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Association of Microvascular Dysfunction With Late-Life Depression
A Systematic Review and Meta-analysis

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Supplemental content

IMPORTANCE The etiologic factors of late-life depression are still poorly understood. Recent evidence suggests that microvascular dysfunction is associated with depression, which may have implications for prevention and treatment. However, this association has not been systematically reviewed.

OBJECTIVE To examine the associations of peripheral and cerebral microvascular dysfunction with late-life depression.

DATA SOURCES A systematic literature search was conducted in MEDLINE and EMBASE for and longitudinal studies published since inception to October 16, 2016, that assessed the associations between microvascular dysfunction and depression.

STUDY SELECTION Three independent researchers performed the study selection based on consensus. Inclusion criteria were a study population 40 years of age or older, a validated method of detecting depression, and validated measures of microvascular function.

DATA EXTRACTION AND SYNTHESIS This systematic review and meta-analysis has been registered at PROSPERO (CRD42016049158) and is reported in accordance with the PRISMA and MOOSE guidelines. Data extraction was performed by an independent researcher.

MAIN OUTCOMES AND MEASURES The following 5 estimates of microvascular dysfunction were considered in participants with or without depression: plasma markers of endothelial function, albuminuria, measurements of skin and muscle microcirculation, retinal arteriolar and venular diameter, and markers for cerebral small vessel disease. Data are reported as pooled odds ratios (ORs) by use of the generic inverse variance method with the use of random-effects models.

RESULTS A total of 712 studies were identified; 48 were included in the meta-analysis, of which 8 described longitudinal data. Data from 43 600 participants, 9203 individuals with depression, and 72 441 person-years (mean follow-up, 3.7 years) were available. Higher levels of plasma endothelial biomarkers (soluble intercellular adhesion molecule–1: OR, 1.58; 95% CI, 1.28-1.96), white matter hyperintensities (OR, 1.29; 95% CI, 1.19-1.39), cerebral microbleeds (OR, 1.18; 95% CI, 1.03-1.34), and cerebral (micro)infarctions (OR, 1.30; 95% CI, 1.21-1.39) were associated with depression. Among the studies available, no significant associations of albuminuria and retinal vessel diameters with depression were reported. Longitudinal data showed a significant association of white matter hyperintensities with incident depression (OR, 1.19; 95% CI, 1.09-1.30).

CONCLUSIONS AND RELEVANCE This meta-analysis shows that both the peripheral and cerebral forms of microvascular dysfunction are associated with higher odds of (incident) late-life depression. This finding may have clinical implications because microvascular dysfunction might provide a potential target for the prevention and treatment of depression.

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Late-life depression is a highly prevalent and heterogeneous disease with high rates of morbidity and mortality.[1,2] It is characterized by recurrent episodes: up to 50% of those who recover from a first episode of depression will experience additional episodes throughout their lifetime.[3-6] Evidence suggests a cerebrovascular etiologic cause[7] because late-life depression has been associated with vascular dementia, stroke, and white matter hyperintensities (WMHs).[8] Moreover, a vascular etiologic cause may explain the high recurrence rate of depression, in addition to the high rate of resistance to antidepressants and/or cognitive behavioral therapy; approximately one-third of patients with depression have treatment-resistant depression.[6,9,10]

Several studies have provided evidence that cerebral small vessel disease may play a role in the etiologic factors of late-life depression.[7,11-18] A meta-analysis from 2014, including 19 studies and 6274 participants, showed significant cross-sectional and longitudinal associations between white matter lesions, a proxy of cerebral small vessel disease, and (incident) depression.[19] However, multiple studies with continuous measures of WMHs were not included in this meta-analysis, and 2 large longitudinal studies became available only recently.[13,20] Furthermore, the growing evidence on alternative markers of microvascular dysfunction (for instance, on biomarkers of endothelial dysfunction) was not taken into account in previous meta-analyses.[21-23]

In view of these considerations, we hypothesize that microvascular dysfunction, both peripheral and cerebral, may be associated with depression. We conducted a systematic review and meta-analysis to investigate this hypothesis, both in cross-sectional and longitudinal studies.

Key Points

Question Are both the peripheral and cerebral forms of microvascular dysfunction associated with late-life depression, as suggested by the vascular depression hypothesis?

Findings This systematic review and meta-analysis of 48 studies comprising 43 600 participants, including 9203 individuals with depression, shows that the cerebral and peripheral forms of microvascular dysfunction were associated with increased odds for (incident) late-life depression, independent of cardiovascular risk factors.

Meaning These findings support the hypothesis that microvascular dysfunction is causally linked to late-life depression. This finding may have clinical implications because microvascular dysfunction might provide a target for the prevention and treatment of depression.

Methods

Search Strategy

We used MEDLINE and EMBASE to conduct a systematic literature search for cross-sectional and longitudinal epidemiologic studies of humans, determining the association between markers of microvascular dysfunction and depressive symptoms and/or depressive disorder, published from inception to October 16, 2016. This study has been registered at PROSPERO (https://www.crd.york.ac.uk/PROSPERO/ [CRD42016049158]) and is reported in accordance with the PRISMA[24] and MOOSE guidelines. We considered the following 5 estimates of microvascular dysfunction: plasma markers of endothelial function, albuminuria, measurements of skin and muscle microcirculation, retinal arteriolar and venular diameter, and markers for cerebral small vessel disease. The exact search strategy and rationale are in the eAppendix in the Supplement.

Selection Criteria and Data Extraction

Three independent researchers performed the study selection (M.J.M.v.A., A.J.H.M.H., and M.T.S.). Population-based or case-control studies that reported on microvascular dysfunction in participants with or without depression were included. **Figure 1** shows the selection procedure. Of the 67 studies included in the review, we extracted the following: baseline characteristics of the study population, study design, number of participants with or without depression, definition of microvascular dysfunction and depression (self-reported questionnaire vs diagnostic psychiatric interview), fully adjusted results including 95% CIs, SD, or range, and confounders included in the analyses. When these data were missing, the principal investigators were contacted for further information. If the principal investigator could not provide the missing data, the study was excluded. The quality of studies was assessed by use of the Newcastle-Ottawa Scale (NOS) for case-control and cohort studies (eTable 1 in the Supplement). This scale uses a 10-point grading system with a maximum score of 9 points for longitudinal studies, 6 points for cross-sectional cohort studies, and 8 points for case-control studies and assesses selection of study groups, comparability of groups, and ascertainment of exposure and outcome.[25] We calculated the percentage of the maximum NOS score for all studies (eTable 1 in the Supplement).

Statistical Analysis

We performed the meta-analysis with Review Manager, version 5.3 (The Nordic Cochrane Centre, The Cochrane Collaboration), by use of the generic inverse variance method with random-effects models. In studies that reported microvascular function as mean (SD) values for participants with depression compared with controls without depression, we calculated odds ratios (ORs) based on the standardized mean difference method in concordance with the *Cochrane Handbook for Systematic Reviews of Interventions*.[26] If only a range of scores was reported, we estimated the SD using the formula (upper limit − lower limit)/4. We used forest plots to display the pooled ORs and 95% CIs, assessed heterogeneity using I^2 statistics (values of 50%-75% indicated moderate heterogeneity, and values of >75% indicated considerable heterogeneity),[26-28] and determined the risk of publication bias by visual inspection of funnel plots, the Egger test, and the trim-and-fill method.[26,29,30] We performed subgroup and meta-regression analysis with R[31] to explore heterogeneity, and we evaluated the methods to assess depression (diagnostic interviews vs self-reported questionnaires), study design (case-control vs cohort study), methods to assess WMHs (semiautomatic volumetry vs subjective rating scale), and study quality as assessed by the NOS score (≥60% vs <60%).

Results

Study Selection and Characteristics

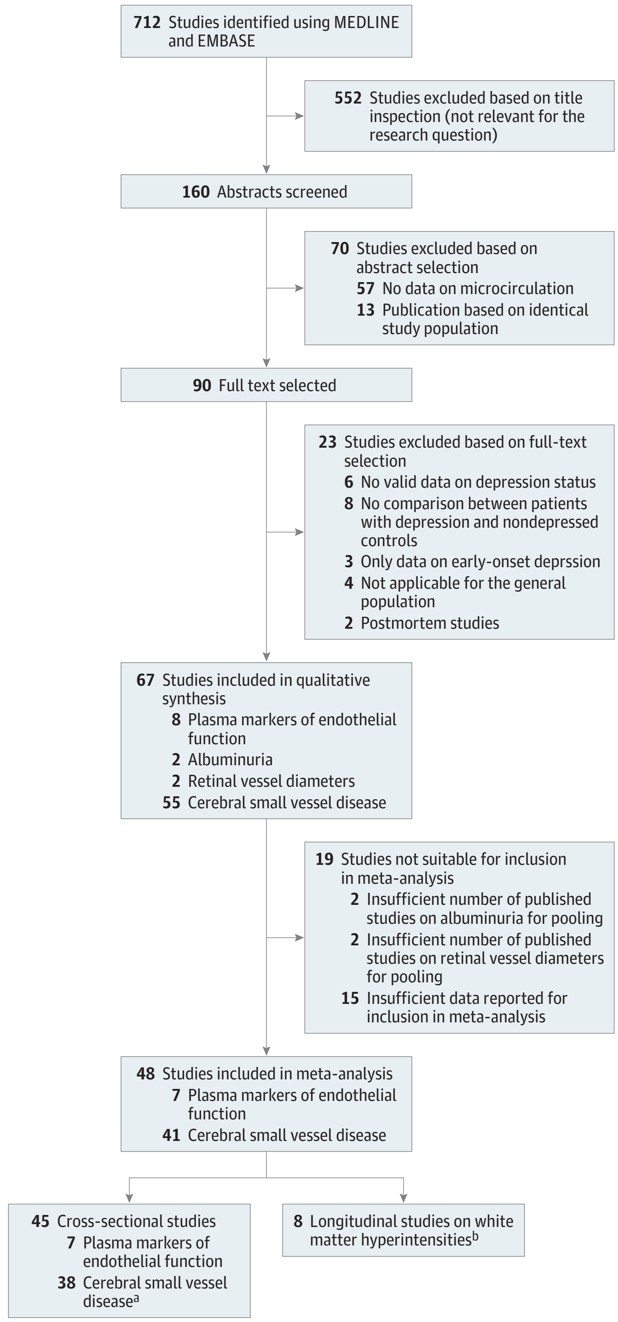
We identified 712 studies, of which 90 full-text articles were assessed for eligibility. Of these, we selected 67 studies that investigated whether microvascular dysfunction was associated with depressive disorder or depressive symptoms. Of these studies, 59 had a cross-sectional design (35 case-control studies and 24 cohort studies), and 8 had a longitudinal design (8 cohort studies). In total, data from 43 600 participants, including 9203 individuals (21.1%) with depression, were included in the meta-analysis. The mean age of participants was 66 years, and 23 544 were female (54.0%). In total, 72 441 person-years were included in longitudinal analyses (mean [SD] follow-up, 3.7 [0.7] years). We found no studies that investigated the association between skin and muscle microcirculation and depressive disorder or depressive symptoms.

All studies included in the review used a dichotomous outcome measure for depression, either by use of a diagnostic interview to assess major depressive disorder or by use of a cutoff for clinically relevant depressive symptoms, including the Mini International Neuropsychiatric Interview or the Structured Clinical Interview for *DSM* for depressive disorder and the Centers for Epidemiological Studies Depression Scale, the Geriatric Depression Scale, the Hamilton Depression Rating Scale, the Beck Depression Inventory, and the Montgomery-Asberg Depression Rating Scale for clinically relevant depressive symptoms. Plasma samples of biomarkers (soluble intercellular adhesion molecule-1 [sICAM-1], soluble vascular cell adhesion molecule-1 [sVCAM-1], e-selectin, and von Willebrand factor [vWF]) for endothelial function were all analyzed by the use of an enzyme-linked immunosorbent assay. Albuminuria was measured by use of the albumin to creatinine ratio or 24-hour urinary albumin excretion. Retinal vessel calibers were measured by the use of stereoscopic color fundus photography. Cerebral small vessel disease was determined by magnetic resonance imaging–defined automated segmentation of WMH volume (33 studies), rating scales for WMH severity (22 studies), microbleeds (4 studies), and/or lacunar or silent infarctions (4 studies). Characteristics of all selected studies are presented in eTable 2 in the Supplement and the outcomes of the selected studies in eTable 3 in the Supplement.

Association of Endothelial Function With Depression

Eight studies investigated the cross-sectional associations between plasma markers of endothelial function and depressive symptoms (n = 6) or depressive disorder (n = 4).[21,32-38] Most studies observed that higher levels of endothelial plasma markers, which indicate dysfunction, were associated with depression.[32,33,35-38] One study described lower sVCAM-1 levels,[34] and another study lower e-selectin levels,[21] in participants with depression compared with controls without depression.

Figure 1. Flowchart of Study Selection



[a] Including 38 studies on white matter hyperintensities, 4 studies on microbleeds, and 4 studies on microinfarctions.

[b] Five studies provided both cross-sectional and longitudinal data.

Seven studies[21,32-35,37,38] were included in the meta-analysis on plasma markers of endothelial function (1 study provided insufficient data[36]). We found a significant association between higher levels of plasma markers of endothelial function and depression (**Figure 2**; pooled OR per SD increase

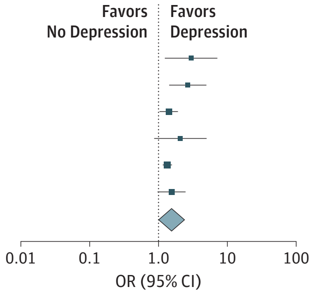
Figure 2. Cross-sectional Association of Endothelial Plasma Markers With Depression

A sICAM-1

Study or Subgroup	Log OR	SE	OR (95% CI)	Weight, %
Dimopoulos et al,[32] 2006	1.08859	0.45038	2.97 (1.23-7.18)	3.1
Lespérance et al,[33] 2004	0.97833	0.3179	2.66 (1.43-4.96)	5.0
Tchalla et al,[37] 2015	0.34466	0.15734	1.41 (1.04-1.92)	9.3
Thomas et al,[34] 2007	0.73237	0.4485	2.08 (0.86-5.01)	3.1
van Dooren et al,[35] 2016	0.3001	0.08027	1.35 (1.15-1.58)	11.8
van Sloten et al,[21] 2014	0.43825	0.24185	1.55 (0.96-2.49)	6.7
Subtotal			1.58 (1.28-1.96)	39.0

Heterogeneity: $\tau^2 = 0.02$, $\chi^2 = 7.72$, $df = 5$ ($P = .17$); $I^2 = 35\%$

Test for overall effect: $z = 4.23$ ($P < .001$)

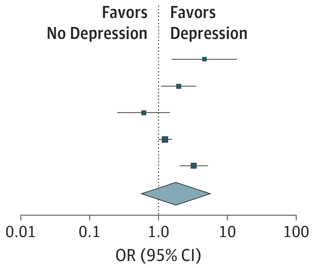


B sVCAM-1

Study or Subgroup	Log OR	SE	OR (95% CI)	Weight, %
Dimopoulos et al,[32] 2006	1.53902	0.56052	4.66 (1.55-13.98)	2.2
Tchalla et al,[37] 2015	0.67803	0.30334	1.97 (1.09-3.57)	5.3
Thomas et al,[34] 2007	-0.4943	0.45221	0.61 (0.25-1.48)	3.1
van Dooren et al,[35] 2016	0.22314	0.12001	1.25 (0.99-1.58)	10.6
van Sloten et al,[21] 2014	1.17865	0.24078	3.25 (2.03-5.21)	6.8
Subtotal			1.82 (1.03-3.22)	27.8

Heterogeneity: $\tau^2 = 0.31$, $\chi^2 = 21.40$, $df = 4$ ($P < .001$); $I^2 = 81\%$

Test for overall effect: $z = 2.05$ ($P = .04$)

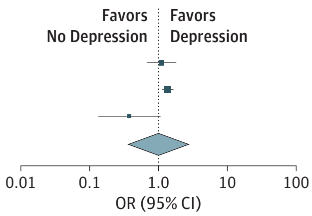


C e-Selection

Study or Subgroup	Log OR	SE	OR (95% CI)	Weight, %
Tully et al,[38] 2016	0.10884	0.25	1.11 (0.68-1.82)	6.5
van Dooren et al,[35] 2016	0.30748	0.1017	1.36 (1.11-1.66)	11.2
van Sloten et al,[21] 2014	-0.96758	0.53293	0.38 (0.13-1.08)	2.4
Subtotal			1.04 (0.64-1.70)	20.0

Heterogeneity: $\tau^2 = 0.12$, $\chi^2 = 5.85$, $df = 2$ ($P = .05$); $I^2 = 66\%$

Test for overall effect: $z = 0.16$ ($P = .87$)

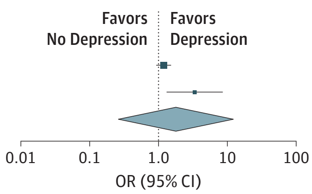


D vWF

Study or Subgroup	Log OR	SE	OR (95% CI)	Weight, %
van Dooren et al,[35] 2016	0.17395	0.12822	1.19 (0.93-1.53)	10.3
van Sloten et al,[21] 2014	1.20896	0.48043	3.35 (1.31-8.59)	2.8
Subtotal			1.80 (0.67-4.86)	13.1

Heterogeneity: $\tau^2 = 0.41$, $\chi^2 = 4.33$, $df = 1$ ($P = .04$); $I^2 = 77\%$

Test for overall effect: $z = 1.16$ ($P = .25$)



Data are reported as pooled odds ratios (ORs) by use of the generic inverse variance method with random-effects models. sICAM-1 indicates soluble intercellular adhesion molecule-1; sVCAM-1, soluble vascular cell adhesion molecule-1; and vWF, von Willebrand factor.

of sICAM-1, 1.58; 95% CI, 1.28-1.96; $P < .001$; $I^2 = 35\%$; pooled OR per SD increase of sVCAM-1, 1.82; 95% CI, 1.03-3.22; $P < .001$; $I^2 = 81\%$; pooled OR per SD increase of e-selectin, 1.04; 95% CI, 0.64-1.70; $P = .87$; $I^2 = 66\%$; pooled OR per SD increase of vWF, 1.80; 95% CI, 0.67-4.86; $P = .25$; $I^2 = 77\%$). We found no evidence of publication bias by the inspection of the funnel plots (eFigure 1 in the Supplement) or the Egger test ($t = 1.569$; $P = .12$).

Association of Albuminuria With Depression

Two studies investigated the association between albuminuria and depression.[22,23] Albuminuria was not significantly associated with depression in patients with (OR, 1.29; 95% CI, 0.96-1.73) or without (OR, 1.07; 95% CI, 0.70-1.63) prior cardiovascular disease.[22] A second study[23] found no significant association between urinary protein (milligrams per gram) and depressive symptoms in participants with chronic kidney disease (OR, 1.07; 95% CI, 0.90-1.26).

Association of Retinal Microvascular Diameters With Depression

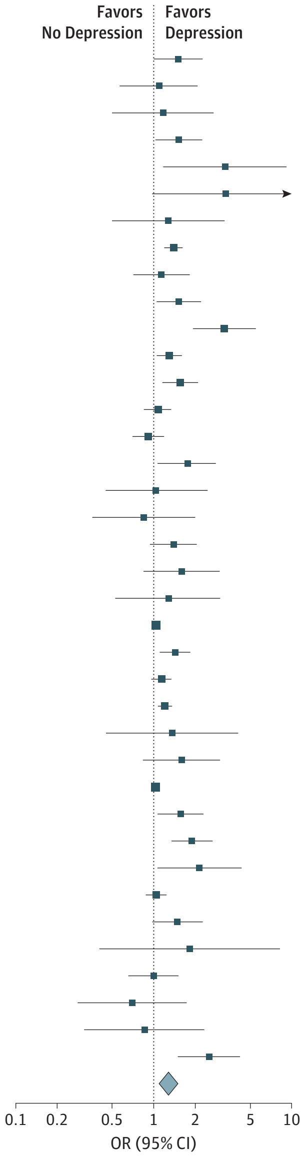
Two studies investigated the association between retinal arteriolar and venular diameters and depression.[39,40] In a subpopulation of participants with diabetes, significant differences were found between controls (mean [SD] arteriolar diameter, 133.1 [5.5] μm; mean [SD] venular diameter, 214.2 [7.5] μm), patients with diabetes (mean [SD] arteriolar diameter, 135.7 [5.6] μm; mean [SD] venular diameter, 208.7 [7.6] μm), and patients with depression and diabetes (mean [SD] arteriolar diameter, 140.3 [5.8]; $P < .01$ for trend; mean [SD]

Figure 3. Cross-sectional Association of White Matter Hyperintensities With Depression

Study or Subgroup	Log OR	SE	OR (95% CI)	Weight, %
Chatterjee et al,[44] 2010	0.4055	0.2089	1.50 (0.97-2.20)	2.4
Chen et al,[45] 2009	0.0862	0.3315	1.09 (0.57-2.09)	1.2
Colloby et al,[46] 2011	0.157	0.4377	1.17 (0.50-2.76)	0.7
Cyprien et al,[47] 2014	0.4187	0.1993	1.52 (1.03-2.25)	2.6
De Groot et al,[11] 2000	1.1939	0.5278	3.30 (1.17-9.28)	0.5
Delaloye et al,[49] 2010	1.2	0.63	3.32 (0.97-11.41)	0.4
Devantier et al,[83] 2016	0.23582	0.48589	1.27 (0.49-3.28)	0.6
Direk et al,[91] 2016	0.33647	0.07656	1.40 (1.20-1.62)	6.3
Feng et al,[51] 2014	0.131	0.2415	1.14 (0.71-1.83)	1.9
Firbank et al,[52] 2005	0.4187	0.1909	1.52 (1.05-2.22)	2.7
Fujishima et al,[53] 2014	1.1787	0.2694	3.25 (1.92-5.52)	1.6
Godin et al,[84] 2008	0.2624	0.109	1.30 (1.05-1.61)	5.0
Greenwald et al,[54] 1998	0.4511	0.1558	1.57 (1.16-2.13)	3.5
Grool et al,[85] 2013	0.0676	0.118	1.07 (0.85-1.35)	4.7
Gudmundsson et al,[55] 2013	-0.0834	0.1417	0.92 (0.70-1.21)	3.9
Hannestad et al,[56] 2006	0.5596	0.2508	1.75 (1.07-2.86)	1.8
Iosifescu et al,[57] 2005	0.0488	0.4422	1.05 (0.44-2.50)	0.7
Janssen et al,[58] 2004	-0.1744	0.4467	0.84 (0.35-2.02)	0.7
Jorm et al,[60] 2005	0.3293	0.2053	1.39 (0.93-2.08)	2.5
Kieseppä et al,[61] 2014	0.4637	0.3256	1.59 (0.84-3.01)	1.2
Köhler et al,[62] 2010	0.239	0.4481	1.27 (0.53-3.06)	0.7
Krishnan et al,[63] 2006	0.0392	0.0196	1.04 (1.00-1.08)	8.2
Kumar et al,[64] 2000	0.35767	0.13139	1.43 (1.11-1.85)	4.2
Lavretsky et al,[86] 2008	0.131	0.0855	1.14 (0.96-1.35)	5.9
Lin et al,[66] 2005	0.18232	0.06009	1.20 (1.07-1.35)	6.9
Paranthaman et al,[17] 2010	0.3075	0.563	1.36 (0.45-4.10)	0.4
Potter et al,[87] 2007	0.47	0.3298	1.60 (0.84-3.05)	1.2
Steffens et al,[73] 1999	0.0324	0.0224	1.04 (0.99-1.08)	8.1
Taylor et al,[75] 2005	0.4511	0.1992	1.57 (1.06-2.32)	2.6
Tudorascu et al,[76] 2014	0.6366	0.1793	1.89 (1.33-2.69)	3.0
Tupler et al,[77] 2002	0.7619	0.3628	2.14 (1.05-4.36)	1.0
van Sloten et al,[13] 2015	0.0392	0.0904	1.04 (0.89-1.21)	5.7
van Uden et al,[78] 2011	0.3988	0.2203	1.49 (0.97-2.29)	2.2
Vardi et al,[78] 2011	0.5988	0.7767	1.82 (0.40-8.34)	0.2
Vataja et al,[80] 2011	0	0.22	1.00 (0.65-1.54)	2.2
Versluis et al,[88] 2006	-0.3566	0.4708	0.70 (0.28-1.76)	0.6
Videbech et al,[81] 2001	-0.1508	0.52	0.86 (0.31-2.38)	0.5
Wu et al,[82] 2014	0.9282	0.2667	2.53 (1.50-4.27)	1.7
Total			1.29 (1.19-1.39)	100

Heterogeneity: $\tau^2 = 0.02$, $\chi^2 = 109.59$, $df = 37$ ($P < .00$); $I^2 = 66\%$

Test for overall effect: $z = 6.59$ ($P < .001$)



Data are reported as pooled odds ratios (ORs) by use of the generic inverse variance method with random-effects models.

venular diameter 209.9 [7.9]; $P = .03$ for trend).[39] In contrast, a large longitudinal cohort study found no association between retinal arteriolar and venular diameters and incident major depressive disorder during 9 years of follow-up (hazard ratio per SD increase in arteriolar diameter, 1.01; 95% CI, 0.93-1.10; and hazard ratio per SD increase in venular diameter, 1.02; 95% CI, 0.94-1.12).[40]

Cross-Sectional Association of Cerebral Small Vessel Disease With Depression

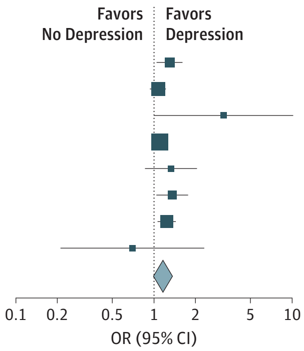
Fifty-five studies investigated the association between cerebral small vessel disease and depression,[11,13,14,17,20,41-91] of which 8 studies had a prospective design.[13,20,70,84,85,88-90] Most studies focused on WMH volumes or WMH severity scores in a case-control or a population-based cohort setting. In addition to studying WMHs, 4 studies also evaluated the association of microbleeds and microinfarctions with depression.[13,51,82,91] Overall, cerebral small vessel disease was associated with depression.

Thirty-eight studies[11,13,17,44-47,49,51-58,60-64,66,73,75-88,91] were included in the meta-analysis on cross-sectional data (**Figure 3**; eFigure 2 and eFigure 3 in the Supplement). A significant association between WMHs and depression was found (pooled OR per SD, 1.29; 95% CI, 1.19-1.39; $P < .001$; $I^2 = 66\%$). A statistically significant association was found between a higher number of microbleeds (pooled OR, 1.18; 95% CI, 1.03-1.34; $P < .05$; $I^2 = 0\%$) and brain (micro) infarctions (pooled OR, 1.30; 95% CI, 1.21-1.39; $P < .001$; $I^2 = 1\%$) and depression. To reduce possible residual confounding by medical comorbidities, we restricted the analysis to studies that corrected for diabetes status or hypertension. The results remained statistically significant when pooling the WMH studies that corrected for diabetes

Figure 4. Longitudinal Association of White Matter Hyperintensities With Depression

Study or Subgroup	Log OR	SE	OR (95% CI)	Weight, %
Godin et al,[84] 2008	0.2623	0.111	1.30 (1.05-1.62)	12.3
Grool et al,[85] 2013	0.0677	0.07	1.07 (0.93-1.24)	22.8
Olesen et al,[70] 2010	1.1663	0.5939	3.21 (1.00-10.26)	0.6
Saavedra Perez et al,[20] 2013	0.0953	0.0507	1.10 (1.00-1.22)	31.1
Steffens et al,[89] 2002	0.2852	0.2228	1.33 (0.86-2.06)	3.7
Teodorczuk et al,[90] 2010	0.30748	0.1358	1.36 (1.04-1.76)	8.9
van Sloten et al,[13] 2015	0.215	0.0778	1.24 (1.06-1.44)	20.1
Versluis et al,[88] 2006	-0.3567	0.615	0.70 (0.21-2.34)	0.5
Total			1.18 (1.08-1.28)	100

Heterogeneity: $\tau^2 = 0.00$, $\chi^2 = 9.56$, $df = 7$ ($P = .22$); $I^2 = 27\%$
Test for overall effect: $z = 3.66$ ($P < .001$)



Data are reported as pooled odds ratios (ORs) by use of the generic inverse variance method with random-effects models. CSVD indicates cerebral small vessel disease.

status (8 studies[13,51,57,60,75,76,84,91]; OR, 1.32; 95% CI, 1.15-1.52; $P < .001$; $I^2 = 46\%$) or hypertension (11 studies[13,54,55,57,63,73,75,76,83,84,91]; OR, 1.18; 95% CI, 1.08-1.29; $P < .001$; $I^2 = 76\%$). When we restricted the analyses to the 16 studies that used a diagnostic interview to diagnose depressive disorder, the pooled OR was 1.34 per SD (95% CI, 1.19-1.51; $P < .001$; $I^2 = 24\%$).[17,44,46,47,55,58,61,64,77,79-84,91] Twenty-two studies used questionnaires to assess depressive symptoms; pooling of these studies resulted in an OR of 1.24 per SD (95% CI, 1.14-1.35; $P < .001$; $I^2 = 69\%$).[11,13,45,49,51-54,56,57,60,62,63,66,73,75,76,78,85-88] We further explored heterogeneity by comparing WMHs as assessed semiautomatically[13,17,45-47,52,53,55,56,58,64,75,76,78-80,83-88,91] vs severity rating scales[11,44,49,51,54,57,60-63,66,73,77,81,82] (OR, 1.31; 95% CI, 1.18-1.46; $P < .001$; $I^2 = 49\%$ vs OR, 1.22; 1.10-1.34; $P < .001$; $I^2 = 66\%$) and case-control[17,44-46,49,53,54,56-58,61,62,64,66,75,77,79-88] vs cohort studies[11,13,47,51,52,55,60,63,73,76,78,91] (OR, 1.36; 95% CI, 1.22-1.52; $P < .001$; $I^2 = 37\%$ vs OR, 1.19; 95% CI, 1.08-1.31; $P < .001$; $I^2 = 74\%$). We restricted analysis to 31 studies[11,13,44-47,49,51,53-58,60-64,75-77,80-87,91] with a high methodological quality, as indicated by a NOS score of 60% or more.[25] White matter hyperintensities were positively associated with depression (pooled OR, 1.35; 95% CI, 1.22-1.50; $P < .001$; $I^2 = 68\%$). Of these studies, 12 used a diagnostic interview.[44,46,47,53,55,61,64,77,80-82,84] Restricting the analyses to these 12 studies resulted in a pooled OR of 1.33 (95% CI, 1.13-1.57; $P < .001$; $I^2 = 43\%$). The pooled OR for the 19 studies that used questionnaires was 1.32 (95% CI, 1.17-1.49; $P < .001$; $I^2 = 70\%$).[11,13,45,49,51,53,54,56,57,60,62,63,75,76,83,85-87,91] In meta-regression analysis, we found a significant association between WMHs and depression (pooled OR per SD, 1.25; 95% CI, 1.05-1.49; $P < .05$; $I^2 = 51\%$) when we included the methods to assess depression (diagnostic interviews vs self-reported questionnaires), study design (case-control vs cohort study), and methods to assess WMHs (semiautomatic volumetry vs subjective rating scale). We found no evidence of publication bias by the inspection of the funnel plots (eFigure 1 in the Supplement), the Egger test ($t = 1.569$; $P = .29$), or the trim-and-fill (eFigure 4 in the Supplement). Owing to the limited number of studies, we could not perform subgroup analyses or valid estimations on publication bias for data on microbleeds and microinfarctions.

Longitudinal Association of Cerebral Small Vessel Disease With Depression

Eight studies were included in the meta-analysis of longitudinal data (**Figure 4**).[13,20,70,84,85,88-90] Only data on WMHs could be pooled, because only 1 longitudinal study[13] investigated the association of microbleeds and brain infarctions with depression. As shown in Figure 4, a statistically significant association between WMHs and the incidence of depression was found (pooled OR, 1.18; 95% CI, 1.08-1.28; $P < .001$; $I^2 = 27\%$) over a mean follow-up of 3.7 years. We found no evidence of publication bias based on the funnel plots (eFigure 5 in the Supplement) or the Egger test ($t = 1.139$; $P = .30$).

Discussion

This extensive meta-analysis on 43 600 participants, including 9203 individuals with depression, shows that generalized microvascular dysfunction is associated with depression, both in cross-sectional and longitudinal settings, independent of cardiovascular risk factors. Multiple markers of microvascular dysfunction, including endothelial plasma markers and markers of cerebral small vessel disease, are cross-sectionally associated with a higher level of depressive symptoms and depressive disorder. In addition, WMHs are associated with incident depression over time. These findings are in agreement with the vascular depression hypothesis and extend this hypothesis, as peripheral microvascular dysfunction may also be associated with depression.[92,93]

In this systematic review with meta-analysis, we evaluated the associations between microvascular dysfunction and depression. We included cross-sectional and longitudinal epidemiologic studies, and are the first, to our knowledge, to consider the association of multiple measures of both cerebral and peripheral microvascular dysfunction with depression. By combining the extensive evidence on WMHs with data from biomarkers of endothelial function, we aim to provide further evidence for the hypothesis that cerebral small vessel disease may originate from endothelial dysfunction. We suggest that generalized microvascular dysfunction, as can be measured throughout the body, is an important pathophysiologic factor that may contribute to the development of depression. Our results confirm and extend 2 previous meta-analyses that addressed the association between WMHs and depression[19,94] by including more than 6 times the number of participants and depression cases, thus increasing statistical power. This number enabled us to overcome the major caveat of high heterogeneity, which was a major methodological issue in previous meta-analyses. The use of diagnostic interviews vs questionnaires to assess depression, and case-control vs cohort study design were found to be the sources of heterogeneity, which has important implications for future studies that investigate the pathophysiologic factors of depression. These variables, however, did not affect the observed associations, which strengthens the validity of our findings. Finally, our study focused on late-life depression, in which vascular pathologic conditions are thought to have the greatest effect, while previous meta-analyses combined early and late-life depression.[19,94]

The association of microvascular dysfunction with depression can be explained by several mechanisms. First, impaired endothelial function in the cerebral microcirculation may lead to cerebral perfusion deficits, resulting in chronic ischemia in the cerebrum.[95] Chronic ischemia could cause structural disruptions of the fiber tracts in the cerebral white matter, which are visualized as WMHs on results of magnetic resonance imaging.[95-98] If the affected regions are involved in mood regulation, this may predispose the individual to the development of depression. Second, microvascular dysfunction is closely linked to and interrelated with chronic low-grade inflammation and/or oxidative stress, which may represent different pathways in the development of depression.[35,99-102] Low-grade inflammation is known to contribute to endothelial dysfunction.[21,35] In addition, the cerebral endothelium may be more vulnerable to oxidative stress, owing to a high production of reactive oxygen species in the brain as a result of the high metabolic demand.[103] Moreover, the brain has limited antioxidant defenses,[104] while damage related to oxidative stress has been described in psychiatric disease[105-107] and may contribute to cerebral dysfunction. However, multiple studies have shown that the association between microvascular dysfunction and depression is only partly dependent on inflammation[21,35,36] or oxidative stress,[21] which suggests that microvascular dysfunction itself represents an independent pathway in the development of depression. Third, cardiometabolic risk factors may be involved in the association between microvascular dysfunction and depression. For instance, increased arterial stiffening may induce microvascular disease and is related to depression.[108] Increased arterial stiffness leads to an increased pulsatile pressure load, which, owing to the low impedance of the cerebral microcirculation, can penetrate deeply into the white matter, thereby inducing microvascular dysfunction and WMHs.[108-110] In addition, other cardiometabolic risk factors, such as decreased physical activity,[111] smoking,[112] obesity,[113] hypertension,[113-115] diabetes,[114,115] and unhealthy diet,[98,116,117] have been associated with both microvascular dysfunction and depression. However, we mainly used results that were adjusted for cardiometabolic risk factors in our meta-analysis. This finding may suggest that microvascular dysfunction represents an independent pathway in the development of depression. Fourth, acute and chronic stress can result in autonomic and hypothalamic-pituitary-adrenal axis dysregulation, which in turn can contribute to both depression and cardiovascular disease.[118] Stress-induced elevated cortisol levels may cause cerebral atrophy, reduced neurogenesis, synaptic plasticity, and monoaminergic signaling, all of which could contribute to the development of depression.[119]

The exact pathogenesis of WMHs is currently undetermined. Several studies have assumed that WMHs are due to ischemia[7,8,120,121]; however, evidence indicates that WMHs originate from cerebral endothelial dysfunction.[122] This evidence is supported by findings that WMHs and microinfarctions are associated with leakage of plasma fluid components, arteriolar wall infiltration, thickening of the arteriolar wall, and changes in perivascular tissue, causing disruption of the normal architecture, including damaged arteriolar smooth muscle cells and fibrin depositions. In addition, the specific anatomy of capillaries (with functional shunts and tight control of capillary flow patterns) could enable 2 distinct mechanisms to induce ischemia within the brain: limited blood supply and limited oxygen extraction due to capillary dysfunction.[123]

Strengths and Limitations

The strengths of this study include the large number of included studies and individuals with depression, resulting in high statistical power, which allowed an extensive exploration of the cause of heterogeneity within the meta-analysis. This meta-analysis is limited by the available literature. Based on the available data, we cannot rule out the possibility of reverse causality. It is plausible to assume that the association between microvascular dysfunction and depression is bidirectional; that is, microvascular dysfunction may cause depression, and vice versa. The proposed temporality was supported by the longitudinal association for WMHs and depression, but could not be confirmed for other markers of microvascular dysfunction. Further longitudinal studies are needed to address this issue. In addition, the interrelationships among medical comorbidities, microvascular dysfunction, and depression could only partly be assessed. Therefore, an important limitation of this meta-analysis and indeed of the source studies is that we cannot exclude residual confounding by variables not considered in the source studies. However, based on our subanalyses, confounding by type 2 diabetes, hypertension, and cardiovascular risk factors is unlikely. In addition, some of the indicators of vascular dysfunction, such as albuminuria, may be less specific and may more likely reflect a general health status, which could have led to an overestimation of the association. Furthermore, most studies on plasma biomarkers of endothelial dysfunction measured multiple biomarkers; therefore, we did not calculate a pooled estimate. Nevertheless, when focusing on the pooled ORs per specific biomarker, the 95% CIs were virtually within the same range. Finally, data on the association between albuminuria, retinal diameters, and depression appeared to be scarce, while data on albuminuria were available only in study populations with disease, and therefore cannot be extrapolated to the general population.

As the cerebral microvasculature is difficult to study, there is a need to develop more advanced and powerful imaging techniques, such as 7-T magnetic resonance imaging and diffuse tensor imaging, which may provide more sensitive research tools with more detailed structural information on microvascular changes as seen in cerebral small vessel disease.[124-127] Furthermore, several state-of-the-art techniques have been developed to investigate the microcirculation throughout the body, such as sublingual intravital microscopy,[128] skin laser-Doppler flowmetry,[113,129] dynamic retinal vessel analysis,[129] and skin capillaroscopy.[130] Large-scale studies using these new techniques are of crucial importance to unravel the association between microvascular dysfunction and depression. In addition, experimental studies are needed to demonstrate the possible causal role of microvascular dysfunction in depression. Multiple drugs, such as angiotensin-converting enzyme inhibitors[131] and statins,[132,133] as well as lifestyle interventions[134,135] have been shown to improve microvascular function; it is not known, however, whether such interventions can improve brain microcirculatory function in general or WMHs specifically.[136] Some evidence exists that angiotensin-converting enzyme inhibitors may be efficacious in the treatment of depression.[137-139] However, larger randomized trials have not been performed. Statins may provide another intervention of interest in depression, although the current literature reports conflicting results.[140-145] Randomized clinical trials in individuals at high risk for or with depression may provide further insight into the role of microcirculatory dysfunction in the prevention and/or treatment of depression.

Conclusions

This meta-analysis shows that generalized microvascular dysfunction is associated with higher odds of depression and that cerebral small vessel disease is associated with an increased risk for the development of depression over time. These findings support the hypothesis that microvascular dysfunction is causally linked to depression. This finding may have clinical implications, as microvascular dysfunction might provide a potential target for the prevention and treatment of depression.

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