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SYSTEMATIC REVIEW AND META-ANALYSIS

Cerebral Small-Vessel Disease and Risk of Incidence of Depression: A Meta-Analysis of Longitudinal Cohort Studies

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BACKGROUND: Results of several longitudinal cohort studies suggested an association between cerebral small-vessel disease and depression. Therefore, we performed a meta-analysis to explore whether cerebral small-vessel disease imparts increased risk for incident depression.

METHODS AND RESULTS: We searched prospective cohort studies relevant to the relationship between cerebral small-vessel disease and incident depression published through September 6, 2019, which yielded 16 cohort studies for meta-analysis based on the relative odds ratio (OR) calculated with fixed- and random-effect models. Baseline white matter hyperintensities (WMHs) (pooled OR, 1.37; 95% CI, 1.14–1.65), enlarged perivascular spaces (pooled OR, 1.33; 95% CI, 1.03–1.71), and cerebral atrophy (pooled OR, 2.83; 95% CI, 1.54–5.23) were significant risk factors for incident depression. Presence of deep WMHs (pooled OR, 1.47; 95% CI, 1.05–2.06) was a stronger predictor of depression than were periventricular WMHs (pooled OR, 1.31; 95% CI, 0.93–1.86). What's more, the pooled OR increased from 1.20 for the second quartile to 1.96 for the fourth quartile, indicating that higher the WMH severity brings greater risk of incident depression (25th–50th: pooled OR, 1.20; 95% CI, 0.68–2.12; 50th–75th; pooled OR, 1.42; 95% CI, 0.81–2.46; 75th–100th: OR, 1.96; 95% CI, 1.06–3.64). These results were stable to subgroup analysis for age, source of participants, follow-up time, and methods for assessing WMHs and depression.

CONCLUSIONS: Cerebral small-vessel disease features such as WMHs, enlarged perivascular spaces, and cerebral atrophy, especially the severity of WMHs and deep WMHs, are risk factors for incident depression.

Key Words: cerebral small-vessel disease ■ cohort studies ■ incident depression ■ meta-analysis

Cerebral small-vessel disease (CSVD) affects small arteries, venules, and capillaries of the brain. The diagnosis of CSVD is based on findings of magnetic resonance imaging (MRI) of white matter lesions, lacunar infarcts, cerebral microbleeds (CMBs), enlarged perivascular spaces (EPVSs), and cerebral atrophy.[1] Numerous studies have explored the association between imaging markers of CSVD with depressive symptoms or mood disorders.[2,3] The vascular depression hypothesis postulates that CSVD may cause depression in elderly persons.

Studies of cross-sectional design[4] and longitudinal studies[5] concurred in showing an association between markers of CSVD and depression. However, systematic evidence for the causal association between MRI CSVD features and incident depression is limited. Three meta-analyses[6–8] have examined the association of white matter hyperintensities (WMHs) and depression, of which 2 found a positive association. One meta-analysis[9] failed to show a significant association between microbleeds and depression, whereas another confirmed an association between

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CLINICAL PERSPECTIVE

What Is New?

- We undertook a new meta-analysis showing that certain cerebral small-vessel disease markers may indicate a causal relationship between cerebral small-vessel disease and incidence of depression because we selected only longitudinal cohort studies that excluded participants with prevalent depression at baseline.
- We found that specific cerebral small-vessel disease features, including white matter hyperintensities, enlarged perivascular spaces, and cerebral atrophy indicated a high risk for incident depression—the association was especially evident in the case of white matter hyperintensities, which bring greater risk for incident depression in proportion to severity of the imaging findings; furthermore, we found that deep white matter hyperintensities, but not periventricular white matter hyperintensities, predicted a higher risk for incident depression.

What Are the Clinical Implications?

- These data may inform the prevention of depression and indicate that location-specific and severity-specific preventative measures may be needed.

Nonstandard Abbreviations and Acronyms

CMBs	cerebral microbleeds
CSVD	cerebral small-vessel disease
DWMHs	deep white matter hyperintensities
EPVSs	enlarged perivascular spaces
MRI	magnetic resonance imaging
OR	odds ratio
PWMHs	periventricular white matter hyperintensities
WMHs	white matter hyperintensities
WMLs	white matter lesions

hippocampal atrophy and depression.[10] However, there is no meta-analysis compiling imaging findings for lacunar infarcts, enlarged perivascular spaces, and cerebral atrophy as potential risk factors for depression. Most importantly, since the previously published meta-analyses compiled cross-sectional and longitudinal studies, they were not robust to confounding effects of baseline depression in the study populations.

In view of these considerations, we undertook a new meta-analysis including only longitudinal cohort studies, with exclusion of cases with baseline depression, thus enabling an exploration of causal effects of CSVD on the incidence of depression. Additionally, we explored effects of WMH location and severity on the risk of incident depression.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Literature Search

We searched online databases (PubMed, Embase, Web of Science, the Cochrane Library, meeting abstracts, and relevant listed references) from January 1, 1947, to September 6, 2019. A combination of several keywords relevant for CSVD were used as the search items (*leukoencephalopathy, stroke lacunar, microbleeds, perivascular spaces, cerebral atrophy*) and for depression (*depression*, depressive symptom*, depressive disorder**). The search was limited to articles published in English that reported human data. The reference lists of eligible articles and relevant reviews were also searched and reviewed. The detailed search strategy is presented in Data S1.

Study Selection

Two researchers independently completed the study selection, and any differences were resolved by consensus. Thus, studies were included if they fulfilled the following criteria: (1) longitudinal and cohort design; (2) baseline CSVD was diagnosed by MRI or computed tomography. The detailed definitions are included in Data S2; (3) participants had neither baseline depressive symptoms nor earlier history of depression; (4) the outcome was incident depression, assessed over a period of at least 2 weeks following the diagnosis of CSVD. Depression rating was defined by standardized criteria (eg, *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition*; *International Classification of Diseases, Tenth Revision* [*ICD-10*]) or validated clinical rating scales (eg, Geriatric Depression Scale-15, Center for Epidemiological Studies Depression Scale, Hospital Anxiety and Depression Scale–Depression, Hamilton Depression Scale, Patient Health Questionnaire-9); (5) the raw data or reported effects were measured by odds ratio (OR) and 95% CI; (6) in cases with multiple articles arising from the same study, the publication with more comprehensive reporting of relevant data was selected. Figure 1 presents the detailed selection procedures. All retrospective cohort studies, case-control studies, cross-sectional studies,

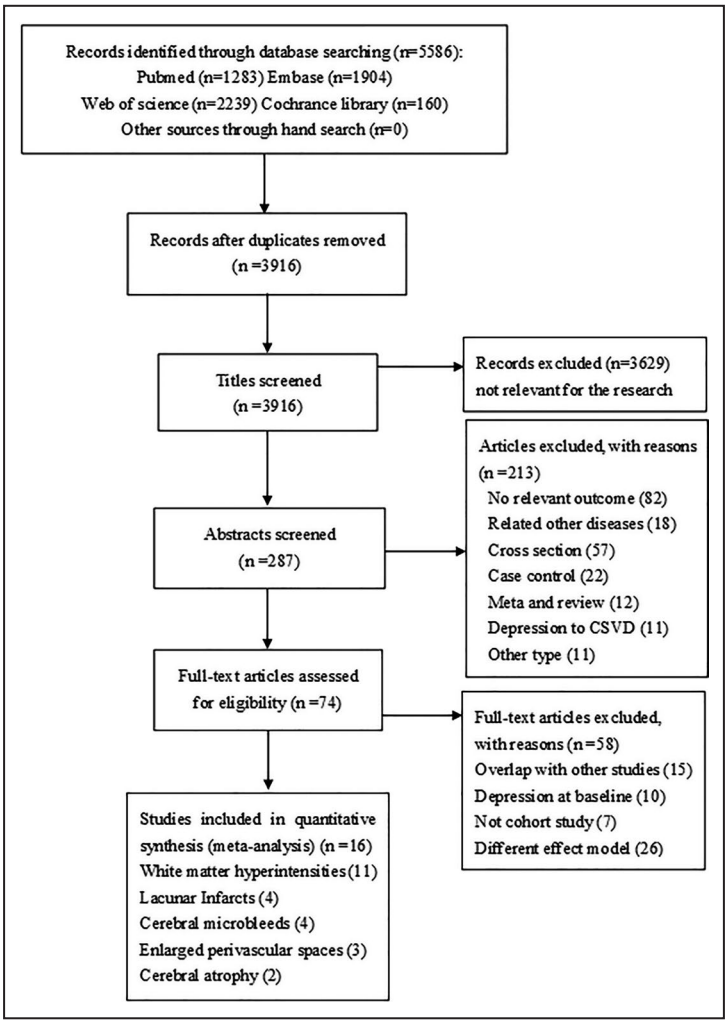

Figure 1. Study flow diagram summarizing identification and selection of publications in the meta-analysis.

case reports, case series, and animal studies were excluded.

Data Extraction

For the 16 studies meeting the above criteria, 2 investigators independently extracted the following information from each study: (1) study characteristics, including name of the first author, publication year, country, participants resource, and follow-up duration; (2) participant details including the sample size, sex, mean age, and the sizes of the incident depression and control groups; (3) CSVD markers and their means of assessment, including imaging model, assessment procedures, and scales of quantification; (4) outcome assessment, including overall incidence of depression, assessment of depression, and means of its diagnosis; (5) statistical analysis, including OR, 95% CI, and adjustment for confounders (age, sex, education level, cognitive function, vascular factors). If multiple analysis models were presented in an individual article, we extracted the OR value from the most fully adjusted model. When the effect estimate was not directly provided, we calculated OR using 2×2 tables.

Quality Assessment

The quality of studies was assessed by the Newcastle-Ottawa Scale for cohort studies.[11] The quality score ranges from 0 to 9 points. We calculated all percentages of maximum Newcastle-Ottawa Scale scores for each study, and any score equal to or exceeding 7 indicated a study of high quality.

Statistical Analysis

All studies reported either incident depression or no depression after CSVD as dichotomous outcomes. For the case of WMHs, we made a dichotomous

judgment of moderate/severe versus mild/none WMHs, with harmonization of different WMHs rating scales' cutoff criteria according to each scale's own definitions. WMHs were dichotomously classified as moderate/severe versus mild/none on the basis of the following cutoffs: Fazekas scale (2–3 versus 0–1), white matter grade (6–9 versus 0–5), Scheltens score, Gothenburg scale (3-2 versus 0–1). For studies assessing WMH volume and presenting results in quartile (25%), we set a cutoff above the median quartile to define moderate/severe WMHs. For lacunar stroke, cerebral microbleeds, and Virchow-Robin spaces, we scored as 1 versus 0 lesion(s) per region, and for regional brain volume, we scored quartiles 3 to 4 versus quartiles 1 to 2.

Considering that relatively few studies were available for each of the CSVD markers, we pooled the effect sizes of different studies using random-effects meta-analyses with generic inverse variance methods. When the heterogeneity was small, we also conducted a fixed-effects meta-analyses as a sensitivity analysis. Between-study heterogeneity was evaluated with the I^2, the Cochran Q statistic, and τ^2; the value of I^2 is 0% to 25%, 25% to 50%, and >50%, indicating low, medium, and high heterogeneity, respectively.[12] When we pooled the effect sizes on the basis of the OR, τ^2 was estimated by the restricted maximum likelihood method. When based on actual incident data, the τ^2 was estimated by the restricted DerSimonian-Laird method. To consider the source of heterogeneity in WMHs, we performed meta-regression analysis to evaluate by applying a mixed-factor model if there was any effect modification by age, participants, follow-up duration, and WMH assessment methods. Furthermore, we conduced subgroup analyses by age (<65/≥65 years), participants (patients/community population), follow-up duration (<1/1–5/≥5 years), WMH evaluation methods (Fazekas scale, white matter grade, Scheltens score, Gothenburg scale), and depression assessment methods (Geriatric Depression Scale-15; Center for Epidemiological Studies Depression Scale; Geriatric Depression Scale, Korean Version; Hamilton Depression Scale-17; *Diagnostic and Statistical Manual of Mental Disorders*). The likelihood of publication bias was first evaluated by the funnel plot because of small study effects. If there was a conspicuous published bias, we performed the "trim-and-fill" analysis to make an adjustment.[13] Finally, the quality of evidence from pooled results was evaluated by the Grading of Recommendations Assessment, Development, and Evaluation approach.

All statistical analyses were performed with R version 3.5.0 (R Core Team, R Foundation for Statistical Computing, 2013, Boston, MA). This study protocol followed the standards presented in Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols Statement and Guidelines.[14]

RESULTS

Literature Search and Study Characteristics

Figure 1 illustrates the study selection process. We initially identified 5586 studies, of which 74 full-text articles were scrutinized. Of these 74 studies, 15 were reported from the same research group; 10 had patients with baseline depression; 7 were not longitudinal cohort studies; and 26 used a general linear regression model, structural equation model, or partial correlation analyses that could not extract the incident data. Thus, we were left with 16 longitudinal cohort studies[5,15–29] for analysis. In total, data from 14 324 participants, including about 3099 individuals (21.6 %) with incident depression, were included in the meta-analysis. The follow-up time ranged from 2 weeks to 10 years. CSVD was assessed solely through MRI in 13 studies (n=11 585), solely through computed tomography in 1 study (n=525), or through either method in 2 studies (n=2214). There were 11 studies (n=8498) focusing on WMHs. Regarding WMHs quantification, 4 studies (n=4601) used volumetry, and 7 studies (n=3897) rated WMHs severity with visual semiquantitative rating scales, including Fazekas scale (2 studies; n=428), white matter grade (2 studies; n=2376), Gothenburg scale (2 studies; n=855) and Scheltens score (1 study; n=238). In addition, there were 4 studies (n=6960) about lacunar infarctions, 4 studies (n=3138) about microbleeds, 3 studies (n=3048) about Virchow-Robin spaces, and 2 studies (n=855) about cerebral atrophy. Detailed characteristics of all 16 selected studies are presented in Table 1. All studies were assessed as high quality, as described in more detail in Table S1. The quality of evidence from pooled results for WMHs (low), lacunar infarcts (very low), CMBs (moderate), EPVSs (moderate), and cerebral atrophy (moderate) are described in Table S2.

Association of CSVD With Incident Depression

WMHs and Incident Depression

Eleven studies were included in the meta-analysis on WMHs, which showed that individuals with baseline WMHs had an increased risk for incident depression (pooled OR, 1.37; 95% CI, 1.14–1.65) (Figure 2A). The between-study heterogeneity here was high and statistically significant (I^2=67.2%; τ^2=0.0392; Q=30.48). The funnel plot indicated conspicuous evidence of publication bias, and we consequently performed the trim-and-fill analysis (Figure S1). Nonetheless,

Table 1. Studies on the Association Between CSVD and Incident Depression

Ref	Author	Year	Country	Population	Follow-Up (y)	Cohort Size (n)	Participants (n)	Mean Age (y)	F (%)	Depression Cases (n)	CSVD Markers	Depression Assessment
1	Liang Y[15]	2018	Hong Kong	Acute ischemic stroke	0.25	4333	725	66	38.3	153	CMBs, EPVSs, LIs	GDS-15 ≥7
2	Zhang X[16]	2017	Chinese	Lacunar stroke	0.25	488	374	61.7	40.9	90	LIs, WMHs, CMB, EPVSs	HAMD-17 ≥7
3	Qiu WQ[17]	2017	USA	The Framingham Heart Study offspring cohort	6.6	1400	1212	60	52.4	110	WMHs, TCBV	CES-D ≥≥16
4	He JR[18]	2017	China	Acute cerebral infarction	2W	238	238	67	31.9	42	WMHs	HAMD-17 ≥7
5	Arba F[19]	2016	Italy; UK; Australia	VISTA	1	5721	2160	64.2	33	416	LIs	HADS-D ≥8
6	van Sloten TT[5]	2015	Netherlands	AGES-Reykjavik study	5.2	5764	1949	74.6	56.6	197	WMHs, LIs, CMBs, VR	GDS-15 ≥6
7	Park JH[20]	2015	Korean	NaSDEK	3	783	54	72.2	52.7	NA	WMHs	SGDS-K ≥8
8	Gudmundsson P[21]	2015	Sweden	H70 and PPSW	10	868	330	70	56.8	26	WMHs, atrophy	DSM-5
9	Tang WK[22]	2014	Chinese Hong Kong	Acute ischemic stroke	0.25	4766	229	NA	NA	75	Pons CMBs	GDS ≥7
10	Saavedra Perez HC[23]	2013	Netherlands	Elderly persons	3.6	1077	961	70	52	60	LIs, WMHs	CES-D ≥16
11	White CL[24]	2011	Columbia, Canada	SPS3 study	2.1	2477	2477	63.2	37	478	LIs	PHQ-9
12	Tang WK[25]	2011	Hong Kong	Acute ischemic stroke	0.25	3219	235	NA	39.1	84	CMBs	GDS ≥7
13	Olesen PJ[26]	2010	Sweden	Swedish Population Register	5	1495	525	72.7	68.6	63	WMHs, atrophy	ICD-10 codes
14	Godin O[27]	2008	three French cities	Three City (3C)-Dijon study	4	1658	956	72.4	60.6	241	WMHs	CES-D ≥17(m), ≥23(f)
15	Verluis CE[28]	2006	Netherlands	PROSPER cohort	2.75	527	484	74.9	43	31	Total WMHs	GDS-15 ≥4
16	Steffens DC[29]	2002	Pennsylvania, California, and North Carolina	CHS	7	5201	1415	≥65	NA	1033	White-matter grade	CES-D ≥7

Adjusted confounders including age, sex, education level, cognitive function and vascular factor. AGES-Reykjavik indicates Age, Gene/Environment Susceptibility–Reykjavik; CES-D, Center for Epidemiological Studies Depression Scale; CHS, Health Care Financing Administration Medica; CMB, cerebral microbleed; CSVD, cerebral small-vessel disease; CT, computed tomography; EPVSs, enlarged perivascular spaces; GDS-15, Geriatric Depression Scale-15; H70, Gerontological and Geriatric Population Studies; HADS-D, Hospital Anxiety and Depression Scale–Depression; HAMD, Hamilton Depression Scale; LI, lacunar infarct; MRI, magnetic resonance imaging; NA, not applicable; NaSDEK, Nationwide Survey on Dementia Epidemiology of Korea; PHQ-9, Patient Health Questionnaire-9; PPSW, Prospective Population Study of Women; PROSPER, Prospective Study of Pravastatin in the Elderly at Risk of Cardiovascular Disease; SGDS-K, Geriatric Depression Scale–Short Form, Korean Version; SPS3, Secondary Prevention of Small Subcortical Strokes study; TCBV, total cerebral brain volume; VISTA, Virtual International Stroke Trials Archive; and WMHs, white matter hyperintensities.

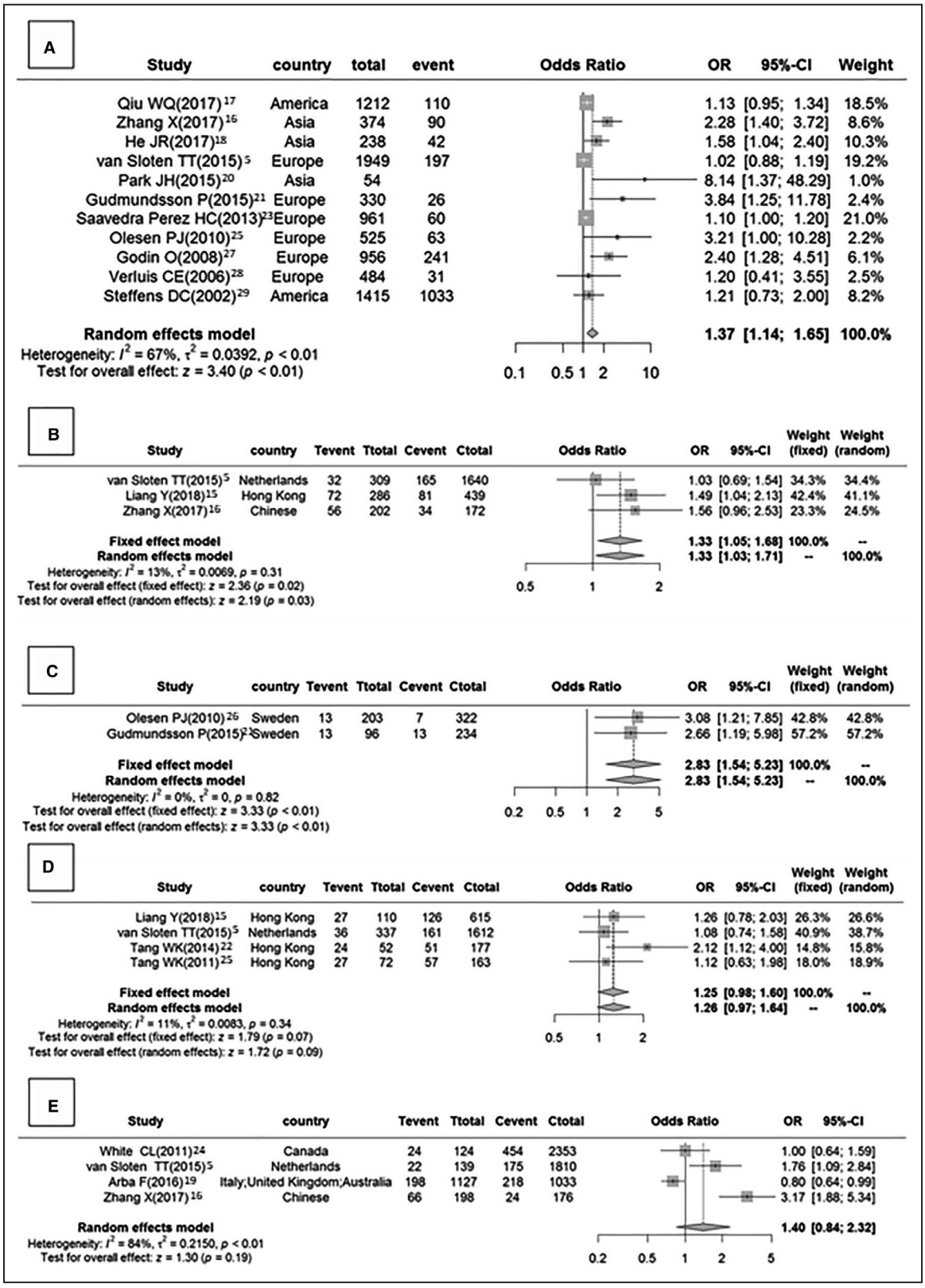

Figure 2. Forest plots of the relationship between white matter hyperintensities (WMHs), enlarged perivascular spaces (EPVSs), cerebral atrophy, cerebral microbleeds (CMBs), and lacunar infarcts (LIs) at baseline and incident depression.

A, WMHs in adjusted estimates; **B,** EPVSs in crude estimates; **C,** cerebral atrophy in crude estimates; **D,** CMBs in crude estimates; **E,** LIs in crude estimates. C_{event} indicates the number of incident depression in non-CSVD; C_{total}, the number of non-CSVD; OR, odds ratio; T_{event}, the number of incident depression in CSVD; and T_{total}, the number of CSVD.

the between-study heterogeneity remained very high. We consequently applied the random-effect model, which showed that baseline WMHs was no longer significantly associated with incident depression (pooled OR, 1.10; 95% CI, 0.90–1.34; I^2=74.7%; τ^2=0.0791; Q=63.13).

Furthermore, in the subgroup analysis of WMH location, we found that presence of deep white matter hyperintensities (DWMHs) was a factor in incident depression (pooled OR, 1.47; 95% CI, 1.05–2.06), but presence of PWMHs was not (pooled OR, 1.31; 95% CI, 0.93–1.86) (Figure 3A). Besides, we saw a trend toward a linear relationship between WMH severity and increasing risk of incident depression (25th–50th: pooled OR, 1.20; 95% CI, 0.68–2.12; 50th–75th: pooled OR, 1.42; 95% CI, 0.81–2.46; 75th–100th: OR, 1.96; 95% CI, 1.06–3.64) (Figure 3B), although without attaining significant *P* value (*P*=0.15).

EPVSs and Incident Depression

The between-study heterogeneity of the 3 EPVSs studies was low and not significant (I^2=13.5%; τ^2=0.0069; Q=2.31). Therefore, we applied the fixed-effect model to evaluate the pooled effect (pooled OR, 1.33; 95% CI, 1.05–1.68) and the random-effect model (pooled OR, 1.33; 95% CI, 1.03–1.71) (Figure 2B). The results from these 2 models and that of the pooled effect

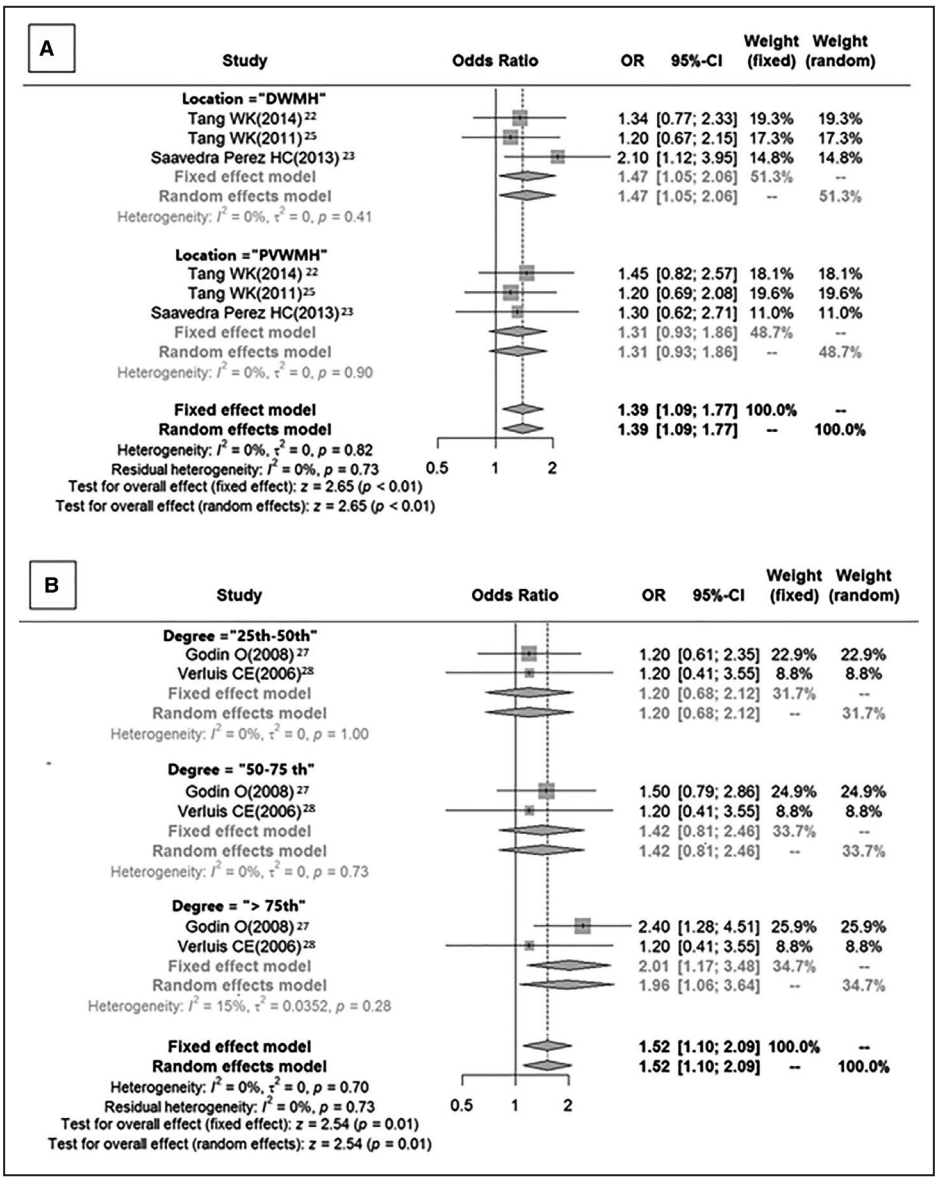

Figure 3. Forest plots of white matter hyperintensity (WMH) location and severity at baseline and incident depression.
A, WMH location; **B,** WMH severity. OR indicates odds ratio.

derived from the OR values (pooled OR, 1.41; 95% CI, 1.07–1.85) (Figure S2A) were of similar magnitude, and concurred in showing that findings of enlarged perivascular spaces could increase the risk of incident depression. No publication bias was found for EPVS data (Figure S3A).

Cerebral Atrophy and Incident Depression

Only 2 studies were available for cerebral atrophy. The pooled results from either the original data or the calculated ORs showed a significant association between temporal atrophy and incident depression (Figure 2C and Figure S2B). Because of low heterogeneity (I^2=0%; τ^2=0) and the very few studies, we applied fixed-effect and random-effect models, both of which had good consistency (pooled OR, 2.83; 95% CI, 1.54–5.23). There was no sign of publication bias (Figure S3B).

Cerebral Microbleed and Incident Depression

Four studies of cerebral microbleed were included. The between-study heterogeneity was low and not statistically significant (I^2=11%; τ^2=0.0083; Q=3.38). Considering the relatively few studies and small heterogeneity, we applied the fixed-effect model (pooled OR, 1.25; 95% CI, 0.98–1.60) and the random-effect model (pooled OR, 1.26; 95% CI, 0.97–1.64) to test the pooled effect (Figure 2D), which did not indicate cerebral microbleeds as a significant risk factor for incident depression. The OR data using the random-effect model showed the same result (pooled OR, 1.62; 95% CI, 0.98–2.66) (Figure S2C). There was no evidence for publication bias for microbleeds (Figure S3C).

Lacunar Infarcts and Incident Depression

Four studies of lacunar infarct were included. Both the exact incident data and the ORs could be extracted from the original studies. The between-study heterogeneity was high and statistically significant. Therefore, we applied the random-effect model. Neither exact incident data (pooled OR, 1.40; 95% CI, 0.84–2.32; I^2=84%; τ^2=0.2150) (Figure 2E) nor OR data (pooled OR, 1.31; 95% CI, 0.71–2.42) indicated statistical significance (Figure S2D). The corresponding funnel plot is presented in Figure S4.

Meta-Regression and Subgroup Analysis

We found high heterogeneity in the analysis comparing moderate/severe WMHs versus mild/none. Therefore, we performed meta-regression analysis, which showed that participants (patients), follow-up duration (1–5 years) and WMHs assessment methods (white matter grade) were the source of heterogeneity and could together entirely explain the overall variation (Table S3). Subgroup analyses of study characteristics suggested that the risk of depression was higher in people aged over 65 years (pooled OR, 1.70; 95% CI, 1.17–2.49) and those with cardiovascular disease (pooled OR, 1.64; 95% CI, 1.16–2.30). Furthermore, the shorter the follow-up time, the higher the risk of depression. WMHs and depression assessment methods have an impact on the risk of depression (Figures S5 and S6).

DISCUSSION

Our meta-analysis shows that certain CSVD markers are strongly associated with incident depression, especially WMHs, EPVSs, and cerebral atrophy. The data may indicate a causal relationship between CSVD and incidence of depression because we selected only longitudinal studies that excluded participants with prevalent depression at baseline. The association is especially evident in the case of WMHs, which bring greater risk for incident depression in proportion to severity of the imaging findings. Furthermore, we find that DWMHs, but not PWMHs, predict a higher risk for incident depression, suggesting neuroanatomic basis of the risk for depression attributable to WMHs. If these associations are indeed causal, presence of DWMHs may therefore predict for onset of depression in the coming years.

Our meta-analysis has several advantages over earlier reports. First, we based our study on a predefined protocol and followed standard guidelines, thus including numerous studies and individuals, which resulted in high statistical power. Second, all selected studies were of longitudinal cohort design, specifically excluding studies with depression at baseline, which is a necessary condition for establishing causality. Furthermore, this analysis is, to our knowledge, the first attempt to identify the causal association of the location and severity of WMHs with incident depression. Third, most of the included studies were of high quality and were properly adjusted for confounders such as age, sex, education level, cognitive function, and vascular risk factors. Finally, subgroup and meta-regression analysis enabled us to identify sources of data heterogeneity; the observed associations proved to be robust to the sources of heterogeneity, which strengthens the validity of our findings.

The several previous meta-analyses on the correlation between WMHs and depression had somewhat discordant results. Two meta-analyses,[7,8] which included both community-based participants and patients, addressed the association of WMHs with

depression in longitudinal and cross-sectional settings but without evident causal analysis. Present findings agree with and extend the interpretation of those previous meta-analyses focusing on WMHs. A recent meta-analysis[6] included cohort studies in adults that showed a consistent association between various CSVD and depression, but the analysis didn't exclude patients with a history of depression. As noted above, by excluding participants with baseline or historical depression, our new meta-analysis supports evaluation of the causal effect of various individual CSVD features on risk of incident depression in prospective cohort study populations. Indeed, our findings give strong support for the hypothesis that WMHs may be a cause of depression, rather than a comorbidity. However, some previous studies of this type have had inconsistent results, presumably due to confounding factors such as the age of participants, different study design, and methods for diagnosis of depression and evaluation of WMHs. Considering these factors, we performed the subgroup analysis, which proved that participants' age, source of participants recruitment, duration of follow-up, WMH evaluation methods, and depression assessment methods all contributed to the overall associations between imaging results and risk of depression. Individuals with ischemic stroke and WMHs have a higher risk of depression than does the community population, likely because ischemia events can cause structural disruptions of the fiber tracts in the cerebral white matter.[30] If connectivity between brain regions involved in mood regulation is then compromised, this may manifest in higher risk for developing depression.[31] Indeed, WMHs are more common in patients with history of ischemic stroke than in the general population.[32] People aged over 65 years had an elevated incidence of depression, which could be explained by vascular depression hypothesis.[33]

Damage to frontal-subcortical circuits is hypothesized to be a pathological condition predisposing the individuals to depression.[34] Indeed, previous imaging studies have suggested that development of depression is related to WMHs localized in the frontal lobe[34] or in the deep white matter,[35] which may contain projections from the frontal lobe. Another study[36] has suggested that DWMHs are associated with risk for developing depression. Our meta-analysis is consistent with these previous results and further indicates that it is the DWMHs, but not PWMHs, that are an independent predictor for incident depression. We suppose that DWMHs are more indicative of impaired connectivity between the frontal lobe and other regions, whereas PWMHs manifest in disturbance of more local cortical circuits, not manifesting in mood disorder.

Previous studies have shown inconsistent results about the impact of severity of WMHs on depression risk. Nys et al[37] concluded that the severity of WMHs was not significantly associated with post-stroke depression. However, the more recent LADIS (Leukoaraiosis and Disability) studies reported a log-linear relationship between volume of WMHs and risk of developing depression in a 3-year follow-up period.[38] In our meta-analysis, volumetric methods were used to assess WMH severity, which showed that higher WMH volumes at baseline indeed increase the risk of developing depression during follow-up. However, since only 2 such studies were available, there is clearly a need for further quantitative analysis of WMH volume as a risk factor for depression.

EPVSs have recently emerged as a marker of CSVD, given their close association with WMHs, lacunae, and cerebral microbleeds.[39] EPVSs are also a marker of neuroinflammation, which likely plays a role in the pathogenesis of depression.[40] Previous studies suggest that EPVSs were associated with depressive symptoms in the general population[39] and in stroke patients.[41] Results of our meta-analysis agree with those previous studies, confirming that individuals with EPVSs may be at higher risk to develop depression.

Cortical atrophy is a common finding in medical imaging of the aging brain[42] and as an expression of CSVD.[1] Previous cross-sectional studies confirmed that late-life depression was associated with atrophy in the frontal and temporal lobes,[43] but one longitudinal population-based study found no association between cerebral atrophy and occurrence of depression at follow-up.[42] The design of our present analysis, which includes only longitudinal studies without baseline depression, reveals a strong association between temporal lobe atrophy and incident depression. While frontal-subcortical circuits are certainly implicated in depression,[44] the present findings call attention to a possible relationship between temporal lobe atrophy and incident depression.

CMBs are common occurrences in ischemic stroke and may be one of the main factors leading to post-stroke depression.[45] However, our meta-analysis found no relationship between CMBs and incident depression. This may relate to the different locations of CMBs, which is a matter for future investigation. Besides, lacunar strokes detected by MRI are one of the common manifestations of CSVD and are a frequent finding in aged depressed patients.[46] However, the present meta-analysis did not indicate a strong association between lacunae and depression. This may be related more to the smaller lesion size (<2.0 cm) than for other stroke subtypes.[47]

Limitations

Some limitations should be considered in our meta-analysis. First, the heterogeneity of studies and

potential publication bias of meta-analysis is hard to avoid. Although we have applied strict standards, our included studies differ in some respects, such as subjects' mean age, follow-up duration, target population, and the assessment methods of WMHs and depression. Therefore, we analyzed data by a random-effect model and explored the heterogeneity by meta-regression, which revealed that follow-up duration, target population, and the WMH assessment methods could together explain 100% of the heterogeneity of WMHs in the pathway to depression in CSVD. Subgroup analyses according to age, different follow-up duration, target population, and the WMH and depression assessment methods were also performed, which indicated that the specific sample composition had great impact on the relationship between CSVD and incident depression. Second, we found evidence for publication bias in the WMH studies, which was accommodated by our trim-and-fill analysis. Third, only 3 studies evaluated EPVSs, and only 2 evaluated cerebral atrophy. Therefore, the evidence linking these 2 markers with incident depression remains weak. Fourth, there were only a few cohort studies of small sample size for lacunar infarcts and cerebral microbleeds, such that the lack of significant relationships with incident depression may be a type II error.

Other limitations arising from the original studies might influence the interpretation of our results. First, the included studies are of observational but not experimental design, such that unmeasured cofactors may have contributed to incident depression, even though CSVD was the only recorded manifestation of the biological pathways. Second, we evaluated only baseline measurements of CSVD without screening the incident CSVD during the follow-up period. Furthermore, the incident depression in the control groups might be attributable to incidence of new CSVD during the follow-up period. Therefore, these studies are not fit to perfectly capture the relationship between baseline CSVD and incident depression. However, this ambiguity seems to be a general limitation of the literature. Finally, we could not evaluate the location of CSVD features (other than WMHs) because of a lack of relevant original anatomic studies, although depression development may well associate with the location of lesions.

Implications and Future Directions

In conclusion, this meta-analysis shows that presence of CSVD to MRI is causally linked to incident depression, which is a finding with important clinical implications. First, CSVD may be a general marker of risk of depression, but specific features of CSVD carry more weight in this association. Therefore, early and effective treatment for CSVD may help prevent the incidence of geriatric depression. Moreover, our meta-analysis indicates that the severity and location of WMHs are closely related to incident depression. This observation not only may help to improve risk prediction of depression but also provides a theoretical anatomic basis for investigating the underlying mechanisms.

CONCLUSIONS

This meta-analysis shows that specific CSVD features, including WMHs, EPVSs, and cerebral atrophy indicate a high risk for incident depression. Furthermore, the severity and location of WMHs are strongly associated with a higher incidence of depression. This finding may provide targets for treatment and prevention strategies of depression in this vulnerable population.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Materials

Data S1–S2
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SUPPLEMENTAL MATERIAL

Supplemental Methods

Data S1

Search strategy for CSVD and incident depression.

Pubmed: 1283 articles until September 06, 2019
#1 Search "Cerebral Small Vessel Diseases"[Mesh]
#2 Search CSVD[Title/Abstract]
#3 Search ("Cerebral Small Vessel Diseases"[Mesh]) OR CSVD[Title/Abstract]
#4 Search "Leukoencephalopathies"[Mesh]
#5 Search ((((white matter lesion*[Title/Abstract]) OR white matter hyperintensitie*[Title/Abstract]) OR WMH*[Title/Abstract]) OR white matter disease*[Title/Abstract]) OR leukoaraosis[Title/Abstract]
#6 Search ("Leukoencephalopathies"[Mesh]) OR (((((white matter lesion*[Title/Abstract]) OR white matter hyperintensitie*[Title/Abstract]) OR WMH*[Title/Abstract]) OR white matter disease*[Title/Abstract]) OR leukoaraosis[Title/Abstract])
#7 Search "Stroke, Lacunar"[Mesh]
#8 Search (((Lacunar Stroke*[Title/Abstract]) OR lacunar infarction*[Title/Abstract]) OR Lacunar Infarct*[Title/Abstract]) OR microinfarction*[Title/Abstract]
#9 Search ("Stroke, Lacunar"[Mesh]) OR ((((Lacunar Stroke*[Title/Abstract]) OR lacunar infarction*[Title/Abstract]) OR Lacunar Infarct*[Title/Abstract]) OR microinfarction*[Title/Abstract])
#10 Search (microbleeds[Title/Abstract]) OR CMBs[Title/Abstract]
#11 Search (perivascular spaces[Title/Abstract]) OR cerebral atrophy[Title/Abstract]
#12 Search (((((("Cerebral Small Vessel Diseases"[Mesh]) OR CSVD[Title/Abstract])) OR (("Leukoencephalopathies"[Mesh]) OR (((((white matter lesion*[Title/Abstract]) OR white matter hyperintensitie*[Title/Abstract]) OR WMH*[Title/Abstract]) OR white matter disease*[Title/Abstract]) OR leukoaraosis[Title/Abstract])))) OR (("Stroke, Lacunar"[Mesh]) OR ((((Lacunar Stroke*[Title/Abstract]) OR lacunar infarction*[Title/Abstract]) OR Lacunar Infarct*[Title/Abstract]) OR microinfarction*[Title/Abstract])))) OR ((((microbleeds[Title/Abstract]) OR CMBs[Title/Abstract])) OR ((perivascular spaces[Title/Abstract]) OR cerebral atrophy[Title/Abstract]))
#13 Search "Depression"[Mesh]
#14 Search ((depression*[Title/Abstract]) OR depressive symptom*[Title/Abstract]) OR depressive disorder*[Title/Abstract]
#15 Search ("Depression"[Mesh]) OR (((depression*[Title/Abstract]) OR depressive symptom*[Title/Abstract]) OR depressive disorder*[Title/Abstract])
#16 Search ((("Depression"[Mesh]) OR (((depression*[Title/Abstract]) OR depressive symptom*[Title/Abstract]) OR depressive disorder*[Title/Abstract]))) AND ((((((("Cerebral Small Vessel Diseases"[Mesh]) OR CSVD[Title/Abstract])) OR (("Leukoencephalopathies"[Mesh]) OR (((((white matter lesion*[Title/Abstract]) OR

white matter hyperintensitie*[Title/Abstract]) OR WMH*[Title/Abstract]) OR white matter disease*[Title/Abstract]) OR leukoaraosis[Title/Abstract]))) OR (("Stroke, Lacunar"[Mesh]) OR ((((Lacunar Stroke*[Title/Abstract]) OR lacunar infarction*[Title/Abstract]) OR Lacunar Infarct*[Title/Abstract]) OR microinfarction*[Title/Abstract]))) OR ((((microbleeds[Title/Abstract]) OR CMBs[Title/Abstract])) OR ((perivascular spaces[Title/Abstract]) OR cerebral atrophy[Title/Abstract])))

Embase: 1904 articles until September 06, 2019

#1 ‘Cerebral small vessel disease’.ab,ti
#2 ‘CSVD’.ab,ti
#3 #1 OR#2
#4 'leukoencephalopathy'/exp
#5 'white matter lesion*’: ab,ti
#6 'white matter hyperintensities':ab,ti
#7 ‘WMH*’:ab,ti
#8 ‘white matter disease*’:ab,ti
#9 ‘leukoaraosis’:ab,ti
#10 #4 OR #5 OR #6 OR #7 OR #8 OR #9
#11 'lacunar stroke'/exp
#12 ‘Stroke, Lacunar’:ab,ti
#13 ‘lacunar infarction*’:ab,ti
#14 ‘Lacunar Infarct*’:ab,ti
#15 ‘microinfarction*’:ab,ti
#16 #11 OR #12 OR #13 OR #14 OR #15
#17 ‘microbleeds’:ab,ti
#18 ‘CMBs’:ab,ti
#19 'perivascular spaces':ab,ti
#20 ‘cerebral atrophy’:ab,ti
#21 #17 OR #18 OR #19 OR #20
#22 #3 OR #10 OR #16 OR #21
#23 'depression'/exp
#24 'depression*':ab,ti
#25 'depressive symptom*':ab,ti
#26 'depressive disorder*':ab,ti
#27 #23 OR #24 OR #25 OR #26
#28 #22 AND #27

Web of Science: 160 articles until September 06, 2019

#1 4548 TS= (Cerebral small vessel disease OR CSVD)
#2 35200 (TS= (leukoencephalopathy OR white matter lesion* OR white matter hyperintensitie* OR WMH* OR white matter disease* OR leukoaraosis)) AND Type: (Article)
#3 3659 (TS= (Stroke, Lacunar OR Lacunar Stroke* OR lacunar infarction* OR

Lacunar Infarct* OR microinfarction*)) AND Type= (Article)
#4 11421 (TS= (microbleeds OR CMBs OR perivascular spaces OR cerebral atrophy)) AND Type = (Article)
#5 48251 #4 OR #3 OR #2 OR #1
#6 389637 (TS= (depression OR depression* OR depressive symptom* OR depressive disorder*)) AND Type = (Article)
#7 2239 #6 AND #5

Cochrane Library: 160 articles until September 06, 2019

#1 MeSH descriptor: [Cerebral small vessel disease] explored all trees
#2 (CSVD): ti,ab,kw
#3 #1 OR #2
#4 MeSH descriptor: [leukoencephalopathies] explored all trees
#5 (white matter lesion*): ti,ab,kw
#6 (white matter hyperintensitie*): ti,ab,kw
#7 (WMH*): ti,ab,kw
#8 (white matter disease*): ti,ab,kw
#9 (leukoaraosis): ti,ab,kw
#10 #4 OR #5 OR #6 OR #7 OR #8 OR #9
#11 MeSH descriptor: [Stroke, Lacunar] explored all trees
#12 (Lacunar Stroke*): ti,ab,kw
#13 (lacunar infarction*): ti,ab,kw
#14 (Lacunar Infarct*): ti,ab,kw
#15 (microinfarction*): ti,ab,kw
#16 #11 OR #12 OR #13 OR #14 OR #15
#17 (microbleeds): ti,ab,kw
#18 (CMBs): ti,ab,kw
#19 (perivascular spaces): ti,ab,kw
#20 (cerebral atrophy): ti,ab,kw
#21 #17 OR #18 OR #19 OR #20
#22 #3 OR #10 OR #16 OR #21
#23 MeSH descriptor: [depression] explored all trees
#24 (depression*): ti,ab,kw
#25 (depressive symptom*): ti,ab,kw
#26 (depressive disorder*): ti,ab,kw
#27 #23 OR #24 OR #25 OR #26
#28 #22 AND #27

Data S2. The definition of CSVD according to MRI characteristics.

(1) WMHs were defined as subcortical or periventricular focal or confluent areas of hyperintensity on T2-weighted imaging, which were assessed by semiquantitative visual rating methods, including Fazekas scale[48], white-matter grade[49,50], Scheltens score[4], Gothenburg scale[51,52] and by quantitative measurements of WMH volume.
(2) LIs were defined as subcortical hyperintense lesions of <20 mm on T2-weighted imaging and fluid attenuated inversion recovery.
(3) CMBs were defined as small (2–10 mm) hypointense lesions on a T2-weighted gradient echo sequence[53].
(4) EPVs were identified as round or linear-shaped lesions with signal intensity equal to the cerebrospinal fluid, which were of high signal on T2 weighted imaging and low signal on fluid-attenuated inversion recovery[54].
(5) Total brain parenchyma volume (an indicator of cerebral atrophy) were computed automatically with a previously described image analysis pipeline[55] and were expressed as the percentage of total intracranial volume. Therefore, articles reporting on any of the above five markers were identified and included.

Table S1. Quality assessment of the included studies by use of the Newcastle-Ottawa Scale (NOS) 40*.

Ref	Year	First author	Selection				Comparability		Outcome			NOS Score
			1	2	3	4	5a	5b	6	7	8	
1	2018	Liang, Y	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/9
2	2017	Zhang, X	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/9
3	2017	Qiu, W. Q	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/9
4	2017	He, J. R	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/9
5	2016	Arba, F	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/9
6	2015	van Sloten, T. T	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/9
7	2015	Park, J. H	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/9
8	2015	Gudmundsson, P	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/9
9	2014	Tang, W. K	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/9
10	2013	Saavedra Perez, H. C	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/9
11	2011	White, C. L	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/9
12	2011	Tang, W. K	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/9
13	2010	Olesen, P. J	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/9
14	2008	Godin, O	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/9
15	2006	Verluis, C. E	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/9
16	2002	Steffens, D. C	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	8/9

Selection 1= Representativeness of the exposed cohort; Selection 2= Selection of the non-exposed cohort ; Selection 3= Ascertaining of exposure; Selection 4= Demonstration that outcome of interest was not present at start of study; Comparability 5= Comparability of cohorts on the basis of the design or analysis; Outcome 6= assessment of outcome; Outcome 7= follow up duration; Outcome 8= adequacy of follow up

Table S2. GRADE classification for CSVD at baseline and incident depression.

CSVD or not for depression
patients or population: patients with CSVD
intervention: CSVD

CSVD markers	outcomes	illustrative and comparative risk (95%CI) assumed risk control	corresponding risk CSVD	Relative effect (95%CI)	No. of participants (studies)	quality of evidence (GRADE)
WMHs	depression	NA	NA	OR 1.37 (1.14 to 1.65)	8498 11	Low ++--
LIs	depression	162 per 1000	214 per 1000 130 to 335	OR 1.40 (0.84 to 2.32)	6960 4	very low +---
CMBs	depression	154 per 1000	186 per 1000 150 to 230	OR 1.26 (0.97 to 1.64)	3138 4	moderate +++-
EPVS	depression	124 per 1000	159 per 1000 128 to 159	OR 1.33 (1.03 to 1.71)	3048 3	moderate +++-
atrophy	depression	36 per 1000	96 per 1000 54 to 163	OR 2.83 (1.54 to 5.23)	855 2	moderate +++-

The quality of evidence in WMHs is low, because of high heterogeneity and publication bias. The quality of evidence in LIs is very low, because the heterogeneity is high and publication bias is found, additionally, the pooled OR is lower from OR data than from original data. The quality of evidence in CMBs, EPVS and atrophy are moderate, because the heterogeneity is low and no publication bias is found. What's more, the pooled OR is higher from OR data than from original data.

Table S3. Meta regression for WMHs at baseline and incident depression.

A. Heterogeneity estimate in model 1.

Model1： ~age + follow + participants + WMH	Value
tau^2 (estimated amount of residual heterogeneity)	0 (SE = 0.2558)
tau (square root of estimated tau^2 value)	0
I^2 (residual heterogeneity / unaccounted variability)	0.00%
H^2 (unaccounted variability / sampling variability)	1.00
R^2 (amount of heterogeneity accounted for)	100.00%
Test for Residual Heterogeneity	
QE(df = 2) = 1.2188	p- value = 0.5437
Test of Moderators (coefficients 2:9):	
QM(df = 8) = 29.2660	
p-value = 0.0003	

B. Model Results of model 1.

	Estimate	Se	Z value	P value	Lower	Upper
intrcpt	-0.0518	0.4888	-0.1060	0.9156	-1.0098	0.9062
Age						
≥65	-0.1024	0.1167	-0.8773	0.3803	-0.3312	0.1264
Follow						
≥5y	1.5710	1.0048	1.5635	0.1179	-0.3984	3.5404
1-5y	2.2510	1.0568	2.1300	0.0332	0.1797	4.3224
Participants						
Patients	0.8777	0.4210	2.0847	0.0371	0.0525	1.7029
WMH						
Gothenburg scale	-0.1575	1.0385	-0.1517	0.8794	-2.1929	1.8779
Scheltens score	-0.2667	0.3473	-0.7679	0.4425	-0.9475	0.4140
Volume	-1.3970	0.9502	-1.4702	0.1415	-3.2593	0.4653
white-matter grade	-2.1039	0.9171	-2.2941	0.0218	-3.9013	-0.3065

Considering the heterogeneity is high in our analysis about WMHs and incident depression including 11 studies, we pooled the effect sizes using mixed-effects model. The τ^2 was estimated by restricted DerSimonian-Laird method. From the result of Table A, we performed meta-regression analysis to evaluate whether age, follow-up duration, participants, and WMH assessment methods and found they could explain the overall variation 100%. There was significant influence in follow-up duration, participants, and WMH assessment methods, but not in age. Therefore, we built model2.

Model 2. Remove age

C. Heterogeneity estimate in model 2.

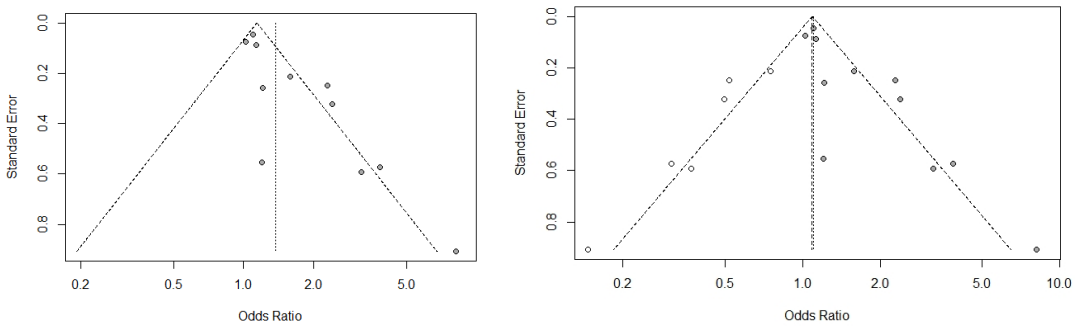
Model1： ~age + follow + participants + WMH	Value
tau^2 (estimated amount of residual heterogeneity)	0 (SE = 0.0158)

tau (square root of estimated tau^2 value)	0
I^2 (residual heterogeneity / unaccounted variability)	0.00%
H^2 (unaccounted variability / sampling variability)	1.00
R^2 (amount of heterogeneity accounted for)	100.00%
Test for Residual Heterogeneity	
QE(df = 3) = 1.9885	p-value = 0.5748
Test of Moderators (coefficients 2:9):	
QM(df = 7) = 28.4962	
p-value = 0.0002	

D. Model Results of model 2.

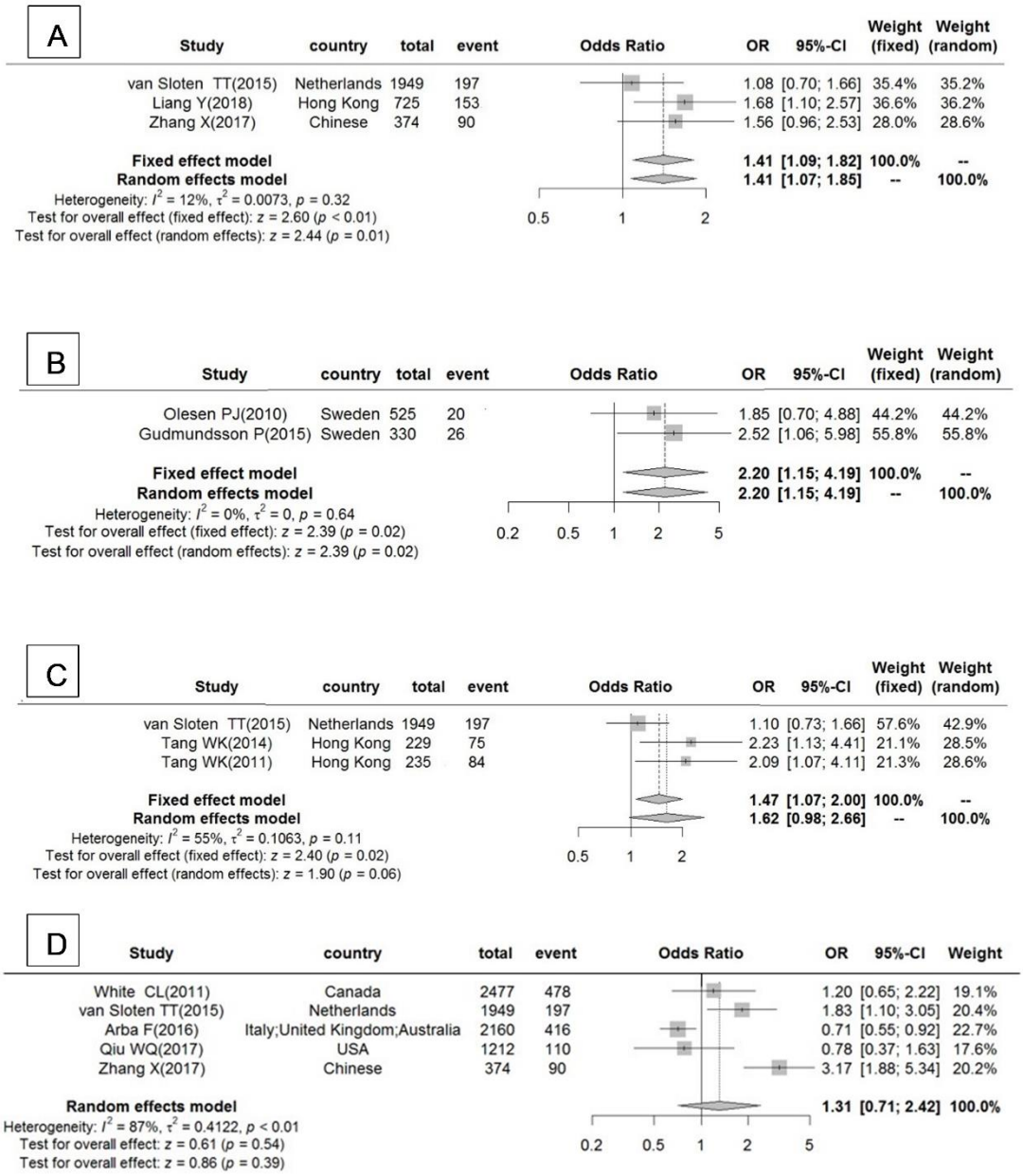
	Estimate	Se	Z value	P value	Lower	Upper
intrcpt	0.0951	0.4592	0.2072	0.8358	-0.8048	0.9951
Follow						
≥5y	1.3662	0.9773	1.3979	0.1621	-0.5493	3.2817
1-5y	2.0016	1.0179	1.9665	0.0492	0.0066	3.9967
Participants						
Patients	0.7308	0.3863	1.8919	0.0585	-0.0263	1.4879
WMH						
Gothenburg scale	-0.2021	1.0372	-0.1948	0.8456	-2.2350	1.8309
Scheltens score	-0.3691	0.3271	-1.1284	0.2592	-1.0103	0.2720
Volume	-1.3970	0.9502	-1.4702	0.1415	-3.2593	0.4653
white-matter grade	-2.0015	0.9096	-2.2004	0.0278	-3.7843	-0.2187

Figure S1. Funnel plot of the association between WMHs and incident depression.



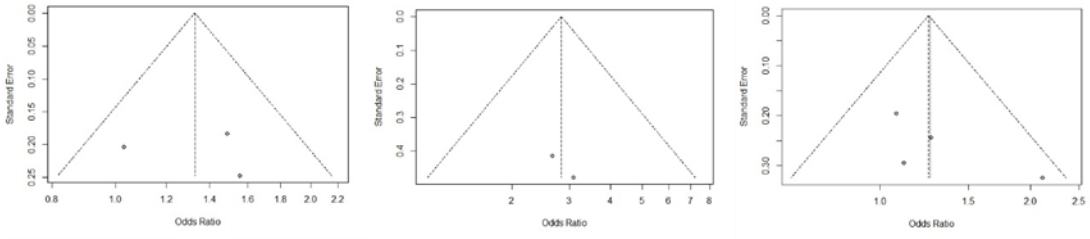
A. Funnel plot**; B.** Funnel plot adjusting with "trim and filled" analysis.

Figure S2A-D. Forest plots of cerebral small vascular disease (CSVD) and incident depression using the odds ratio data.



A. enlarged perivascular spaces (EPVs); B. cerebral atrophy; C. cerebral microbleeds (CMBs); D. lacunar infarcts (LIs); total=participants size; event=the number of incident depression; OR=Odds Ratio; CI=confidence interval

Figure S3A-C. Funnel plot of the association between EPVs, cerebral atrophy, cerebral microbleeds and incident depression.



A. enlarged perivascular spaces (EPVs); B. cerebral atrophy; C. cerebral microbleeds (CMBs)

Figure S4. A. Funnel plot of the association between lacunar infarcts and incident depression; B. Funnel plot of the association between lacunar infarcts and incident depression after adjusting by "trim and fill" analysis.

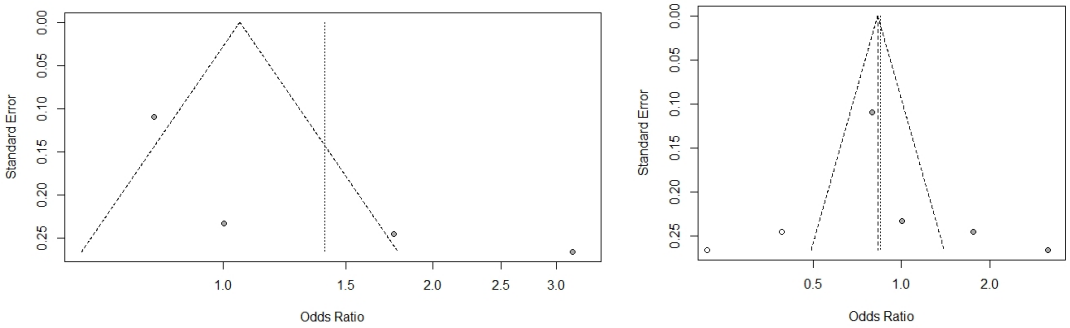
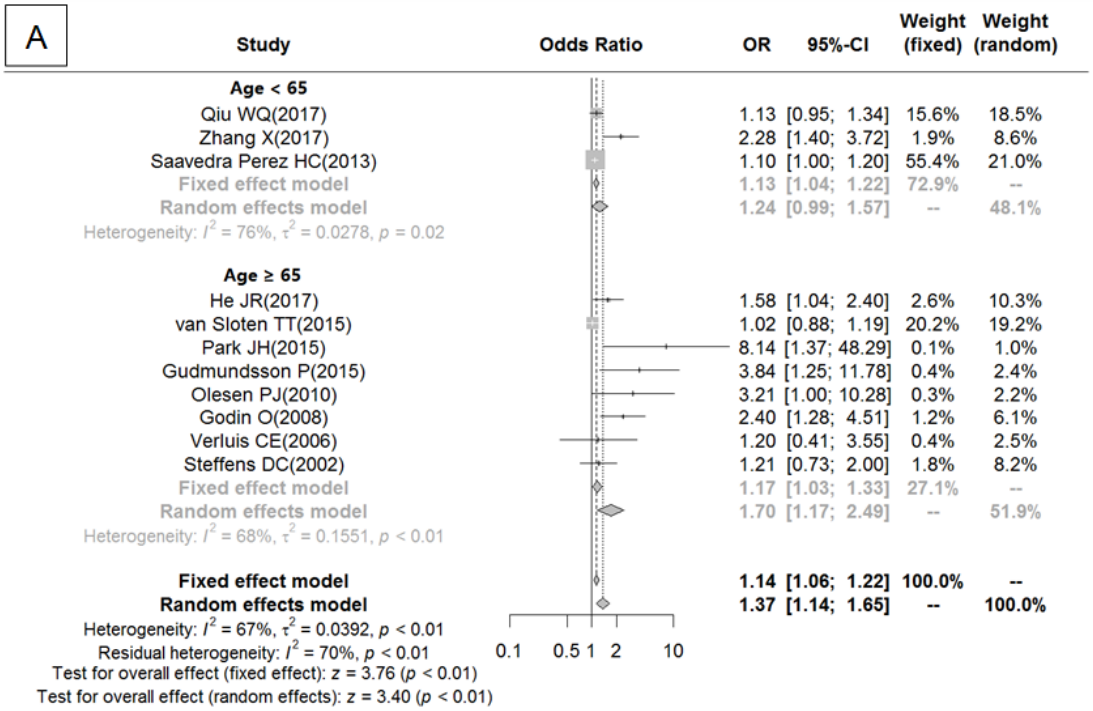
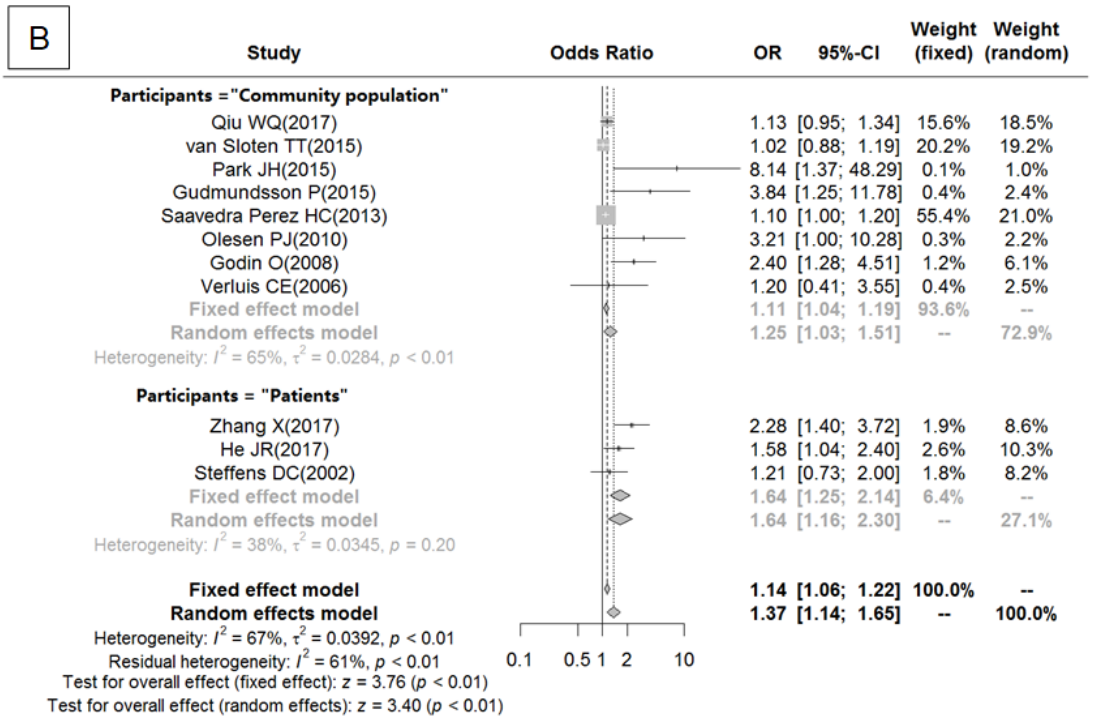
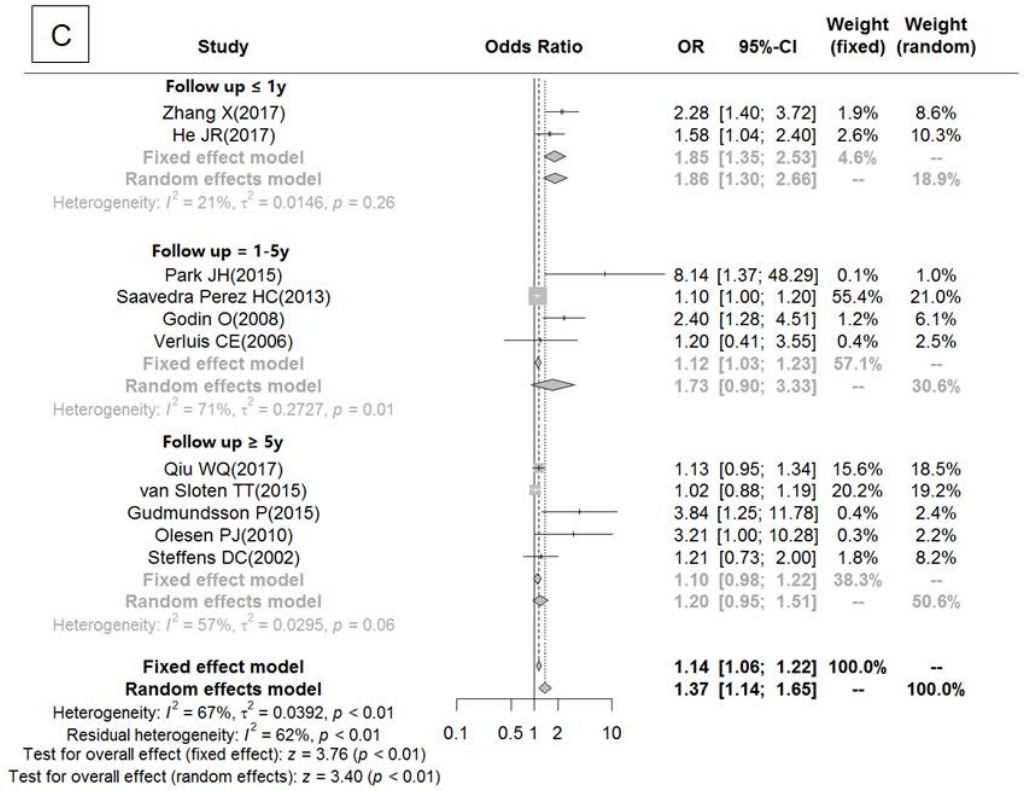
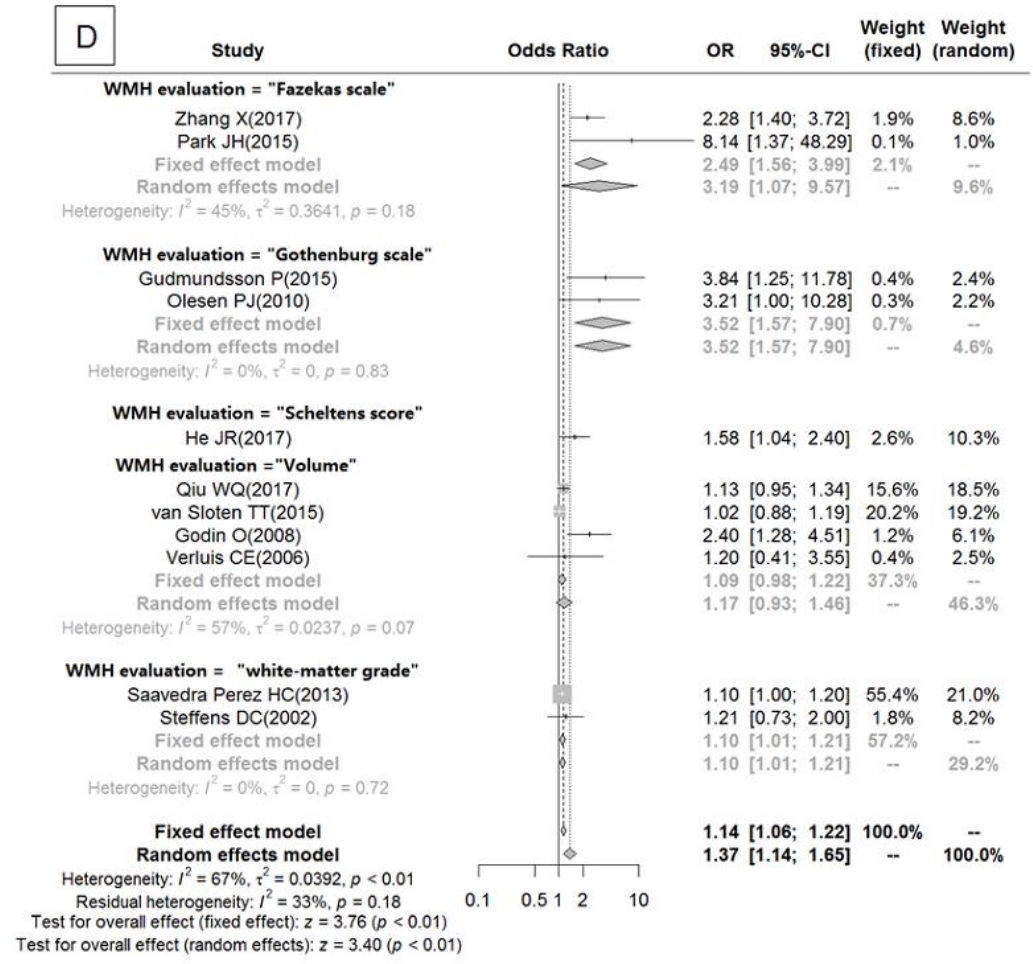


Figure S5A-D. Subgroup analysis about WMHs.



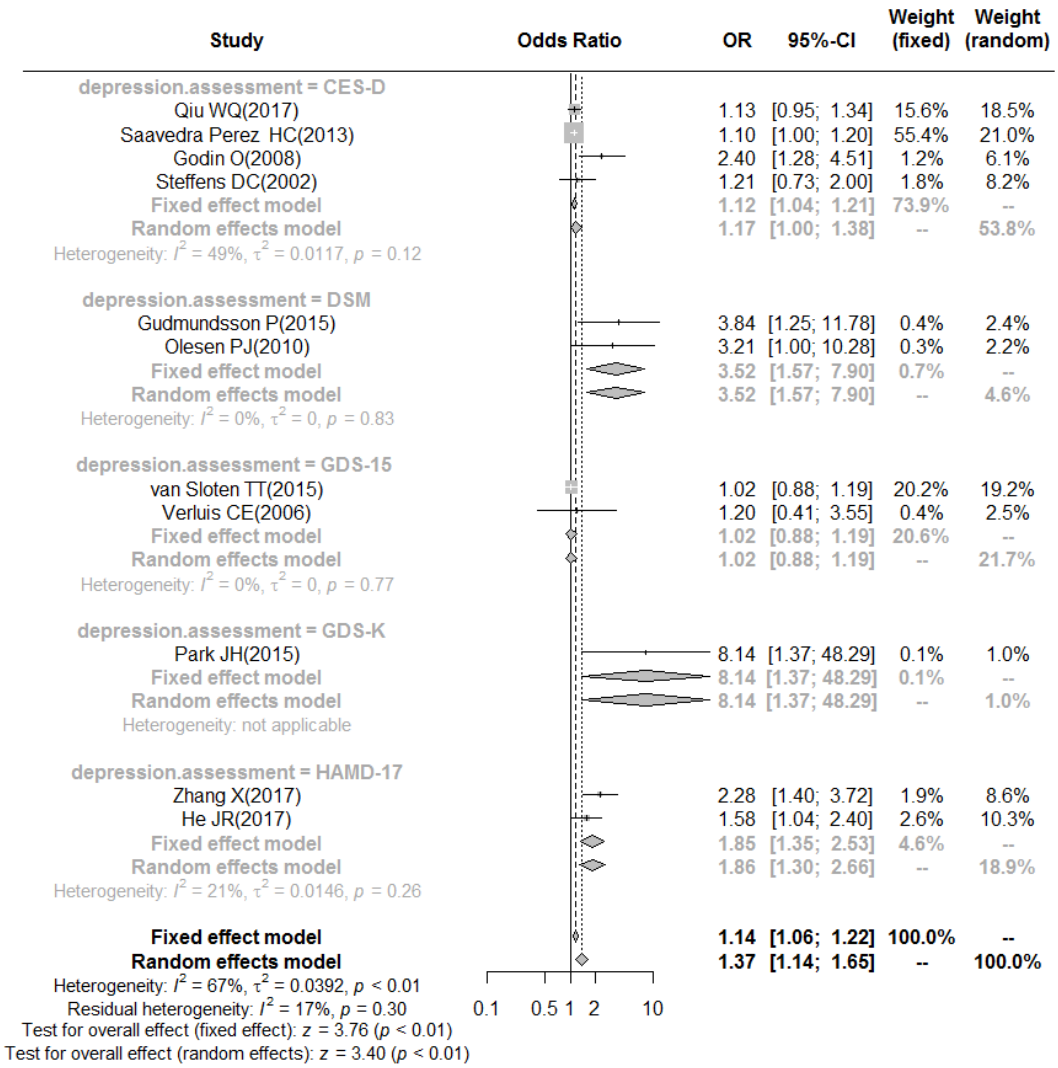



C
Study
Odds Ratio
OR
95%-CI
Weight (fixed)
Weight (random)
Follow up ≤ 1y
Zhang X(2017) 2.28 [1.40; 3.72] 1.9% 8.6%
He JR(2017) 1.58 [1.04; 2.40] 2.6% 10.3%
Fixed effect model 1.85 [1.35; 2.53] 4.6% --
Random effects model 1.86 [1.30; 2.66] -- 18.9%
Heterogeneity: I^2 = 21%, τ^2 = 0.0146, p = 0.26
Follow up = 1-5y
Park JH(2015) 8.14 [1.37; 48.29] 0.1% 1.0%
Saavedra Perez HC(2013) 1.10 [1.00; 1.20] 55.4% 21.0%
Godin O(2008) 2.40 [1.28; 4.51] 1.2% 6.1%
Verluis CE(2006) 1.20 [0.41; 3.55] 0.4% 2.5%
Fixed effect model 1.12 [1.03; 1.23] 57.1% --
Random effects model 1.73 [0.90; 3.33] -- 30.6%
Heterogeneity: I^2 = 71%, τ^2 = 0.2727, p = 0.01
Follow up ≥ 5y
Qiu WQ(2017) 1.13 [0.95; 1.34] 15.6% 18.5%
van Sloten TT(2015) 1.02 [0.88; 1.19] 20.2% 19.2%
Gudmundsson P(2015) 3.84 [1.25; 11.78] 0.4% 2.4%
Olesen PJ(2010) 3.21 [1.00; 10.28] 0.3% 2.2%
Steffens DC(2002) 1.21 [0.73; 2.00] 1.8% 8.2%
Fixed effect model 1.10 [0.98; 1.22] 38.3% --
Random effects model 1.20 [0.95; 1.51] -- 50.6%
Heterogeneity: I^2 = 57%, τ^2 = 0.0295, p = 0.06
Fixed effect model 1.14 [1.06; 1.22] 100.0% --
Random effects model 1.37 [1.14; 1.65] -- 100.0%
Heterogeneity: I^2 = 67%, τ^2 = 0.0392, p < 0.01
Residual heterogeneity: I^2 = 62%, p < 0.01
0.1 0.5 1 2 10
Test for overall effect (fixed effect): z = 3.76 (p < 0.01)
Test for overall effect (random effects): z = 3.40 (p < 0.01)


D
Study
Odds Ratio
OR
95%-CI
Weight (fixed)
Weight (random)
WMH evaluation = "Fazekas scale"
Zhang X(2017) 2.28 [1.40; 3.72] 1.9% 8.6%
Park JH(2015) 8.14 [1.37; 48.29] 0.1% 1.0%
Fixed effect model 2.49 [1.56; 3.99] 2.1% --
Random effects model 3.19 [1.07; 9.57] -- 9.6%
Heterogeneity: I^2 = 45%, τ^2 = 0.3641, p = 0.18
WMH evaluation = "Gothenburg scale"
Gudmundsson P(2015) 3.84 [1.25; 11.78] 0.4% 2.4%
Olesen PJ(2010) 3.21 [1.00; 10.28] 0.3% 2.2%
Fixed effect model 3.52 [1.57; 7.90] 0.7% --
Random effects model 3.52 [1.57; 7.90] -- 4.6%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.83
WMH evaluation = "Scheltens score"
He JR(2017) 1.58 [1.04; 2.40] 2.6% 10.3%
WMH evaluation ="Volume"
Qiu WQ(2017) 1.13 [0.95; 1.34] 15.6% 18.5%
van Sloten TT(2015) 1.02 [0.88; 1.19] 20.2% 19.2%
Godin O(2008) 2.40 [1.28; 4.51] 1.2% 6.1%
Verluis CE(2006) 1.20 [0.41; 3.55] 0.4% 2.5%
Fixed effect model 1.09 [0.98; 1.22] 37.3% --
Random effects model 1.17 [0.93; 1.46] -- 46.3%
Heterogeneity: I^2 = 57%, τ^2 = 0.0237, p = 0.07
WMH evaluation = "white-matter grade"
Saavedra Perez HC(2013) 1.10 [1.00; 1.20] 55.4% 21.0%
Steffens DC(2002) 1.21 [0.73; 2.00] 1.8% 8.2%
Fixed effect model 1.10 [1.01; 1.21] 57.2% --
Random effects model 1.10 [1.01; 1.21] -- 29.2%
Heterogeneity: I^2 = 0%, τ^2 = 0, p = 0.72
Fixed effect model 1.14 [1.06; 1.22] 100.0% --
Random effects model 1.37 [1.14; 1.65] -- 100.0%
Heterogeneity: I^2 = 67%, τ^2 = 0.0392, p < 0.01
Residual heterogeneity: I^2 = 33%, p = 0.18
0.1 0.5 1 2 10
Test for overall effect (fixed effect): z = 3.76 (p < 0.01)
Test for overall effect (random effects): z = 3.40 (p < 0.01)

A. age group analysis; **B.** participants group analysis; **C.** follow-up duration group analysis; **D.** WMHs evaluation group analysis; OR=Odds Ratio; CI=confidence interval.

Figure S6. Subgroup analysis about depression assessment methods.



OR=Odds Ratio; CI=confidence interval.