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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[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 behavior 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[18]. 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[20]. *van Sloten et al.*[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[23]. With regard to cerebral microbleeds, no association was reported in the study by *van Sloten et al.*[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[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[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[24]. The microcirculation delivers oxygen and nutrients to, and removes waste from, the tissue[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[26]. Nowadays, state-of-the-art technologies enable the non-invasive assessment of MVD in different organs, including the skin, eye, brain, and plasma[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[20].

Biomarkers of endothelial dysfunction measured in plasma have been related to LLD in cross-sectional studies[28,29]. Longitudinal evidence comes from one study that investigated the association of direct and indirect markers of MVD with an incidence of LLD[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[30]. In addition, endothelial dysfunction has been associated with a persistent course of depression[31]. More evidence for the role of endothelial dysfunction in LLD was found in a recent study by *Massardo et al.*[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[34]. 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[48].

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[67]. 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[68]. Indeed, in cross-sectional studies, LLD has been associated with brain atrophy, particularly in the hippocampus and the orbitofrontal cortex[69].

Longitudinal studies that provide insight into temporality of the association between neurodegeneration and LLD are scarce. A lower total brain volume[22], temporal lobe atrophy[70], and a smaller corpus callosum[71] 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.*[21].

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[72]. 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[73].

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[74].

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 LDD is limited and needs further exploration.

Screening for depression

LLD is often persistent in individuals with cardiovascular diseases (CVD) such as CSVD[21] and type 2 diabetes[39], and it is itself related to an increased risk to develop CVD and all-cause mortality[75,76]. 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[77], the European Society of Cardiology guidelines for the diagnosis and treatment of heart failure[78], and the American Heart Association Prevention Committee of the Council on Cardiovascular Nursing[79]. 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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Authors' Contributions

Geraets, A, Köhler S and Schram M wrote the manuscript.

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Not applicable.

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Not applicable.

REFERENCES

1. Blazer DG. Depression in late life: review and commentary. *J Gerontol A Biol Sci Med Sci* 2003;58:249-65. DOI PubMed
2. Diniz BS, Butters MA, Albert SM, Dew MA, Reynolds CF 3rd. Late-life depression and risk of vascular dementia and Alzheimer's disease: systematic review and meta-analysis of community-based cohort studies. *Br J Psychiatry* 2013;202:329-35. DOI PubMed PMC
3. Laborde-Lahoz P, El-Gabalawy R, Kinley J, Kirwin PD, Sareen J, Pietrzak RH. Subsyndromal depression among older adults in the USA: prevalence, comorbidity, and risk for new-onset psychiatric disorders in late life. *Int J Geriatr Psychiatry* 2015;30:677-85. DOI PubMed
4. Lenze EJ, Rogers JC, Martire LM, et al. The Association of late-life depression and anxiety with physical disability: a review of the literature and prospectus for future research. *The American Journal of Geriatric Psychiatry* 2001;9:113-35. PubMed
5. Djernes JK. Prevalence and predictors of depression in populations of elderly: a review. *Acta Psychiatr Scand* 2006;113:372-87. DOI PubMed
6. WHO. Depression and other common mental disorders: global health estimates. heepsAvailable form: https://apps.who.int/iris/handle/10665/254610 [Last accessed on 25Mar 2022].
7. Lenze, EJ, Sheffrin M, Driscoll HC, et al. Incomplete response in late-life depression: getting to remission. *Dialogues Clin Neurosci* 2009;10:419-30. DOI PubMed PMC
8. Paroni G, Seripa D, Fontana A, et al. Klotho gene and selective serotonin reuptake inhibitors: response to treatment in late-life major depressive disorder. *Mol Neurobiol* 2017;54:1340-51. DOI PubMed
9. Schaakxs R, Comijs HC, Lamers F, Kok RM, Beekman ATF, Penninx BWJH. Associations between age and the course of major depressive disorder: a 2-year longitudinal cohort study. *The Lancet Psychiatry* 2018;5:581-90. DOI PubMed

10. Comijs HC, Nieuwesteeg J, Kok R, et al. The two-year course of late-life depression; results from the Netherlands study of depression in older persons. *BMC Psychiatry* 2015;15:20. DOI PubMed PMC
11. Alexopoulos GS. Depression in the elderly. *Lancet* 2005;365:1961-70. DOI PubMed
12. Alexopoulos GS, Meyers BS, Young RC, Campbell S, Silbersweig D, Charlson M. "Vascular depression" hypothesis. *Arch Gen Psychiatry* 1997;54:915-22. DOI PubMed
13. Alexopoulos GS. Mechanisms and treatment of late-life depression. *Transl Psychiatry* 2019;9:188. DOI PubMed PMC
14. Krishnan KR, Hays JC, Blazer DG. MRI-defined vascular depression. *Am J Psychiatry* 1997;154:497-501. DOI PubMed
15. Souery D, Papakostas GI, Trivedi MH. Treatment-resistant depression. *J Clin Psychiatry* 2006;67:16-22. Available from: https://www.psychiatrist.com/read.
16. Trivedi MH, Rush AJ, Wisniewski SR, et al; STAR*D Study Team. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. *Am J Psychiatry* 2006;163:28-40. DOI PubMed
17. Aizenstein HJ, Baskys A, Boldrini M, et al. Vascular depression consensus report - a critical update. *BMC Med* 2016;14:161. DOI PubMed PMC
18. Wardlaw JM, Smith C, Dichgans M. Mechanisms of sporadic cerebral small vessel disease: insights from neuroimaging. *The Lancet Neurology* 2013;12:483-97. DOI PubMed PMC
19. Nestler EJ, Barrot M, Dileone RJ, Eisch AJ, Gold SJ, Monteggia LM. Neurobiology of depression. *Neuron* 2002;34:13-25. DOI PubMed
20. Agtmaal MJM, Houben AJHM, Pouwer F, Stehouwer CDA, Schram MT. Association of microvascular dysfunction with late-life depression: a systematic review and meta-analysis. *JAMA Psychiatry* 2017;74:729-39. DOI PubMed PMC
21. Geraets AF, Köhler S, Jansen JF, et al. The association of markers of cerebral small vessel disease and brain atrophy with incidence and course of depressive symptoms - the maastricht study. *J Affect Disord* 2021;292:439-47. DOI PubMed
22. van Sloten TT, Sigurdsson S, van Buchem MA, et al. Cerebral small vessel disease and association with higher incidence of depressive symptoms in a general elderly population: the ages-reykjavik study. *Am J Psychiatry* 2015;172:570-8. DOI PubMed PMC
23. Perez HC, Direk N, Hofman A, Vernooij MW, Tiemeier H, Ikram MA. Silent brain infarcts: a cause of depression in the elderly? *Psychiatry Res* 2013;211:180-2. DOI PubMed
24. Houben AJHM, Martens RJH, Stehouwer CDA. Assessing microvascular function in humans from a chronic disease perspective. *J Am Soc Nephrol* 2017;28:3461-72. DOI PubMed PMC
25. Aird WC. Phenotypic heterogeneity of the endothelium: I. Structure, function, and mechanisms. *Circ Res* 2007;100:158-73. DOI PubMed
26. . Hall, J.E. and A.C. Guyton, textbook of medical physiology. 2011. 12th edn: p. 157-66. ISBN:978-1-4160-4574-8. DOI
27. Li W, Schram MT, Sörensen BM, et al. Microvascular phenotyping in the maastricht study: design and main findings, 2010-2018. *Am J Epidemiol* 2020;189:873-84. DOI PubMed PMC
28. van Sloten TT, Schram MT, Adriaanse MC, et al. Endothelial dysfunction is associated with a greater depressive symptom score in a general elderly population: the Hoorn study. *Psychol Med* 2014;44:1403-16. DOI PubMed
29. van Dooren FE, Schram MT, Schalkwijk CG, et al. Associations of low grade inflammation and endothelial dysfunction with depression - the Maastricht study. *Brain behav immun* 2016;56:390-6. DOI PubMed
30. Geraets AFJ, van Agtmaal MJM, Stehouwer CDA, et al. Association of markers of microvascular dysfunction with prevalent and incident depressive symptoms: the Maastricht study. *Hypertension* 2020;76:342-9. DOI PubMed
31. Janssen EPCJ, Köhler S, Geraets AFJ, et al. Low-grade inflammation and endothelial dysfunction predict four-year risk and course of depressive symptoms: The Maastricht study. *Brain Behav Immun* 2021;97:61-7. DOI PubMed
32. Massardo T, Quintana JC, Jaimovich R, et al. Regional brain perfusion is associated with endothelial dysfunction markers in major depressive disorder. *Neuropsychobiology* 2021;80:214-24. DOI PubMed
33. Alberti KG, Eckel RH, Grundy SM, et al; International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart; Lung; and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; International Association for the Study of Obesity. Harmonizing the metabolic syndrome: a joint interim statement of the international diabetes federation task force on epidemiology and prevention; national heart, lung, and blood institute; American heart association; world heart federation; international atherosclerosis society; and international association for the study of obesity. *Circulation* 2009;120:1640-5. DOI PubMed
34. Saklayen MG. The global epidemic of the metabolic syndrome. *Curr Hypertens Rep* 2018;20:12. DOI PubMed PMC
35. Shu MJ, Zhai FF, Zhang DD, et al. Metabolic syndrome, intracranial arterial stenosis and cerebral small vessel disease in community-dwelling populations. *Stroke Vasc Neurol* 2021;6:589-94. DOI PubMed PMC
36. Pan A, Keum N, Okereke OI, et al. Bidirectional association between depression and metabolic syndrome: a systematic review and meta-analysis of epidemiological studies. *Diabetes Care* 2012;35:1171-80. DOI PubMed PMC
37. Takeuchi T, Nakao M, Nomura K, Yano E. Association of metabolic syndrome with depression and anxiety in Japanese men. *Diabetes Metab* 2009;35:32-6. DOI PubMed
38. Roy T, Lloyd CE. Epidemiology of depression and diabetes: a systematic review. *Journal of Affective Disorders* 2012;142:S8-S21. DOI PubMed
39. Nefs G, Pouwer F, Denollet J, Pop V. The course of depressive symptoms in primary care patients with type 2 diabetes: results from the diabetes, depression, type D Personality Zuidoost-Brabant (DiaDDZoB) study. *Diabetologia* 2012;55:608-16. DOI PubMed

PMC

40. Sloten T, Schram M. Understanding depression in type 2 diabetes: a biological approach in observational studies. *F1000Res* 2018;7:1283. DOI PubMed PMC
41. Biessels GJ, Nobili F, Teunissen CE, Simó R, Scheltens P. Understanding multifactorial brain changes in type 2 diabetes: a biomarker perspective. *The Lancet Neurology* 2020;19:699-710. DOI PubMed
42. Wardlaw JM, Smith EE, Biessels GJ, et al. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. *The Lancet Neurology* 2013;12:822-38. DOI PubMed PMC
43. Wang X, Bao W, Liu J, et al. Inflammatory markers and risk of type 2 diabetes: a systematic review and meta-analysis. *Diabetes Care* 2013;36:166-75. DOI PubMed PMC
44. Leonard BE. Inflammation, depression and dementia: are they connected? *Neurochem Res* 2007;32:1749-56. DOI PubMed
45. Pasco JA, Nicholson GC, Williams LJ, et al. Association of high-sensitivity C-reactive protein with de novo major depression. *Br J Psychiatry* 2010;197:372-7. DOI PubMed
46. Tong A, Wang X, Li F, Xu F, Li Q, Zhang F. Risk of depressive symptoms associated with impaired glucose metabolism, newly diagnosed diabetes, and previously diagnosed diabetes: a meta-analysis of prospective cohort studies. *Acta Diabetol* 2016;53:589-98. DOI PubMed
47. Beran M, Muzambi R, Geraets A, et al; European Depression in Diabetes (EDID) Research Consortium. The bidirectional longitudinal association between depressive symptoms and HbA_{1c} : a systematic review and meta-analysis. *Diabet Med* 2022;39:e14671. DOI PubMed
48. Meurs M, Roest AM, Wolffenbuttel BH, Stolk RP, de Jonge P, Rosmalen JG. Association of depressive and anxiety disorders with diagnosed versus undiagnosed diabetes: an epidemiological study of 90,686 participants. *Psychosom Med* 2016;78:233-41. DOI PubMed
49. Geraets AFJ, Köhler S, Muzambi R, et al. The association of hyperglycaemia and insulin resistance with incident depressive symptoms over 4 years of follow-up: The Maastricht Study. *Diabetologia* 2020;63:2315-28. DOI PubMed PMC
50. Janssen EP, Köhler S, Stehouwer CD, et al. The patient health questionnaire-9 as a screening tool for depression in individuals with type 2 diabetes mellitus: the Maastricht study. *J Am Geriatr Soc* 2016;64:e201-6. DOI PubMed
51. Valkanova V, Ebmeier KP, Allan CL. CRP, IL-6 and depression: a systematic review and meta-analysis of longitudinal studies. *J Affect Disord* 2013;150:736-44. DOI PubMed
52. Copeland WE, Shanahan L, Worthman C, Angold A, Costelloet EJ. Cumulative depression episodes predict later C-reactive protein levels: a prospective analysis. *Biol Psychiatry* 2012;71:15-21. DOI
53. Chocano-Bedoya PO, Mirzaei F, O'Reilly EJ, et al. C-reactive protein, interleukin-6, soluble tumor necrosis factor α receptor 2 and incident clinical depression. *J Affect Disord* 2014;163:25-32. DOI PubMed PMC
54. Baune BT, Smith E, Reppermund S, et al. Inflammatory biomarkers predict depressive, but not anxiety symptoms during aging: the prospective Sydney memory and aging study. *Psychoneuroendocrinology* 2012;37:1521-30. DOI
55. Wium-Andersen MK, Ørsted DD, Nielsen SF, Nordestgaard BG. Elevated C-reactive protein levels, psychological distress, and depression in 73, 131 individuals. *JAMA Psychiatry* 2013;70:176-84. DOI PubMed
56. Zalli A, Jovanova O, Hoogendijk WJ, Tiemeier H, Carvalho LA. Low-grade inflammation predicts persistence of depressive symptoms. *Psychopharmacology (Berl)* 2016;233:1669-78. DOI PubMed PMC
57. van den Biggelaar AH, Gussekloo J, de Craen AJ, et al. Inflammation and interleukin-1 signaling network contribute to depressive symptoms but not cognitive decline in old age. *Exp Gerontol* 2007;42:693-701. DOI
58. Stewart JC, Rand KL, Muldoon MF, Kamarck TW. A prospective evaluation of the directionality of the depression-inflammation relationship. *Brain Behav Immun* 2009;23:936-44. DOI PubMed PMC
59. Dantzer R, O'Connor JC, Freund GG, Johnson RW, Kelley KW. From inflammation to sickness and depression: when the immune system subjugates the brain. *Nat Rev Neurosci* 2008;9:46-56. DOI PubMed PMC
60. Romeo HE, Tio DL, Rahman SU, Chiappelli F, Taylor AN. The glossopharyngeal nerve as a novel pathway in immune-to-brain communication: relevance to neuroimmune surveillance of the oral cavity. *Journal of Neuroimmunology* 2001;115:91-100. DOI PubMed
61. Vitkovic L, Konsman JP, Bockaert J, Dantzer R, Homburger V, Jacque C. Cytokine signals propagate through the brain. *Mol Psychiatry* 2000;5:604-15. DOI PubMed
62. Banks WA. The blood-brain barrier in psychoneuroimmunology. *Neurol Clin* 2006;24:413-9. DOI PubMed
63. Schiltz JC, Sawchenko PE. Distinct brain vascular cell types manifest inducible cyclooxygenase expression as a function of the strength and nature of immune insults. *J Neurosci* 2002;22:5606-18. DOI PubMed PMC
64. Schiepers OJ, Wichers MC, Maes M. Cytokines and major depression. *Prog Neuropsychopharmacol Biol Psychiatry* 2005;29:201-17. DOI PubMed
65. Zunszain PA, Anacker C, Cattaneo A, Carvalho LA, Pariante CM. Glucocorticoids, cytokines and brain abnormalities in depression. *Prog Neuropsychopharmacol Biol Psychiatry* 2011;35:722-9. DOI PubMed PMC
66. Strawbridge R, Arnone D, Danese A, Papadopoulos A, Herane Vives A, Cleare AJ. Inflammation and clinical response to treatment in depression: a meta-analysis. *Eur Neuropsychopharmacol* 2015;25:1532-43. DOI PubMed
67. Baquero M, Martín N. Depressive symptoms in neurodegenerative diseases. *World J Clin Cases* 2015;3:682-93. DOI PubMed PMC
68. Burgut FT, Benaur M, Hencliffe C. Late-life depression: a neuropsychiatric approach. *Expert Rev Neurother* 2006;6:65-72. DOI

PubMed

69. Tittmann M, Günther T, Sacher J, et al. Structural brain changes in early-onset and late-onset depression: an update of volumetric MRI findings. *Int J Imaging Syst Technol* 2014;24:149-60. DOI
70. Gudmundsson P, Olesen PJ, Simoni M, et al. White matter lesions and temporal lobe atrophy related to incidence of both dementia and major depression in 70-year-olds followed over 10 years. *Eur J Neurol* 2015;22:781-8, e49. DOI PubMed
71. Cyprien F, Courtet P, Poulain V, et al. Corpus callosum size may predict late-life depression in women: a 10-year follow-up study. *J Affect Disord* 2014;165:16-23. DOI PubMed
72. Almeida OP, Burton EJ, Ferrier N, McKeith IG, O'Brien JT. Depression with late onset is associated with right frontal lobe atrophy. *Psychol Med* 2003;33:675-81. DOI PubMed
73. Sapolsky RM. Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders. *Arch Gen Psychiatry* 2000;57:925-35. DOI PubMed
74. Disabato BM, Sheline YI. Biological basis of late life depression. *Curr Psychiatry Rep* 2012;14:273-9. DOI PubMed PMC
75. Scott KM. Prevention of CVD in depression. In: Baune BT, Tully PJ, editors. Cardiovascular Diseases and Depression. Cham: Springer International Publishing; 2016. p. 509-17. DOI
76. Dooren FE, Nefs G, Schram MT, Verhey FR, Denollet J, Pouwer F. Depression and risk of mortality in people with diabetes mellitus: a systematic review and meta-analysis. *PLoS One* 2013;8:e57058. DOI PubMed PMC
77. Perk J, De Backer G, Gohlke H, et al; European Association for Cardiovascular Prevention & Rehabilitation (EACPR); ESC Committee for Practice Guidelines (CPG). European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The fifth joint task force of the European society of cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of nine societies and by invited experts). *Eur Heart J* 2012;33:1635-701. DOI PubMed
78. McMurray JJ, Adamopoulos S, Anker SD, et al; ESC Committee for Practice Guidelines. ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: the task force for the diagnosis and treatment of acute and chronic heart failure 2012 of the European society of cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur Heart J* 2012;33:1787-847. DOI PubMed
79. Lichtman JH, Bigger JT Jr, Blumenthal JA, et al; American Heart Association Prevention Committee of the Council on Cardiovascular Nursing; American Heart Association Council on Clinical Cardiology; American Heart Association Council on Epidemiology and Prevention; American Heart Association Interdisciplinary Council on Quality of Care and Outcomes Research. , American Psychiatric Association. depression and coronary heart disease: recommendations for screening, referral, and treatment: a science advisory from the American heart association prevention committee of the council on cardiovascular nursing, council on clinical cardiology, council on epidemiology and prevention, and interdisciplinary council on quality of care and outcomes research: endorsed by the American psychiatric association. *Circulation* 2008;118:1768-75. DOI PubMed
80. Stewart A, Driscoll A, Hare D. National survey of Australian cardiologists' beliefs and practice regarding screening, diagnosis and management of depression. *Heart, Lung and Circulation* 2009;18:S5. DOI
81. Young-Hyman D, Groot DM, Hill-Briggs F, et al. Psychosocial care for people with diabetes: a position statement of the American diabetes association. *Diabetes Care* 2016;39:2126-40. DOI PubMed PMC
82. Barents ESE, Bilo HJG, Bouma M, et al. Diabetes mellitus type 2. Available from: https://richtlijnen.nhg.org/standaarden/diabetes-mellitus-type-2 [Last accessed on 25 Mar 2022]. DOI
83. Trangle, M., J. Gursky, and R. Haight, Adult depression in primary care. ICSI Inst Clin Syst Improv. Available from: https://www.icsi.org/guideline/depression/ [Last accessed on 25 Mar 2022]. DOI
84. Stehouwer CDA. Microvascular Dysfunction and hyperglycemia: a vicious cycle with widespread consequences. *Diabetes* 2018;67:1729-41. DOI PubMed
85. Ambrose JA, Barua RS. The pathophysiology of cigarette smoking and cardiovascular disease: an update. *J Am Coll Cardiol* 2004;43:1731-7. DOI PubMed
86. Fluharty M, Taylor AE, Grabski M, Munafò MR. The association of cigarette smoking with depression and anxiety: a systematic review. *Nicotine Tob Res* 2017;19:3-13. DOI PubMed PMC
87. Trimbos-instituut.ADDENDUM OUDEREN BIJ DE MDR DEPRESSIE. Available from: https://www.trimbos.nl/docs/b0822cf7-b915-44a2-9a55-db6ea341267a.pdf [Last accessed on 25 Mar 2022]. DOI
88. Petrak F, Baumeister H, Skinner TC, Brown A, Holt RIG. Depression and diabetes: treatment and health-care delivery. *The Lancet Diabetes & Endocrinology* 2015;3:472-85. DOI PubMed
89. Bennett S, Thomas AJ. Depression and dementia: cause, consequence or coincidence? *Maturitas* 2014;79:184-90. DOI PubMed
90. Barnes DE, Yaffe K, Byers AL, McCormick M, Schaefer C, Whitmer RA. Midlife vs late-life depressive symptoms and risk of dementia: differential effects for Alzheimer disease and vascular dementia. *Arch Gen Psychiatry* 2012;69:493-8. DOI PubMed PMC
91. Köhler S, Buntinx F, Palmer K, van den Akker M. Depression, vascular factors, and risk of dementia in primary care: a retrospective cohort study. *J Am Geriatr Soc* 2015;63:692-8. DOI PubMed
92. Heintz H, Monette P, Epstein-Lubow G, Smith L, Rowlett S, Forester BP. Emerging collaborative care models for dementia care in the primary care setting: a narrative review. *Am J Geriatr Psychiatry* 2020;28:320-30. DOI PubMed
93. Köhler-Forsberg O, N Lydholm C, Hjorthøj C, et al. Efficacy of anti-inflammatory treatment on major depressive disorder or depressive symptoms: meta-analysis of clinical trials. *Acta Psychiatr Scand* 2019;139:404-19. DOI PubMed