Vascular and metabolic risk factors of late-life depression

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Abstract

Late-life depression (LLD) is a common complex mood disorder with high comorbidity of both psychiatric and physical diseases, cognitive decline, and increased mortality. The mechanisms underlying LLD are incompletely understood. The heterogeneity of depression complicates research into the underlying mechanisms, and factors involved in LLD may differ from those involved in early-life depression. This narrative review provides an overview of (micro-)vascular and metabolic factors involved in the development of LLD. Evidence suggests that cerebral small vessel disease, generalized microvascular dysfunction, and metabolic risk factors, including diabetes and inflammation, may contribute to the development of LLD, while the role of neurodegeneration needs further in-depth investigation. Accordingly, vascular and metabolic factors may provide promising targets for the prevention and improvement of treatment of LLD. Guidelines to screen for LLD in cardiovascular care need further implementation, as do integrated care approaches that treat LLD and diabetes jointly. However, intervention studies are needed to assess which interventions are appropriate and most effective in clinical practice.

Keywords: Depression, etiology, cerebral small vessel disease, microvascular dysfunction, metabolic syndrome, diabetes, inflammation, neurodegeneration

INTRODUCTION

Late-life depression (LLD) is a common complex mood disorder with high comorbidity of both psychiatric and physical diseases, cognitive decline, and increased mortality risk\cite{1-4}. Although no clear definition exists,
LLD is mostly defined as a depression above the age of 60 years. The prevalence of major depressive disorder varies largely and ranges from 0.9% to 42% among older adults, and clinically relevant depressive symptoms are present in 7.2% to 49%[5]. Globally, the prevalence of LLD is rising, particularly in lower-income countries, which reflects both the overall growth and aging of the global population[6]. Although antidepressant medication is available, in more than half of the individuals with LLD, remission is not achieved with first-line antidepressant medication[7,8]. Older age appears to be a consistent and important risk factor for a poorer, more persistent course of depression[9]. Among individuals aged above 60 years with depression, 61% reported a persistent, chronic course of depressive symptoms[10]. Accordingly, the etiology of LLD may differ from that involved in early life.

It is important to distinguish between early-onset and late-onset LLD. Early-onset depression might predispose to LLD by accumulating depressive episodes over life and is associated with a family history of mood disorders, while late-onset depression is more associated with dementia, cognitive impairment, and brain abnormalities. These overt differences generated mechanistic hypotheses on the role of vascular and metabolic risk factors and their involvement in the development of LLD[11]. In this narrative review, we provide an overview of (micro-)vascular and metabolic mechanisms involved in the development of LLD.

**VASCULAR DEPRESSION HYPOTHESIS**

The “vascular depression” hypothesis, introduced independently by Alexopoulos et al. and Krishnan et al. in 1997, proposes that cerebral small vessel disease (CSVD), in the form of hyperintense regions, microbleeds, and lacunes in the brain’s white matter, may predispose, precipitate, or perpetuate depression[12-14]. This hypothesis was based on the observation that cerebrovascular risk factors are frequently present in individuals with depression, the comorbidity of depression with cerebrovascular lesions, and the frequent development of depression after stroke. Moreover, such a vascular etiology may explain the high recurrence and persistence rate of LLD, in addition to high treatment resistance to antidepressants and/or cognitive behavioral therapy[8,15,16]. However, the multifold pathogenesis of vascular depression as a possible subtype of LLD needs further elucidation[17].

**Cerebral small vessel disease**

Accumulating evidence suggests that CSVD may contribute to the onset of LLD by inducing chronic ischemia in brain tissue[18]. CSVD may eventually result in cognitive and behavioral problems[19]. Several brain regions are involved in LLD. Abnormalities in the prefrontal and cingulate cortex, hippocampus, striatum, amygdala, and thalamus have been related to depression[19]. All these regions are interconnected and related to cognitive and emotional functions. Lesions in the prefrontal and cingulate cortex and hippocampus may result in memory problems and feelings of guilt, hopelessness, and worthlessness; lesions in the striatum and amygdala might result in a loss of interest and pleasure; and lesions in the hypothalamus may result in sleep problems and changes in appetite. In cases where frontal-limbic systems are involved in mood regulation or their communicating pathways are disrupted by brain lesions, this may lead to LLD[17].

A systematic review and meta-analysis of van Agtmaal et al.[20] investigated the associations of several markers of CSVD with both prevalent LLD and incident LLD. The results show a longitudinal association between higher white matter hyperintensity volume and incident LLD[20]. However, the individual studies included in the meta-analyses showed mixed results, which may be due to suboptimal assessment of white matter hyperintensities (rating scales vs. semi-automated volumetry) or depression (self-reported vs. clinical diagnosis), or to the variation in age of included populations (from 18 to ≥ 80 years). As CSVD is more common among the elderly, its relevance for depression is expected to become larger with age. In agreement with this hypothesis, a recent study by Geraets et al.[21] showed that white matter hyperintensity
volume was only associated with incident depression in individuals above the age of 60 years, while no significant association was found in individuals below the age of 60 years.

Only a few studies investigated the association of specific features of CSVD other than white matter hyperintensity volumes, such as lacunar infarcts and cerebral microbleeds, with LLD\textsuperscript{[20]}. \textit{van Sloten et al.}\textsuperscript{[22]} observed an association between lacunar infarcts and incident depressive symptoms in the AGES-Reykjavik Study, while the population-based Rotterdam Study did not find an association between lacunar infarcts and LLD\textsuperscript{[23]}. With regard to cerebral microbleeds, no association was reported in the study by \textit{van Sloten et al.}\textsuperscript{[22]}. One study combined the presence of lacunar infarcts, cerebral microbleeds, and white matter hyperintensities in a combined CSVD score, but did not report an association between this combined CSVD score and incident depression\textsuperscript{[21]}.

In short, convincing evidence shows a role of white matter hyperintensities in the development of LLD, while the involvement of other features of CSVD remains unclear, potentially due to a paucity of studies. Although evidence is mainly based on white matter hyperintensities, it supports the contribution of CSVD in the development of LLD.

**Generalized microvascular dysfunction**

More recent evidence has shown that microvascular dysfunction (MVD) could be a generalized process underlying the development of many chronic diseases including LLD\textsuperscript{[20]}. This may mean that not only cerebral MVD but also generalized MVD may contribute to the development of LLD. MVD is defined as dysfunction of the microcirculation that consists of blood vessels with a diameter < 150 μm, including arterioles, capillaries, venules, and some specialized structures such as arteriovenous shunts\textsuperscript{[24]}. The microcirculation delivers oxygen and nutrients to, and removes waste from, the tissue\textsuperscript{[25]}. Furthermore, it plays an important role in the autoregulation of blood pressure, especially in cerebral autoregulation, in which the blood pressure remains constant despite large variabilities in the periphery\textsuperscript{[26]}. Nowadays, state-of-the-art technologies enable the non-invasive assessment of MVD in different organs, including the skin, eye, brain, and plasma\textsuperscript{[27]}. Such novel measurements could be an alternative to measuring MVD and are much cheaper than brain MRI. Whether MVD is a generalized phenomenon throughout the body and the brain remains to be elucidated, but both markers of generalized MVD and CSVD have been associated with LLD\textsuperscript{[20]}.

Biomarkers of endothelial dysfunction measured in plasma have been related to LLD in cross-sectional studies\textsuperscript{[28,29]}. Longitudinal evidence comes from one study that investigated the association of direct and indirect markers of MVD with an incidence of LLD\textsuperscript{[30]}. In this study, a lower flicker light-induced retinal arteriolar dilation was associated with a 1.23-fold increased risk for LLD. Furthermore, plasma markers of endothelial dysfunction were found to be associated with a 1.19-fold increased risk for LLD. No association was observed between a lower flicker light-induced retinal venular dilation and a lower heat-induced skin hyperemic response with incident LLD after adjustment for demographic, cardiovascular, and lifestyle factors\textsuperscript{[30]}. In addition, endothelial dysfunction has been associated with a persistent course of depression\textsuperscript{[31]}. More evidence for the role of endothelial dysfunction in LLD was found in a recent study by \textit{Massardo et al.}\textsuperscript{[32]}, in which markers of endothelial dysfunction in patients with depression were associated with changes in regional cerebral blood flow.

In summary, although only one study investigated the longitudinal associations of markers of MVD measured outside the brain with LLD, the results of this study are in line with the results of cross-sectional studies and suggest a role of generalized MVD in the development of LLD.
METABOLIC SYNDROME

Not only MVD but also upstream vascular and metabolic risk factors, e.g., hypertension, dyslipidemia, hyperglycemia, and obesity, may be involved in the etiology of LLD\[^{13}\]. Metabolic syndrome (MetS) clusters these factors in one term, and it is defined as at least three out of the following criteria; central obesity, hypertriglyceridemia, low high-density lipoprotein cholesterol, hypertension, and hyperglycemia\[^{33}\]. It is estimated that over a billion people worldwide are affected by MetS, making it highly relevant to study in relation to depression\[^{14}\]. Previous studies have shown that the severity of MetS increases the risk for white matter hyperintensities and lacunar infarcts\[^{35}\], which may explain its association with LLD\[^{20}\].

A systematic review and meta-analysis of epidemiological studies indeed found convincing evidence for the involvement of vascular and metabolic risk factors in depression\[^{36}\]. Nine longitudinal cohort studies investigated the association between baseline risk factors of MetS and incident depression. Four studies enrolled participants aged > 65 years; the other five studies enrolled young to middle-aged groups. Although moderate heterogeneity was detected ($I^2 = 56.8\%$), the pooled adjusted OR for MetS predicting future risk of depression was 1.49 (95% CI 1.19-1.89). In separate analyses, central obesity [1.20 (1.07-1.35)], hypertriglyceridemia [1.20 (1.05-1.38)], and low high-density lipoprotein cholesterol [1.39 (1.19-1.62)] were associated with an increased risk of depression, while no associations were observed for hyperglycemia [1.05 (0.78-1.42)] and hypertension [0.96 (0.72-1.29)]. However, the results of these individual risk factors must be interpreted with caution, as studies into hyperglycemia and hypertension showed substantial heterogeneity. This may have hampered the chances of finding an association. In addition, analyses were not adjusted for important confounders such as other indicators of MetS. None of the studies adjusted for the use of antidepressant medication. In addition, one study was probably over-adjusted for type 2 diabetes in the analysis of hyperglycemia\[^{37}\]. Furthermore, individual risk factors were evaluated into different categories in each study, which substantially reduces the power of such analysis. Future studies should assess the joint involvement of MetS risk factors on a continuous scale. However, the clustering of risk factors into MetS may have led to a sharper contrast of individuals at high vascular and metabolic risk. Furthermore, this shows that the clustering of individual risk factors has an additive effect, i.e., the effects are partly non-overlapping.

In summary, there is observational evidence showing the importance of vascular and metabolic risk factors in depression, with the most evidence for central obesity, hypertriglyceridemia, and low high-density lipoprotein cholesterol.

DIABETES

The prevalence of depression is nearly doubled in individuals with type 2 diabetes as compared with the general population, with prevalence rates of 6.5%-33%\[^{38}\]. In addition, depression appears to be highly persistent and/or recurrent in type 2 diabetes\[^{39}\]. Hyperglycemia is a key feature of type 2 diabetes and has been proposed as an underlying mechanism involved in the etiology of LLD\[^{40}\]. Both fluctuations in plasma glucose and prolonged hyperglycemia may damage neurons in the brain directly by biological changes and consequently lead to depression\[^{40}\] and cognitive impairment\[^{41}\]. Alternatively, hyperglycemia might indirectly lead to depression via generalized MVD\[^{42}\] and low-grade inflammation\[^{43}\], which both may consequently lead to CSVD\[^{18,44}\] and subsequent depression\[^{42,45}\]. In addition, type 2 diabetes is known to be strongly associated with vascular and metabolic risk factors including hypertension, dyslipidemia, and obesity.
Several meta-analyses have been performed to elucidate the role of hyperglycemia in the development of LLD. A meta-analysis from 2016 of prospective studies found an association between prevalent diabetes and incident depression but not between impaired glucose metabolism (IGM) or newly diagnosed type 2 diabetes and incident depression, compared with normal glucose metabolism\[46\]. These results may have been underpowered for IGM, as the absolute numbers of individuals with IGM and depression were low. A more recent meta-analysis found evidence that continuous hyperglycemia levels may be involved in the development of depression\[47\]. This is in line with the results of a large-scale cross-sectional study that showed an association between both diagnosed and undiagnosed diabetes and a higher prevalence of depression\[46\].

Diabetes might also increase the risk of depression because of disease burden\[46\]. However, one study has shown that disease burden alone may only partially explain the increased risk for depression\[49\]. The suggestion that somatic symptoms related to diabetes underly the increased risk of depression in diabetes is also unlikely, as a population-based study observed no differences in affective and somatic symptoms in individuals with and individuals without type 2 diabetes\[50\].

In summary, while convincing support is found for the involvement of type 2 diabetes in depression, only a few studies investigated the association between continuous levels of hyperglycemia and depression. Disease burden of diabetes may only explain part of the increased risk for depression in diabetes.

INFLAMMATION

Recent evidence suggests that inflammation may contribute to symptoms relevant to a number of psychiatric disorders and particularly depression. Numerous studies have found elevated peripheral and central inflammatory cytokines and acute phase proteins in depression. Studies have shown convincing evidence for a longitudinal association of low-grade inflammation with depression\[31,51-58\]. This association has been suggested to become stronger with age due to more peripheral immune activation and chronic neuro-inflammation in aging\[51\].

Although the exact pathophysiological pathways through which inflammation may contribute to LLD are still unclear, several pathways have been proposed. Dantzer et al.\[59\] concluded that pro-inflammatory cytokines may lead to depression via different pathways: (1) the neural pathway, in which locally produced cytokines activate primary afferent nerves in the brain during infection\[60\]; (2) the humoral pathway, in which Toll-like receptors outside the blood–brain barrier produce pro-inflammatory cytokines that enter the brain via fluid diffusion\[61\]; (3) cytokine transporters at the blood–brain barrier, through which pro-inflammatory cytokines overflowing in the systemic circulation can gain access to the brain\[62\]; and (4) IL-1 receptors that are located on endothelial cells of brain venules. Activation of these IL-1 receptors by circulating cytokines results in the local production of prostaglandins\[63\]. Engagement of these immune-to-brain communication pathways ultimately leads to the production of pro-inflammatory cytokines by microglial cells in the brain, which consequently can induce symptoms of depression\[59\]. In addition, CSVD itself can contribute to increased levels of inflammation within the brain\[18\]. In addition, there is evidence suggesting that inflammation can cause hyperactivity of the hypothalamic-pituitary-adrenal (HPA) axis by disturbing the negative feedback inhibition of circulating corticosteroids on the HPA axis\[64\]. This leads to chronically elevated cortisol levels, which in turn are known to be associated with depression, and causes hypotrophy in the hypothalamus, hippocampus, and pre-frontal cortex\[65\]. Furthermore, a recent meta-analysis showed that antidepressant treatment responders had lower levels of pro-inflammatory markers (e.g., TNF-) than non-responders, whereas treatment resistance in depression was associated with persistently elevated inflammation markers\[66\].
In conclusion, although convincing evidence has related low-grade inflammation to the incidence of LLD, the pathophysiological pathways are not yet completely understood.

**NEURODEGENERATION**

Neurodegeneration of the brain in general or specific brain regions could be involved in the development of LLD as well. Depression is common in neurodegenerative diseases such as Alzheimer’s disease and frontotemporal dementia. It can be a psychological response to experiences of emerging cognitive decline and functional limitations, but it has also been suggested that LLD itself may be an indication of latent neurodegeneration. Indeed, in cross-sectional studies, LLD has been associated with brain atrophy, particularly in the hippocampus and the orbitofrontal cortex.

Longitudinal studies that provide insight into temporality of the association between neurodegeneration and LLD are scarce. A lower total brain volume, temporal lobe atrophy, and a smaller corpus callosum have been related to the incidence of LLD. However, no association between total white matter, grey matter, or cerebrospinal fluid volume (as a marker of brain atrophy) and the incidence of LLD was found in the study by Geraets et al.

Brain atrophy might also be a consequence of depression. The “glucocorticoid cascade hypothesis” proposes that increased secretion of glucocorticoids by prolonged HPA axis activation can produce permanent brain damage by apoptosis of brain tissue. Both glucocorticoid and mineralocorticoid steroid receptors are present in high concentrations in the hippocampus and frontal cortex, and chronically elevated glucocorticoid levels can produce neuronal dysfunction with decreased glucose uptake, reduced dendritic arborization, and, ultimately, neuronal death and cell loss in the hippocampus in animals.

In summary, structural neuroimaging data from cross-sectional studies provide support for the involvement of the frontal-limbic pathway in LLD. However, the findings are inconclusive and the studies are highly heterogeneous. In addition, longitudinal evidence that may provide insight into the etiology is scarce.

**IMPLICATIONS FOR RESEARCH AND CLINICAL PRACTICE**

This narrative review provides an overview of several vascular and metabolic risk factors that may be involved in the development of LLD. MRI research supports the role of white matter hyperintensities in the development of LLD, while the role of other markers of CSVD remains understudied. In addition, increasing evidence supports the involvement of generalized MVD in LLD, although longitudinal evidence is scarce. Furthermore, convincing evidence has shown that MetS, diabetes, and inflammation are important mechanisms in the development of LLD. Longitudinal evidence for the role of neurodegeneration in the development of LLD is limited and needs further exploration.

**Screening for depression**

LLD is often persistent in individuals with cardiovascular diseases (CVD) such as CSVD and type 2 diabetes, and it is itself related to an increased risk to develop CVD and all-cause mortality. Therefore, early recognition and treatment of LLD are important. MVD, MetS, type 2 diabetes, and an inflammatory profile may identify those individuals at high risk for (chronic or persistent) LLD. However, more research is needed to investigate the effect of screening for LLD in healthcare settings. Screening for LLD using a depression questionnaire such as the PHQ-9 is recommended by several CVD management guidelines, e.g., the European Guidelines on cardiovascular diseases prevention in clinical practice, the European Society of Cardiology guidelines for the diagnosis and treatment of heart failure, and the American Heart Association Prevention Committee of the Council on Cardiovascular Nursing. However, only a small
percentage of cardiologists may routinely screen for depression in their patients, while most cardiologists do not consider this their responsibility[80]. In addition, specific guidelines to identify and manage depression have been developed in diabetes care[81,82]. The implementation of these guidelines is highly recommended, as only ~50% of primary care depressed patients are recognized as having depression[83].

**Cardiovascular risk management**

Vascular and metabolic risk factors may provide potential targets for the prevention and treatment of LLD. However, more evidence is needed to evaluate the causality of associations of MVD and MetS treatment with LLD incidence and prognosis. CVD risk management, including treatment of hypertension, hypercholesteremia, hyperglycemia, obesity, smoking behavior, physical activity, nutrition, and stress management, is often used in routine primary care to prevent CVD. In addition to medication, lifestyle modifications, such as exercise, may favorably influence the risk of CVD[84]. This CVD risk management may also be effective in the prevention of LLD. For example, cigarette smoking has been related to an increased risk for both cardiovascular disease[85] and depression[86]. However, studies that evaluate whether CVD risk management is effective in the reduction of LLD are scarce. In the Dutch guidelines for psychiatric care, screening for CVD risk factors in patients with LLD is recommended[87]. To what extent this recommendation is implemented, as well as which interventions strategies are effective for both clinical outcomes, is a subject for future research.

**Collaborative care**

With regard to diabetes, integrated care approaches that treat LLD and diabetes jointly need implementation. Although research has shown a positive effect of such collaborative care[88], implementation in clinical practice proves to be difficult[88]. In addition, LLD and diabetes might share the same antecedents such as obesity, MVD, inflammation, and physical inactivity. Consequently, future research is needed to study the effect of prevention efforts aimed at targeting these antecedents to concurrently prevent LLD and diabetes.

The complex relationship between LLD and dementia demands for further research. Both diseases show similar neurobiological abnormalities[89], which requires further refinement and validation of clinical diagnostic criteria. LLD may be a higher risk factor for vascular dementia than Alzheimer’s disease[2], while in the latter case, LLD is suggested to be a prodromal symptom[90]. In clinical practice, it is important to actively monitor symptoms. Dutch guidelines recommend screening for vascular risk factors in the case of LLD[87]. In the case of cognitive decline, this might indicate a vascular cause of dementia[91]. Effective collaborative dementia care approaches have been developed but need further implementation[92].

**Anti-inflammatory treatment**

Many randomized controlled trials have investigated the effect of anti-inflammatory treatment on depression. A meta-analysis of 36 clinical trials including almost 10,000 patients showed that anti-inflammatory agents can improve depression[93]. Non-steroidal anti-inflammatory drugs, cytokine inhibitors, statins, glucocorticoids, and minocycline may improve depressive symptoms as monotherapy in comparison to placebo. Furthermore, non-steroidal anti-inflammatory drugs, statins and glucocorticoids may be effective as an add-on treatment, as compared to antidepressants combined with placebo. The results also suggest positive effects on depressive symptoms among patients with somatic comorbidities. However, due to large heterogeneity and a high risk of bias, the results of this meta-analysis should be interpreted with caution. Future studies should include longer follow-up periods, several measures of biomarkers over time, multiple anti-inflammatory agents, and explore whether subgroups of patients may benefit more from a specific treatment (e.g., patients with elevated levels of specific biomarkers). In addition, more research is needed to investigate side effects and optimal dosage and duration of anti-
inflammatory treatment.

CONCLUSION

Convincing evidence supports a role of white matter hyperintensities, generalized microvascular dysfunction, MetS, diabetes, and inflammation in the development of LLD, while the involvement of neurodegeneration needs further in-depth investigation. Guidelines to screen for LLD in cardiovascular care need implementation, as do integrated care approaches that treat LLD and diabetes jointly. However, more research is needed to investigate the effect of interventions in clinical practice.

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