcortical ischemic depression. *Biol Psychiatry* 55:390–397.
14. Aizenstein HJ, Baskys A, Boldrini M, Butters MA, Diniz BS, Jaiswal MK, *et al.* (2016): Vascular depression consensus report - A critical update. *BMC Med* 14:161.
15. Alexopoulos GS (2019): Mechanisms and treatment of late-life depression. *Transl Psychiatry* 9:188.
16. Wardlaw JM, Smith C, Dichgans M (2019): Small vessel disease: Mechanisms and clinical implications. *Lancet Neurol* 18:684–696.
17. van Sloten TT, Sedaghat S, Carnethon MR, Launer LJ, Stehouwer CDA (2020): Cerebral microvascular complications of type 2 diabetes: Stroke, cognitive dysfunction, and depression. *Lancet Diabetes Endocrinol* 8:325–336.
18. Dudek KA, Dion-Albert L, Kaufmann FN, Tuck E, Lebel M, Menard C (2021): Neurobiology of resilience in depression: Immune and vascular insights from human and animal studies. *Eur J Neurosci* 53:183–221.
19. Cathomas F, Murrough JW, Nestler EJ, Han MH, Russo SJ (2019): Neurobiology of resilience: Interface between mind and body. *Biol Psychiatry* 86:410–420.

20. Tsyglakova M, McDaniel D, Hodes GE (2019): Immune mechanisms of stress susceptibility and resilience: Lessons from animal models. *Front Neuroendocrinol* 54:100771.
21. Sweeney MD, Zhao Z, Montagne A, Nelson AR, Zlokovic BV (2019): Blood-brain barrier: From physiology to disease and back. *Physiol Rev* 99:21–78.
22. Willie CK, Tzeng YC, Fisher JA, Ainslie PN (2014): Integrative regulation of human brain blood flow. *J Physiol* 592:841–859.
23. Stehouwer CDA (2018): Microvascular dysfunction and hyperglycemia: A vicious cycle with widespread consequences. *Diabetes* 67:1729–1741.
24. Gudmundsson P, Skoog I, Waern M, Blennow K, Pálsson S, Rosengren L, Gustafson D (2007): The relationship between cerebrospinal fluid biomarkers and depression in elderly women. *Am J Geriatr Psychiatry* 15:832–838.
25. Bechter K, Reiber H, Herzog S, Fuchs D, Tumani H, Maxeiner HG (2010): Cerebrospinal fluid analysis in affective and schizophrenic spectrum disorders: Identification of subgroups with immune responses and blood-CSF barrier dysfunction. *J Psychiatr Res* 44:321–330.
26. Zachrisson OC, Balldin J, Ekman R, Naesh O, Rosengren L, Agren H, Blennow K (2000): No evident neuronal damage after electroconvulsive therapy. *Psychiatry Res* 96:157–165.
27. Niklasson F, Agren H (1984): Brain energy metabolism and blood-brain barrier permeability in depressive patients: Analyses of creatine, creatinine, urate, and albumin in CSF and blood. *Biol Psychiatry* 19:1183–1206.
28. Thomas AJ, Perry R, Kalaria RN, Oakley A, McMeekin W, O'Brien JT (2003): Neuropathological evidence for ischemia in the white matter of the dorsolateral prefrontal cortex in late-life depression. *Int J Geriatr Psychiatry* 18:7–13.

29. Thomas AJ, Ferrier IN, Kalaria RN, Woodward SA, Ballard C, Oakley A, *et al.* (2000): Elevation in late-life depression of intercellular adhesion molecule-1 expression in the dorsolateral prefrontal cortex. *Am J Psychiatry* 157:1682–1684.
30. Miguel-Hidalgo JJ, Overholser JC, Jurjus GJ, Meltzer HY, Dieter L, Konick L, *et al.* (2011): Vascular and extravascular immunoreactivity for intercellular adhesion molecule 1 in the orbitofrontal cortex of subjects with major depression: Age-dependent changes. *J Affect Disord* 132:422–431.
31. Rajkowska G, Hughes J, Stockmeier CA, Javier Miguel-Hidalgo J, Maciag D (2013): Coverage of blood vessels by astrocytic endfeet is reduced in major depressive disorder. *Biol Psychiatry* 73:613–621.
32. Menard C, Pfau ML, Hodes GE, Kana V, Wang VX, Bouchard S, *et al.* (2017): Social stress induces neurovascular pathology promoting depression. *Nat Neurosci* 20:1752–1760.
33. Dudek KA, Dion-Albert L, Lebel M, LeClair K, Labrecque S, Tuck E, *et al.* (2020): Molecular adaptations of the blood-brain barrier promote stress resilience vs. depression. *Proc Natl Acad Sci U S A* 117:3326–3336.
34. Russo SJ, Nestler EJ (2013): The brain reward circuitry in mood disorders. *Nat Rev Neurosci* 14:609–625.
35. Direk N, Koudstaal PJ, Hofman A, Ikram MA, Hoogendijk WJ, Tiemeier H (2012): Cerebral hemodynamics and incident depression: The Rotterdam Study. *Biol Psychiatry* 72:318–323.
36. de Castro AG, Bajbouj M, Schlattmann P, Lemke H, Heuser I, Neu P (2008): Cerebrovascular reactivity in depressed patients without vascular risk factors. *J Psychiatr Res* 42:78–82.

37. Lemke H, de Castro AG, Schlattmann P, Heuser I, Neu P (2010): Cerebrovascular reactivity over time-course - From major depressive episode to remission. *J Psychiatr Res* 44:132–136.
38. Matsuo K, Onodera Y, Hamamoto T, Muraki K, Kato N, Kato T (2005): Hypofrontality and microvascular dysregulation in remitted late-onset depression assessed by functional near-infrared spectroscopy. *Neuroimage* 26:234–242.
39. Neu P, Schlattmann P, Schilling A, Hartmann A (2004): Cerebrovascular reactivity in major depression: A pilot study. *Psychosom Med* 66:6–8.
40. Tiemeier H, Bakker SL, Hofman A, Koudstaal PJ, Breteler MM (2002): Cerebral haemodynamics and depression in the elderly. *J Neurol Neurosurg Psychiatry* 73:34–39.
41. Vakilian A, Iranmanesh F (2010): Assessment of cerebrovascular reactivity during major depression and after remission of disease. *Ann Indian Acad Neurol* 13:52–56.
42. Abi Zeid Daou M, Boyd BD, Donahue MJ, Albert K, Taylor WD (2017): Frontocingulate cerebral blood flow and cerebrovascular reactivity associated with antidepressant response in late-life depression. *J Affect Disord* 215:103–110.
43. Thrippleton MJ, Backes WH, Sourbron S, Ingrisch M, van Osch MJP, Dichgans M, *et al.* (2019): Quantifying blood-brain barrier leakage in small vessel disease: Review and consensus recommendations. *Alzheimers Dement* 15:840–858.
44. Luo MY, Guo ZN, Qu Y, Zhang P, Wang Z, Jin H, *et al.* (2019): Compromised dynamic cerebral autoregulation in patients with depression. *Front Psychiatry* 10:373.
45. Miyazawa T, Shibata S, Nagai K, Hirasawa A, Kobayashi Y, Koshiba H, Kozaki K (2018): Relationship between cerebral blood flow estimated by transcranial Doppler ultrasound and single-photon emission computed tomography in elderly people with dementia. *J Appl Physiol* (1985) 125:1576–1584.

46. Alosco ML, Spitznagel MB, Cohen R, Raz N, Sweet LH, Josephson R, *et al.* (2014): Reduced cerebral perfusion predicts greater depressive symptoms and cognitive dysfunction at a 1-year follow-up in patients with heart failure. *Int J Geriatr Psychiatry* 29:428–436.
47. Wang J, Li R, Liu M, Nie Z, Jin L, Lu Z, Li Y (2020): Impaired cerebral hemodynamics in late-onset depression: Computed tomography angiography, computed tomography perfusion, and magnetic resonance imaging evaluation. *Quant Imaging Med Surg* 10:1763–1774.
48. Liao W, Wang Z, Zhang X, Shu H, Wang Z, Liu D, Zhang Z (2017): Cerebral blood flow changes in remitted early- and late-onset depression patients. *Oncotarget* 8:76214–76222.
49. Abi Zeid Daou M, Boyd BD, Donahue MJ, Albert K, Taylor WD (2018): Anterior-posterior gradient differences in lobar and cingulate cortex cerebral blood flow in late-life depression. *J Psychiatr Res* 97:1–7.
50. Cheung CY, Ikram MK, Chen C, Wong TY (2017): Imaging retina to study dementia and stroke. *Prog Retin Eye Res* 57:89–107.
51. Nguyen TT, Kreis AJ, Kawasaki R, Wang JJ, Seifert BU, Vilser W, *et al.* (2009): Reproducibility of the retinal vascular response to flicker light in Asians. *Curr Eye Res* 34:1082–1088.
52. Geraets AFJ, van Agtmaal MJM, Stehouwer CDA, Sörensen BM, Berendschot TTJM, Webers CAB, *et al.* (2020): Association of markers of microvascular dysfunction with prevalent and incident depressive symptoms: The Maastricht Study. *Hypertension* 76:342–349.
53. Ikram MK, Lujendijk HJ, Hofman A, de Jong PT, Breteler MM, Vingerling JR, Tiemeier H (2010): Retinal vascular calibers and risk of late-life depression: The Rotterdam Study. *Am J Geriatr Psychiatry* 18:452–455.

54. Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, Frayne R, *et al.* (2013): Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *Lancet Neurol* 12:822–838.
55. Rensma SP, van Sloten TT, Launer LJ, Stehouwer CDA (2018): Cerebral small vessel disease and risk of incident stroke, dementia and depression, and all-cause mortality: A systematic review and meta-analysis. *Neurosci Biobehav Rev* 90:164–173.
56. Fang Y, Qin T, Liu W, Ran L, Yang Y, Huang H, *et al.* (2020): Cerebral small-vessel disease and risk of incidence of depression: A meta-analysis of longitudinal cohort studies. *J Am Heart Assoc* 9:e016512.
57. van Agtmaal MJM, Houben AJHM, Pouwer F, Stehouwer CDA, Schram MT (2017): Association of microvascular dysfunction with late-life depression: A systematic review and meta-analysis. *JAMA Psychiatry* 74:729–739.
58. van Sloten TT, Sigurdsson S, van Buchem MA, Phillips CL, Jonsson PV, Ding J, *et al.* (2015): Cerebral small vessel disease and association with higher incidence of depressive symptoms in a general elderly population: The AGES-Reykjavik Study. *Am J Psychiatry* 172:570–578.
59. Tsopelas C, Stewart R, Savva GM, Brayne C, Ince P, Thomas A, *et al.* (2011): Neuropathological correlates of late-life depression in older people. *Br J Psychiatry* 198:109–114.
60. Thomas AJ, O'Brien JT, Davis S, Ballard C, Barber R, Kalaria RN, Perry RH (2002): Ischemic basis for deep white matter hyperintensities in major depression: A neuropathological study. *Arch Gen Psychiatry* 59:785–792.
61. Thomas AJ, Ferrier IN, Kalaria RN, Perry RH, Brown A, O'Brien JT (2001): A neuropathological study of vascular factors in late-life depression. *J Neurol Neurosurg Psychiatry* 70:83–87.

62. Santos M, Gold G, Kövari E, Herrmann FR, Hof PR, Bouras C, Giannakopoulos P (2010): Neuropathological analysis of lacunes and microvascular lesions in late-onset depression. *Neuropathol Appl Neurobiol* 36:661–672.
63. Santos M, Gold G, Kövari E, Herrmann FR, Bozikas VP, Bouras C, Giannakopoulos P (2009): Differential impact of lacunes and microvascular lesions on poststroke depression. *Stroke* 40:3557–3562.
64. O'Brien J, Thomas A, Ballard C, Brown A, Ferrier N, Jaros E, Perry R (2001): Cognitive impairment in depression is not associated with neuropathologic evidence of increased vascular or Alzheimer-type pathology. *Biol Psychiatry* 49:130–136.
65. Lloyd AJ, Grace JB, Jaros E, Perry RH, Fairbairn AF, Swann AG, *et al.* (2001): Depression in late life, cognitive decline and white matter pathology in two clinico-pathologically investigated cases. *Int J Geriatr Psychiatry* 16:281–287.
66. Ishii S, Weintraub N, Mervis JR (2009): Apathy: A common psychiatric syndrome in the elderly. *J Am Med Dir Assoc* 10:381–393.
67. van Dalen JW, van Wanrooij LL, Moll van Charante EP, Brayne C, van Gool WA, Richard E (2018): Association of apathy with risk of incident dementia: A systematic review and meta-analysis. *JAMA Psychiatry* 75:1012–1021.
68. Pan A, Sun Q, Okereke OI, Rexrode KM, Hu FB (2011): Depression and risk of stroke morbidity and mortality: A meta-analysis and systematic review. *JAMA* 306:1241–1249.
69. Dong JY, Zhang YH, Tong J, Qin LQ (2012): Depression and risk of stroke: A meta-analysis of prospective studies. *Stroke* 43:32–37.
70. Gunning-Dixon FM, Walton M, Cheng J, Acuna J, Klimstra S, Zimmerman ME, *et al.* (2010): MRI signal hyperintensities and treatment remission of geriatric depression. *J Affect Disord* 126:395–401.

71. Demnitz N, Anatórk M, Allan CL, Filippini N, Griffanti L, Mackay CE, *et al.* (2020): Association of trajectories of depressive symptoms with vascular risk, cognitive function and adverse brain outcomes: The Whitehall II MRI sub-study. *J Psychiatr Res* 131:85–93.
72. Singh-Manoux A, Dugravot A, Fournier A, Abell J, Ebmeier K, Kivimäki M, Sabia S (2017): Trajectories of depressive symptoms before diagnosis of dementia: A 28-year follow-up study. *JAMA Psychiatry* 74:712–718.
73. Mirza SS, Wolters FJ, Swanson SA, Koudstaal PJ, Hofman A, Tiemeier H, Ikram MA (2016): 10-year trajectories of depressive symptoms and risk of dementia: A population-based study. *Lancet Psychiatry* 3:628–635.
74. Wouts L, van Kessel M, Beekman ATF, Marijnissen RM, Oude Voshaar RC (2020): Empirical support for the vascular apathy hypothesis: A structured review. *Int J Geriatr Psychiatry* 35:3–11.
75. Smith PJ, Blumenthal JA, Hinderliter AL, Watkins LL, Hoffman BM, Sherwood A (2018): Microvascular endothelial function and neurocognition among adults with major depressive disorder. *Am J Geriatr Psychiatry* 26:1061–1069.
76. Rensma SP, van Sloten TT, Houben AJHM, Köhler S, van Boxtel MPJ, Berendschot TTJM, *et al.* (2020): Microvascular dysfunction is associated with worse cognitive performance: The Maastricht Study. *Hypertension* 75:237–245.
77. Schmidt R, Seiler S, Loitfelder M (2016): Longitudinal change of small-vessel disease-related brain abnormalities. *J Cereb Blood Flow Metab* 36:26–39.
78. IST-3 collaborative group (2015): Association between brain imaging signs, early and late outcomes, and response to intravenous alteplase after acute ischaemic stroke in the third International Stroke Trial (IST-3): Secondary analysis of a randomised controlled trial. *Lancet Neurol* 14:485–496.

79. Appleton JP, Woodhouse LJ, Adami A, Becker JL, Berge E, Cala LA, *et al.* (2020): Imaging markers of small vessel disease and brain frailty, and outcomes in acute stroke. *Neurology* 94:e439–e452.
80. Brown WR, Thore CR (2011): Review: Cerebral microvascular pathology in ageing and neurodegeneration. *Neuropathol Appl Neurobiol* 37:56–74.
81. Ungvari Z, Tarantini S, Sorond F, Merkely B, Csiszar A (2020): Mechanisms of vascular aging, a geroscience perspective: JACC focus seminar. *J Am Coll Cardiol* 75:931–941.
82. Ostir GV, Eschbach K, Markides KS, Goodwin JS (2003): Neighbourhood composition and depressive symptoms among older Mexican Americans. *J Epidemiol Community Health* 57:987–992.
83. Kubzansky LD, Subramanian SV, Kawachi I, Fay ME, Soobader MJ, Berkman LF (2005): Neighborhood contextual influences on depressive symptoms in the elderly. *Am J Epidemiol* 162:253–260.
84. Tracey KJ (2009): Reflex control of immunity. *Nat Rev Immunol* 9:418–428.
85. Lupien SJ, McEwen BS, Gunnar MR, Heim C (2009): Effects of stress throughout the lifespan on the brain, behaviour and cognition. *Nat Rev Neurosci* 10:434–445.
86. Zhang Y, Lu W, Wang Z, Zhang R, Xie Y, Guo S, *et al.* (2020): Reduced neuronal cAMP in the nucleus accumbens damages blood-brain barrier integrity and promotes stress vulnerability. *Biol Psychiatry* 87:526–537.
87. Heidt T, Sager HB, Courties G, Dutta P, Iwamoto Y, Zaltsman A, *et al.* (2014): Chronic variable stress activates hematopoietic stem cells. *Nat Med* 20:754–758.
88. Cheng Y, Dese S, Martinez A, Worthen RJ, Jope RS, Beurel E (2018): TNF $\alpha$  disrupts blood brain barrier integrity to maintain prolonged depressive-like behavior in mice. *Brain Behav Immun* 69:556–567.

89. Climie RE, van Sloten TT, Bruno RM, Taddei S, Empana JP, Stehouwer CDA, *et al.* (2019): Macrovasculature and microvasculature at the crossroads between type 2 diabetes mellitus and hypertension. *Hypertension* 73:1138–1149.
90. Mitchell GF (2008): Effects of central arterial aging on the structure and function of the peripheral vasculature: Implications for end-organ damage. *J Appl Physiol* (1985) 105:1652–1660.
91. van Sloten TT, Boutouyrie P, Tafflet M, Offredo L, Thomas F, Guibout C, *et al.* (2019): Carotid artery stiffness and incident depressive symptoms: The Paris Prospective Study III. *Biol Psychiatry* 85:498–505.
92. van Sloten TT, Mitchell GF, Sigurdsson S, van Buchem MA, Jonsson PV, Garcia ME, *et al.* (2016): Associations between arterial stiffness, depressive symptoms and cerebral small vessel disease: Cross-sectional findings from the AGES-Reykjavik Study. *J Psychiatry Neurosci* 41:162–168.
93. Armstrong NM, Meoni LA, Carlson MC, Xue QL, Bandeen-Roche K, Gallo JJ, Gross AL (2017): Cardiovascular risk factors and risk of incident depression throughout adulthood among men: The Johns Hopkins Precursors Study. *J Affect Disord* 214:60–66.
94. Zimmerman JA, Mast BT, Miles T, Markides KS (2009): Vascular risk and depression in the Hispanic Established Population for the Epidemiologic Study of the Elderly (EPESE). *Int J Geriatr Psychiatry* 24:409–416.
95. Luijendijk HJ, Stricker BH, Hofman A, Witteman JC, Tiemeier H (2008): Cerebrovascular risk factors and incident depression in community-dwelling elderly. *Acta Psychiatr Scand* 118:139–148.
96. Mast BT, Miles T, Penninx BW, Yaffe K, Rosano C, Satterfield S, *et al.* (2008): Vascular disease and future risk of depressive symptomatology in older adults: Findings from the Health, Aging, and Body Composition study. *Biol Psychiatry* 64:320–326.

97. Briggs R, Carey D, Kennelly SP, Kenny RA (2018): Longitudinal association between orthostatic hypotension at 30 seconds post-standing and late-life depression. *Hypertension* 71:946–954.
98. Zhou TL, Kroon AA, Henry RMA, Koster A, Dagnelie PC, Bosma H, *et al.* (2021): Exercise SBP response and incident depressive symptoms: The Maastricht Study. *J Hypertens* 39:494–502.
99. van Sloten T, Schram M (2018): Understanding depression in type 2 diabetes: A biological approach in observational studies. *7:F1000 Faculty Rev*–1283.
100. Lyra E Silva NM, Lam MP, Soares CN, Munoz DP, Milev R, De Felice FG (2019): Insulin resistance as a shared pathogenic mechanism between depression and type 2 diabetes. *Front Psychiatry* 10:57.
101. Nguyen TT, Wong TY, Islam FM, Hubbard L, Ajilore O, Haroon E, *et al.* (2010): Evidence of early retinal microvascular changes in patients with type 2 diabetes and depression. *Psychosom Med* 72:535–538.
102. Rensma SP, van Sloten TT, Ding J, Sigurdsson S, Stehouwer CDA, Gudnason V, Launer LJ (2020): Type 2 diabetes, change in depressive symptoms over time, and cerebral small vessel disease: Longitudinal data of the AGES-Reykjavik Study. *Diabetes Care* 43:1781–1787.
103. Dregan A, Rayner L, Davis KAS, Bakolis I, Arias de la Torre J, Das-Munshi J, *et al.* (2020): Associations between depression, arterial stiffness, and metabolic syndrome among adults in the UK Biobank Population Study: A mediation analysis. *JAMA Psychiatry* 77:598–606.
104. Taylor WD, Schultz SK, Panaite V, Steffens DC (2018): Perspectives on the management of vascular depression. *Am J Psychiatry* 175:1169–1175.

105. Kahl KG, Westhoff-Bleck M, Krüger TH (2017): Effects of psychopharmacological treatment with antidepressants on the vascular system. *Vascul Pharmacol* 96–98:11–18.
106. Hu MX, Turner D, Generala E, Bos D, Ikram MK, Ikram MA, *et al.* (2020): Exercise interventions for the prevention of depression: A systematic review of meta-analyses. *BMC Public Health* 20:1255.
107. Jones RA, Lawlor ER, Birch JM, Patel MI, Werneck AO, Hoare E, *et al.* (2021): The impact of adult behavioural weight management interventions on mental health: A systematic review and meta-analysis. *Obes Rev* 22:e13150.
108. Trauernicht AK, Sun H, Patel KP, Mayhan WG (2003): Enalapril prevents impaired nitric oxide synthase-dependent dilatation of cerebral arterioles in diabetic rats. *Stroke* 34:2698–2703.
109. Yamakawa H, Jezova M, Ando H, Saavedra JM (2003): Normalization of endothelial and inducible nitric oxide synthase expression in brain microvessels of spontaneously hypertensive rats by angiotensin II AT1 receptor inhibition. *J Cereb Blood Flow Metab* 23:371–380.
110. Ando H, Zhou J, Macova M, Imboden H, Saavedra JM (2004): Angiotensin II AT1 receptor blockade reverses pathological hypertrophy and inflammation in brain microvessels of spontaneously hypertensive rats. *Stroke* 35:1726–1731.
111. Luo H, Wu PF, Cao Y, Jin M, Shen TT, Wang J, *et al.* (2020): Angiotensin-converting enzyme inhibitor rapidly ameliorates depressive-type behaviors via bradykinin-dependent activation of mammalian target of rapamycin complex 1. *Biol Psychiatry* 88:415–425.
112. Kessing LV, Rytgaard HC, Ekstrøm CT, Torp-Pedersen C, Berk M, Gerds TA (2020): Antihypertensive drugs and risk of depression: A nationwide population-based study. *Hypertension* 76:1263–1279.

113. Boal AH, Smith DJ, McCallum L, Muir S, Touyz RM, Dominiczak AF, Padmanabhan S (2016): Monotherapy with major antihypertensive drug classes and risk of hospital admissions for mood disorders. *Hypertension* 68:1132–1138.
114. Cao YY, Xiang X, Song J, Tian YH, Wang MY, Wang XW, *et al.* (2019): Distinct effects of antihypertensives on depression in the real-world setting: A retrospective cohort study. *J Affect Disord* 259:386–391.
115. Shaw RJ, Mackay D, Pell JP, Padmanabhan S, Bailey DS, Smith DJ (2020): The relationship between antihypertensive medications and mood disorders: Analysis of linked healthcare data for 1.8 million patients. *Psychol Med*:1–9.
116. Agustini B, Mohebbi M, Woods RL, McNeil JJ, Nelson MR, Shah RC, *et al.* (2020): The association of antihypertensive use and depressive symptoms in a large older population with hypertension living in Australia and the United States: A cross-sectional study. *J Hum Hypertens* 34:787–794.
117. Farkas E, De Jong GI, Apró E, Keuker JI, Luiten PG (2001): Calcium antagonists decrease capillary wall damage in aging hypertensive rat brain. *Neurobiol Aging* 22:299–309.
118. Taragano FE, Bagnatti P, Allegri RF (2005): A double-blind, randomized clinical trial to assess the augmentation with nimodipine of antidepressant therapy in the treatment of “vascular depression”. *Int Psychogeriatr* 17:487–498.
119. Molero Y, Cipriani A, Larsson H, Lichtenstein P, D’Onofrio BM, Fazel S (2020): Associations between statin use and suicidality, depression, anxiety, and seizures: A Swedish total-population cohort study. *Lancet Psychiatry* 7:982–990.
120. Köhler O, Gasse C, Petersen L, Ingstrup KG, Nierenberg AA, Mors O, Østergaard SD (2016): The effect of concomitant treatment with SSRIs and statins: A population-based study. *Am J Psychiatry* 173:807–815.

121. Woo YS, Lim HK, Wang SM, Bahk WM (2020): Clinical evidence of antidepressant effects of insulin and anti-hyperglycemic agents and implications for the pathophysiology of depression-A literature review. *Int J Mol Sci* 21:6969.
122. Yatham MS, Yatham KS, Ravindran AV, Sullivan F (2019): Do statins have an effect on depressive symptoms? A systematic review and meta-analysis. *J Affect Disord* 257:55–63.
123. Köhler-Forsberg O, N Lydholm C, Hjorthøj C, Nordentoft M, Mors O, Benros ME (2019): Efficacy of anti-inflammatory treatment on major depressive disorder or depressive symptoms: Meta-analysis of clinical trials. *Acta Psychiatr Scand* 139:404–419.
124. Ménard C, Pfau ML, Hodes GE, Russo SJ (2017): Immune and neuroendocrine mechanisms of stress vulnerability and resilience. *Neuropsychopharmacology* 42:62–80.
125. van Sloten TT, Protogerou AD, Henry RM, Schram MT, Launer LJ, Stehouwer CD (2015): Association between arterial stiffness, cerebral small vessel disease and cognitive impairment: A systematic review and meta-analysis. *Neurosci Biobehav Rev* 53:121–130.
126. Bath PM, Wardlaw JM (2015): Pharmacological treatment and prevention of cerebral small vessel disease: A review of potential interventions. *Int J Stroke* 10:469–478.
127. Houben AJHM, Martens RJH, Stehouwer CDA (2017): Assessing microvascular function in humans from a chronic disease perspective. *J Am Soc Nephrol* 28:3461–3472.
128. Sörensen BM, Houben AJ, Berendschot TT, Schouten JS, Kroon AA, van der Kallen CJ, *et al.* (2016): Prediabetes and type 2 diabetes are associated with generalized microvascular dysfunction: The Maastricht Study. *Circulation* 134:1339–1352.
129. Elschot EP, Backes WH, Postma AA, van Oostenbrugge RJ, Staals J, Rouhl RPW, Jansen JFA (2021): A comprehensive view on MRI techniques for imaging blood-brain barrier integrity. *Invest Radiol* 56:10–19.

130. van Bussel FC, Backes WH, Hofman PA, van Oostenbrugge RJ, Kessels AG, van Boxtel MP, *et al.* (2015): On the interplay of microvasculature, parenchyma, and memory in type 2 diabetes. *Diabetes Care* 38:876–882.
131. Arts T, Siero JCW, Biessels GJ, Zwanenburg JJM (2021): Automated assessment of cerebral arterial perforator function on 7T MRI. *J Magn Reson Imaging* 53:234–241.
132. Kisler K, Nelson AR, Montagne A, Zlokovic BV (2017): Cerebral blood flow regulation and neurovascular dysfunction in Alzheimer disease. *Nat Rev Neurosci* 18:419–434.
133. Novak V, Hajjar I (2010): The relationship between blood pressure and cognitive function. *Nat Rev Cardiol* 7:686–698.
134. Østergaard L, Aamand R, Gutiérrez-Jiménez E, Ho YC, Blicher JU, Madsen SM, *et al.* (2013): The capillary dysfunction hypothesis of Alzheimer’s disease. *Neurobiol Aging* 34:1018–1031.
135. Sweeney MD, Sagare AP, Zlokovic BV (2018): Blood-brain barrier breakdown in Alzheimer disease and other neurodegenerative disorders. *Nat Rev Neurol* 14:133–150.
136. Mitchell GF, van Buchem MA, Sigurdsson S, Gotlib JD, Jonsdottir MK, Kjartansson Ó, *et al.* (2011): Arterial stiffness, pressure and flow pulsatility and brain structure and function: The Age, Gene/Environment Susceptibility--Reykjavik study. *Brain* 134:3398–3407.
137. Raichle ME, Gusnard DA (2002): Appraising the brain’s energy budget. *Proc Natl Acad Sci U S A* 99:10237–10239.
138. Thrippleton MJ, Shi Y, Blair G, Hamilton I, Waiter G, Schwarzbauer C, *et al.* (2018): Cerebrovascular reactivity measurement in cerebral small vessel disease: Rationale and reproducibility of a protocol for MRI acquisition and image processing. *Int J Stroke* 13:195–206.

139. Ainslie PN, Duffin J (2009): Integration of cerebrovascular CO<sub>2</sub> reactivity and chemoreflex control of breathing: Mechanisms of regulation, measurement, and interpretation. *Am J Physiol Regul Integr Comp Physiol* 296:R1473–R1495.

**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).

**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.

**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).

**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 rapport (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	Core functions of the cerebral microcirculation, defined as cerebral vessels <150 µm (arterioles, capillaries, and venules), are 1) to optimize the delivery of nutrients and removal of waste

Dysfunction	products in response to variations in neuronal activity, 2) to maintain the cerebral interstitial milieu for proper cell function, and 3) to 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	<p>Ratio of cerebrospinal fluid albumin to serum albumin level.</p> <p>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.</p>
Cerebrovascular Reactivity	<p>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).</p>

**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)

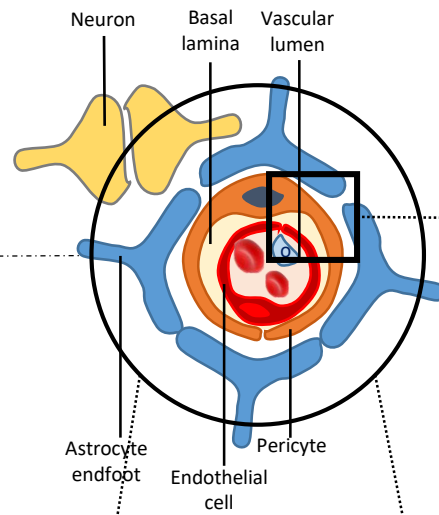
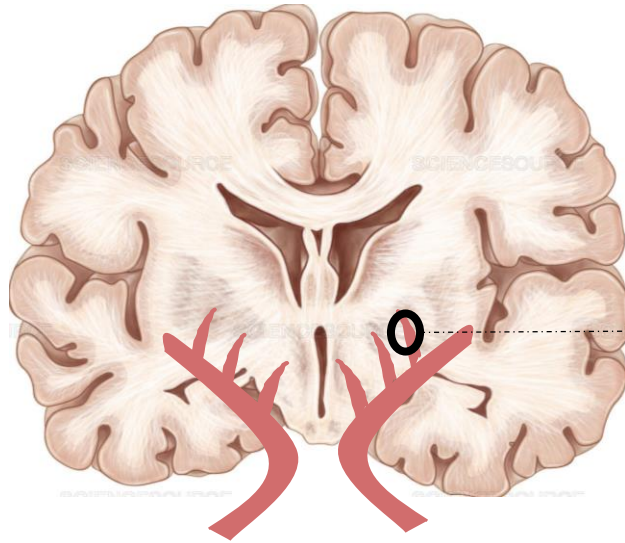
		found altered regional or global cerebral perfusion independently of cerebral atrophy.
Retinal Microvascular Changes	DVA; fundoscopy	One prospective study (52) showed that lower flicker light-induced vasodilatation is associated with increased risk of depression, but another prospective study (53) did 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.

Studies evaluated major depressive disorder according to the 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).

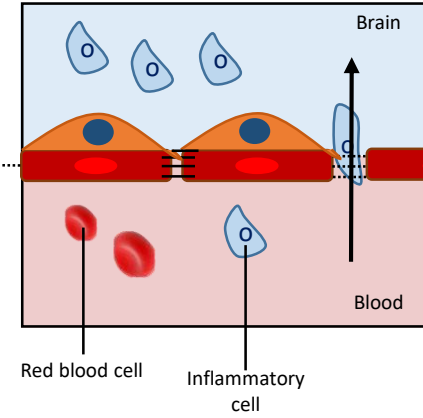
ASL, arterial spin labeling; DVA, dynamic vessel analysis; FLAIR, fluid-attenuated inversion recovery; MRI, magnetic resonance imaging; PC-MRA, phase-contrast magnetic resonance angiography; Qalb, cerebrospinal fluid/plasma albumin ratio; SPECT, single-photon emission computed tomography; TCD, transcranial doppler; T1W, T1-weighted MRI images; T2W, T2-weighted MRI images; T2\*W, T2-star weighted MRI images.

“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

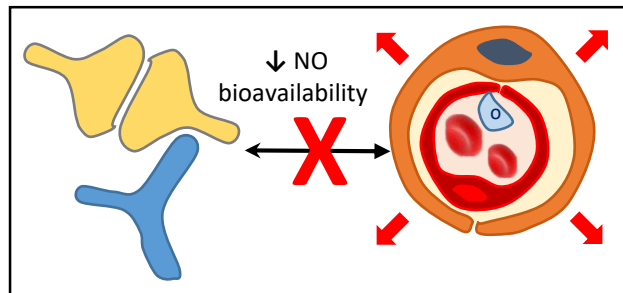
(24,35,40,52,53,59). Studies included older adults (>60 years or older) only (24,35,38,40,42,47–49,53,59–62,64) or also included younger individuals (25–27,36,37,39,41,44,46,52). Of the studies investigating older individuals only, some excluded individuals with a depressive disorder before late life (38,47,48,62,65), whereas others did not (24,35,40,42,49,52,53,59–61,64).



**A) blood-brain barrier permeability ↑**



**B) Neurovascular coupling ↓**



**C) Cerebral autoregulation ↓**

