International Psychogeriatrics (2014), 26:7, 1101–1109 © International Psychogeriatric Association 2014
doi:10.1017/S1041610214000568

REVIEW

Lacunar stroke, deep white matter disease and depression: a meta-analysis

Peter Egeto,[1] Corinne E. Fischer,[1,2] Zahinoor Ismail,[3,4] Eric E. Smith[5,6] and Tom A. Schweizer[1,7,8]

[1]*Keenan Research Centre of the Li Ka Shing Knowledge Institute, St. Michael's Hospital, 30 Bond Street, Toronto, Canada*
[2]*Department of Psychiatry, Faculty of Medicine, University of Toronto, 27 King's College Circle, Toronto, Canada*
[3]*Departments of Psychiatry and Clinical Neurosciences, University of Calgary, 3330 Hospital Drive NW, Calgary, Canada*
[4]*Centre for Addiction and Mental Health, Geriatric Mental Health Program, Toronto, Canada*
[5]*Hotchkiss Brain Institute, University of Calgary, 3330 Hospital Drive NW, Calgary, Canada*
[6]*Department of Clinical Neurosciences, Radiology and Community Health Sciences, University of Calgary, 2500 University Drive NW, Calgary, Canada*
[7]*Institute of Biomaterials and Biomedical Engineering, Faculty of Medicine, University of Toronto, 27 King's College Circle, Toronto, Canada*
[8]*Department of Surgery, Faculty of Medicine, University of Toronto, 27 King's College Circle, Toronto, Canada*

ABSTRACT

Background: Lacunar stroke is a small (<2 cm) infarction that accounts for approximately 20% of all strokes. While a third of all stroke patients experience depressive symptoms, the prevalence of depression in the lacunar stroke patient population is unclear. This meta-analysis aimed to synthesize the evidence on the effect of lacunar stroke and deep white matter disease on depressive symptoms.

Methods: A systematic search of electronic databases was conducted, resulting in the inclusion of 12 studies. Analyses were performed on the effects of lacunar stroke, volume and location of lacunes on depression prevalence, and the effect on depression severity. The effects estimates were calculated in random-effects models.

Results: None of the analyses produced statistically significant results. Lacunar stroke patients had a non-significantly higher prevalence of depression compared to patients with non-lacunar cerebrovascular diseases (OR = 1.46, 95% CI: 0.88–2.43, $p = 0.15$). Neither thalamic (OR = 1.37 (0.85–2.20), $p = 0.19$), deep white matter (RR = 1.16 (0.85–1.57), $p = 0.35$), multiple lacunes (OR = 1.34 (0.81–2.22), $p = 0.25$), or the volume of lacunes (MD = −4.71 (−351.59–342.18), $p = 0.98$) had an effect on depression prevalence. Lastly, lacunar stroke did not influence depressive symptom severity (MD = 0.96 (−1.57–3.48), $p = 0.46$).

Conclusions: The pooled group of patients with lacunar stroke and deep white matter disease appear to have a similar prevalence of depression compared to those with other types of cerebrovascular diseases. However, the small number of studies, heterogeneous comparison groups, and high statistical heterogeneity between studies posed an obstacle to the meta-analysis. To determine appropriate screening and treatment approaches, future research will need to separate lacunar stroke and deep white matter disease patients, and include larger sample sizes and healthy control groups to determine their distinct contributions to depression.

Key words: lacunar stroke, depression, post-stroke depression, microvascular, leukoaraiosis

Introduction

Lacunar stroke is a small (<2 cm) infarction that generally originates from a single perforating artery (Sacco *et al.*, 2006). The pathology typically presents as a non-atheromatous thickening of portions of small arteries and/or arterioles, in conjunction with the breakdown of muscular and elastic fibers (Bailey *et al.*, 2012). Infarction or arteriolar occlusion can occur at later stages secondary to severe vessel wall damage (Ogata, 1999). Lacunar stroke accounts for approximately 25% of ischemic stroke, and 20% of all strokes (Sudlow and Warlow, 1997). In terms of disease progression and prognosis, lacunar stroke patients have slightly lower rates of stroke recurrence and

Correspondence should be addressed to: Dr. Tom A. Schweizer, PhD, Director, Neuroscience Research Program, Keenan Research Centre of the Li Ka Shing Knowledge Institute, St. Michael's Hospital, 30 Bond Street, Toronto, Ontario, M5B 1W8, Canada. Phone: +416 864-5504; Fax: +416 864-5857. Email: schweizert@smh.ca. Received 29 Jan 2014; revision requested 7 Feb 2014; revised version received 3 Mar 2014; accepted 5 Mar 2014. First published online 9 April 2014.

https://doi.org/10.1017/S1041610214000568 Published online by Cambridge University Press

mortality in the short term (1–2 years) compared to those with non-lacunar stroke (e.g. cortical infarct, hemorrhagic stroke), though the rates between the two tend to converge after the first few years (Sacco *et al.*, 2006). Lacunar stroke is accompanied by deficits across a wide range of cognitive domains (e.g. memory, attention, language, processing speed) (Edwards *et al.*, 2013), and the prevalence of post-stroke mild cognitive impairment (MCI) and dementia is 37% (Makin *et al.*, 2013).

In addition to cognitive impairment, depression may also be associated with lacunar stroke. When taking all types of stroke into account, 33% of stroke patients report depressive symptoms as early as a month after stroke occurrence (Hackett *et al.*, 2005). However, the development of depression is not rigidly linked to disease onset. In fact, patients are six times more likely to develop depression even two or more years following the occurrence of their stroke (Whyte *et al.*, 2004). Importantly, this association is not mediated by disability, which can also contribute to post-stroke depression (Ramasubbu *et al.*, 1998). This psychiatric co-morbidity is a significant clinical factor, as the presence of depression in stroke patients raises the risk of mortality three-fold within a decade after stroke (Everson *et al.*, 1998). Evidence has linked lesion location to the development of post-stroke depression (PSD), offering the possibility that lacunes in certain brain regions may contribute to a greater likelihood of depression. Specifically, some of the brain regions linked to PSD include the left frontal and bilateral prefrontal lobes, left frontal and right occipital lobe (Hutter and Kreitschmann-Andermahr, 2013), though these claims have been challenged (Carson *et al.*, 2000; Provinciali and Coccia, 2002; Bhogal *et al.*, 2004; Paolucci *et al.*, 2006; Santos *et al.*, 2009b).

An alternate account for PSD posits that the accumulation of vascular lesions such as lacunes, rather than location-specific macrovascular lesions, is a better predictor of the development of depression. A recent study found that interim strokes, transient ischemic attacks (TIA), and possibly white matter hyperintensities (WMH) were more likely to explain the rates of PSD than the severity or laterality of strokes (Brodaty *et al.*, 2007). White matter hyperintensities, detected by T2-weighted magnetic resonance imaging (MRI), are the result of white matter lesions (WML) or lacunar stroke (Fazekas *et al.*, 1993). White matter lesions are thought to develop due to increased blood-brain barrier permeability, which can allow the leakage of blood proteins in the surrounding space and result in vascular inflammation and demyelination (Farrall and Wardlaw, 2009). The association between WML and depression has been established (Herrmann *et al.*, 2008; Arnone *et al.*, 2012); however, the role of lacunar stroke is less clear.

To our knowledge, this meta-analysis is the first attempt to quantitatively analyze the literature on the association between lacunar stroke and depression, focusing on cohort and case-control studies that recruited patients with lacunar stroke and/or depression. Data from twelve studies were analyzed for the impact of lacunar stroke in general, lacunar volume, thalamic, deep white matter and multiple lacunes on the incidence of depression, as well as the effect of lacunes on the severity of depressive symptoms. Elucidating the links between lacunar stroke and depression will be important for clinical diagnostics and treatment approaches.

Methods

Study selection criteria

Pubmed, MEDLINE and EMBASE were searched for articles written in the English language that assessed the interactions between lacunar stroke and depression using the keywords "depressi*" in combination with either "lacun*," "microvascular," "small vessel disease," or "leukoaraiosis," up to September 25th, 2013. A caveat of the lacunar stroke patient population is that many have concurrent white matter lesions. Because of the established links between white matter disease and small-vessel ischemic injury (Fernando *et al.*, 2006; Young *et al.*, 2008; Gouw *et al.*, 2011), lacunar stroke and deep WML were grouped for the purpose of this meta-analysis. However, studies that reported effect sizes adjusted for co-variables mitigated this confound. Studies were restricted to clinical studies of human participants who either harbored lacunes or delineated deep white matter disease and were being assessed for depressive symptoms, or those who presented with depressive symptoms and examined for the presence of lacunes or deep white matter disease. Case studies and reviews were excluded. In order to be included in the meta-analysis, studies had to include a comparison group, patients had to be dementia-free, lacunar stroke identification must have been done using imaging (e.g. MRI, CT) as opposed to neuropathological analysis, the presence of depression must have been established using a validated and commonly used measure (e.g. Diagnostic and Statistical Manual of Mental Disorders (American Psychiatric Association, 1994), Hamilton Depression Rating Scale (Hamilton, 1960)), and had to either provide an odds ratio (OR), risk ratio (RR), or the appropriate data to allow for the computation of an effects estimate. The rationale behind excluding neuropathological

https://doi.org/10.1017/S1041610214000568 Published online by Cambridge University Press

studies was to focus on the psychiatric effects of vascular lesions that are detectable by imaging technologies available in hospitals. If an association is found between lacunar stroke and depression, then detection of these lesions can also have implications for psychiatric treatment. Additionally, autopsy studies are uncommon and the patients in such studies may not be representative of lacunar stroke patients, while neuroimaging is routinely performed in stroke patients. Publication bias was assessed using a funnel plot, and the methodological quality of the studies was assessed using the Newcastle-Ottawa Scale (NOS), which uses a checklist to quantitatively assess studies based on their participant selection, comparability, and outcomes (Wells *et al.*, 2011).

Data synthesis and analysis

The study search and data extraction (sample size, study design, patient source, demographics, outcome measures, ORs or RRs or the raw data) were performed by P.E. When reported, effect estimates adjusted for co-variables such as age or gender were used for analysis. However, unadjusted estimates were extracted if adjusted estimates were not reported. If an OR or RR was not reported at all, then an OR or RR was calculated from the raw data. If neither raw data nor an OR/RR was provided, the study was excluded. The log of the ratio measures and their standard errors were calculated using the inverse-variance weighting method, and these estimates were included in the meta-analysis in random-effects models. The mean difference rather than a ratio measure was calculated for lacunar stroke volume and depression severity. While multiple brain regions are implicated in the development or presence of depression (Provinciali and Coccia, 2002), only thalamic and deep white matter lacunes were analyzed here; there was insufficient data in the studies that passed the inclusion criteria to analyze other brain regions. The statistical heterogeneity of the effect estimates of analyses was assessed using the I^2 test, which describes the percentage of variation across the studies which is due to differences between study results rather than chance (Higgins *et al.*, 2003). Data entry and analyses were performed using RevMan version 5.2 (the Nordic Cochrane Centre, Copenhagen, Denmark). The methods and findings reported in the present meta-analysis are based on the PRISMA (Moher *et al.*, 2009) guidelines.

Results

The process of the study search is depicted in Figure 1. The initial search yielded 1,952 citations.

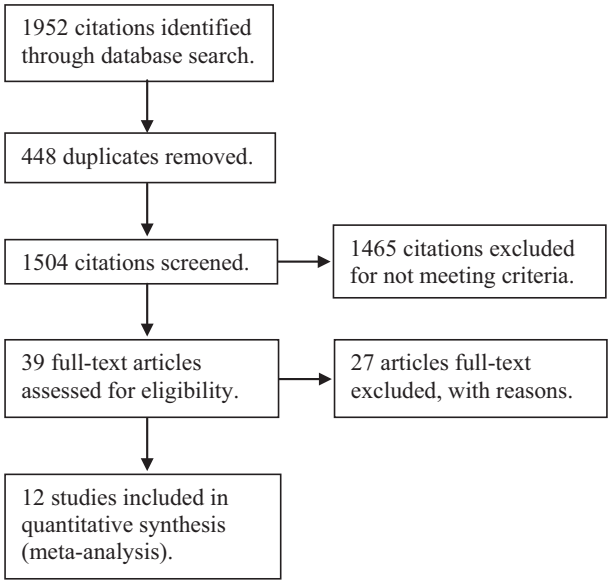


Figure 1. Flow chart of study selection process.

After the removal of 448 duplicates, 1,465 citations were excluded for not meeting the criteria outlined above, based on information garnered from their abstracts. Out of the 39 full-text articles reviewed, 27 studies were excluded for not reporting data on depressive symptoms in lacunar stroke patients (Aharon-Peretz *et al.*, 2000; van der Flier *et al.*, 2005; Jokinen *et al.*, 2006; Ramos-Estebanez *et al.*, 2008; Staekenborg *et al.*, 2010; Teodorczuk *et al.*, 2010; Man *et al.*, 2011; van Norden *et al.*, 2011; Xiong *et al.*, 2011; Firbank *et al.*, 2012; Grool *et al.*, 2012; Soriano-Raya *et al.*, 2012; Troisi *et al.*, 2012; Ogawa *et al.*, 2013; van Norden *et al.*, 2013; Wolfson *et al.*, 2013), reporting on the same patients (Grool *et al.*, 2013), not reporting data in a usable format (O'Brien *et al.*, 2006; Jokinen *et al.*, 2009; Fu *et al.*, 2010; Lavretsky *et al.*, 2010; Huijts *et al.*, 2012; Huijts *et al.*, 2013; Brookes *et al.*, 2013), or using neuropathological rather than imaging diagnoses (Thomas *et al.*, 2003; Santos *et al.*, 2009a; 2010). The study characteristics and demographics are summarized in Table 1. Eleven of the 12 included studies were cohort studies, one was a case-control design (Chatterjee *et al.*, 2010). While longitudinal studies are often considered to be a superior design, only three studies were longitudinal (Lavretsky *et al.*, 2008; Grool *et al.*, 2011b; White *et al.*, 2011). The mean score on the NOS methodological quality checklist was 7.3, but note that due to variability in the study-checklist compatibility, there is no single maximum score. The NOS score and the maximum for each individual study is depicted in Table 1. The imperfections of the NOS scale have been discussed previously (Stang, 2010).

https://doi.org/10.1017/S1041610214000568 Published online by Cambridge University Press

Table 1. Study characteristics

REFERENCE	SAMPLE SIZE	MEAN AGE (±SD)	SOURCE OF PATIENTS	COMPARISON GROUPS	DEPRESSION CRITERIA	DEPRESSION PREVALENCE IN LACUNAR PATIENTS[A]	NOS SCORES
Appelros and Viitanen (2004)	253	74.5 (NA)	Multiple sources	NLS	GDS (score >5)	OR = 0.5 (0.3–0.9)	8/8
Bella *et al.* (2010)	89	70.4 (7.4)	Cerebrovascular clinic	WMH	HDRS (score ≥8)	0.37	8/8
Chatterjee *et al.* (2010)	182	70.4 (10.3)	Community	NDS	DSM-IV, MADRS (score >17)	0.33	9/9
Chen *et al.* (2009)	127	64.4 (10.6)	Stroke clinic	NDLS	GDS (score ≥7)	NA	6/8
Grool *et al.* (2011)	585	63 (7.9)	Hospital	AD	PHQ-9 (score ≥6)	0.49	8/8
Grool *et al.* (2012)	578	63 (7.9)	Hospital	AD	PHQ-9 (score NA)[b]	NA	8/8
Kim *et al.* (2013)	254	73.8 (6.9)	Hospital	WMH	CGA-NPI (score not stated)	OR = 1.04 (1.01–1.08)	6/7
Komaki *et al.* (2008)	123	49.0 (15.7)	Neuropsychiatry clinic	DWIA	DSM-IV, HDRS (score not stated)	0.18	5/8
Lavretsky *et al.* (2008)	270	74.6 (8.1)	Dementia clinic	SIVD	MUDS (score not stated)	OR = 2.17 (1.16–4.07)	7/7
Tang *et al.* (2011)	235	66.3 (11.2)	Stroke clinic	LODWM	GDS (score ≥7)	0.36	8/8
Van Uden *et al.* (2011)	498	56.6 (8.8)	Neurology clinic	CSVD	CES-D (score ≥16)	0.41	7/7
White *et al.* (2011)	2477	63.2 (10.7)	Hospital	LOT	PHQ-9 (score not stated)	0.19	8/8

Abbreviations: atherosclerotic disease (AD), caregiver administered Neuropsychiatric Inventory (CGA-NPI), Centre of Epidemiological Studies Depression Scale (CES-D), cerebral small vessel disease (CSVD), Diagnostic and Statistical Manual of Mental Disorders IV (DSM-IV), depressed without imaging abnormality (DWIA), Geriatric Depression Scale (GDS), Hamilton Depression rating Scale (HDRS), lacunes outside of deep white matter (LODWM), lacunes outside of thalamus (LOT), Montgomery Asberg Depression Rating Scale (MADRS), Minimum Uniform Dataset (MUDS), non-depressed stroke (NDLS), non-lacunar stroke (NLS), Patient Health Questionairre-9 (PHQ-9), subcortical ischemic vascular disease (SIVD), and white matter hyperintensities (WMH).
[a]Not all studies provided the prevalence of depression, or the data to calculate the prevalence in lacunar stroke patients. Most of them, however, reported the OR for lacunar stroke patients versus comparison groups. Two studies did not provide the prevalence or an OR of general lacunar stroke for depression.
[b]Grool *et al.* (2012) did not use cut-off for the PHQ-9; instead, "mood" and "motivational" profiles were derived from the questionnaire. The mood profile analysis was used for this meta-analysis.

There were a total of 5,029 patients used in the analyses, with a mean age of 65.1±10.5. A random-effects meta-analysis was performed on the contribution of general lacunar stroke (Appelros and Viitanen, 2004; Lavretsky *et al.*, 2008; Chatterjee *et al.*, 2010; Grool *et al.*, 2011a; van Uden *et al.*, 2011; Kim *et al.*, 2013), thalamic (Lavretsky *et al.*, 2008; Tang *et al.*, 2011; White *et al.*, 2011), deep white matter (Grool *et al.*, 2011b; Tang *et al.*, 2011; White *et al.*, 2011), multiple (Chen *et al.*, 2009; White *et al.*, 2011), and volume (Chen *et al.*, 2009; Tang *et al.*, 2011) of lacunes on depression, as well as the effects on depression severity (Komaki *et al.*, 2008; Bella *et al.*, 2010) (measured using the Hamilton Depression Rating Scale, HDRS (Hamilton, 1960)). The forest plots of the meta-analyses results is presented in Figure 2. The OR with 95% confidence interval (CI; in parentheses) of depression from lacunar stroke was 1.46 (0.88–2.43), $p = 0.15$. The lacunar stroke patients were compared to other patients with non-lacunar stroke (cortical infarct, intracerebral hemorrhage) (Appelros and Viitanen, 2004), atherosclerotic diseases (coronary artery disease, cerebrovascular disease, peripheral arterial disease, abdominal aortic aneurysm) (Grool *et al.*, 2011a), WMH (Kim *et al.*, 2013), subcortical ischemic vascular disease (Lavretsky *et al.*, 2008), cerebral small vessel disease (either with early onset depression or non-depressed) (van Uden *et al.*, 2011), and non-depressed stroke survivors (Chatterjee *et al.*, 2010). The OR (95% CI) of depression from thalamic lacunar stroke was 1.37 (0.85–2.20), $p = 0.19$. Lacunar stroke patients

https://doi.org/10.1017/S1041610214000568 Published online by Cambridge University Press

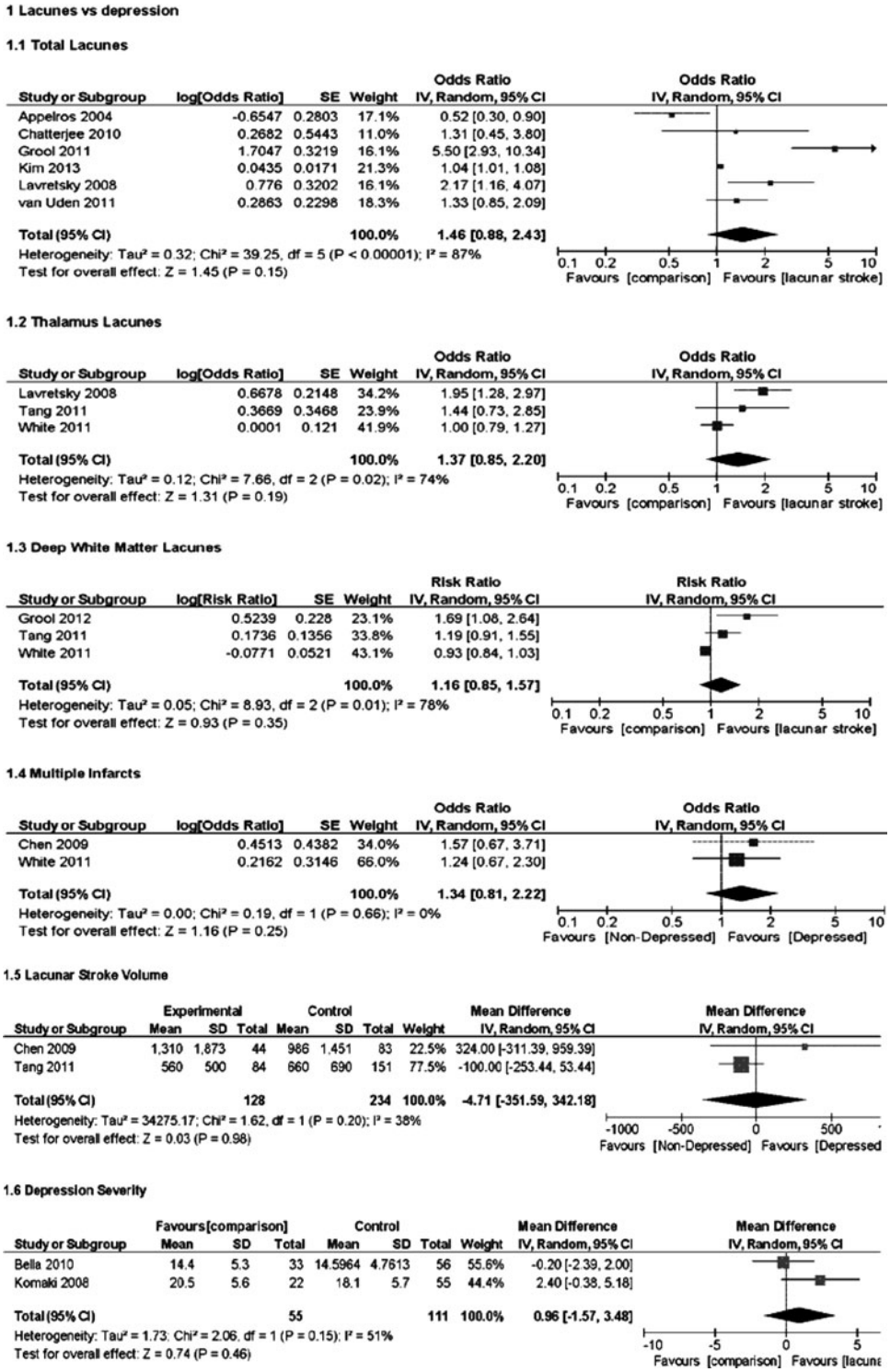


Figure 2. Forest plots of the six analyses. The OR for the general lacunes analysis was 1.46 (0.88–2.43). The OR for thalamic lacunes: 1.37 (0.85–2.20); RR for deep white matter lacunes: 1.16 (0.85–1.57); OR for multiple lacunes: 1.34 (0.81–2.22); MD for lacunar volume: −4.71 (−351.59–342.18); MD for depression severity: 0.96 (−1.57–3.48). All analyses $p > 0.05$.

were compared to patients with subcortical ischemic vascular disease (Lavretsky *et al.*, 2008) and non-depressed patients with thalamic lacunes (Tang *et al.*, 2011; White *et al.*, 2011). Patients with deep white matter (DWM) lacunes had a non significantly higher risk of developing depression (RR = 1.16 (0.85–1.57), $p = 0.35$) compared to patients with atherosclerotic diseases (Grool *et al.*, 2011a) and non-depressed patients with deep white matter lacunes (Tang *et al.*, 2011; White

https://doi.org/10.1017/S1041610214000568 Published online by Cambridge University Press

et al., 2011). The OR (95% CI) for depressed versus non-depressed patients harboring multiple lacunes was 1.34 (0.81–2.22), $p = 0.25$. Lacunar stroke patients with and without depression were compared (Chen *et al.*, 2009; White *et al.*, 2011). There was no statistical difference between the lacunar volume of depressed versus non-depressed lacunar stroke patients (mean difference (MD) = −4.71 (−351.59–342.18), $p = 0.98$). Patients with lacunar stroke had non-significantly more severe depressive symptoms: mean difference = 0.96 (−1.57–3.48), $p = 0.46$. Here, lacunar stroke patients were compared to patients with WMH (Bella *et al.*, 2010) and those with major depressive disorder but without imaging abnormalities (i.e. no WML or lacunar stroke) (Komaki *et al.*, 2008).

The statistical heterogeneity between studies was high among most analyses: $I^2 = 87\%$ for general lacunar stroke, 74% for the thalamic lacunar stroke, 78% for the deep white matter, 0% for multiple lacunes, 38% for the lacunar stroke volume, and 51% for the depression severity analyses. Visual interpretation of funnel plots did not indicate obvious publication bias (supplemental Figure S1). A statistical test (e.g. Begg's test (Begg and Mazumdar, 1994)) was not performed due to the low number of studies and the low statistical power it would in turn yield.

Discussion

While stroke has been associated with depression (Hackett *et al.*, 2005), the contribution of lacunar stroke is unclear. Twelve studies examining the prevalence of depressive symptoms in patients with lacunar stroke and deep white matter disease were submitted to a random-effects meta-analysis, with separate analyses for the effect of general, multiple, volume, and location specific lacunar strokes on depression prevalence, as well as the effects on depressive symptom severity. None of the analyses produced statistically significant results. Lacunar stroke patients had a non-significantly increased odds of depression compared to other patient groups (see Table 1 for the details of comparison groups by study), at $p = 0.15$. Similarly, while thalamic, deep white matter, and multiple lacunar strokes contributed to slightly increased depression, neither of these results were significant. Lastly, there was no effect of lacunar volume on depression, and no difference in the severity of depressive symptoms between patient groups.

A number of issues were present with the data, one of which was the variability in the comparison groups. First, the history of depression in patients is not described in most of the studies, though a subset likely did experience prior depressive symptoms. This has the potential to alter the symptoms and pathology of depression patients. Second, none of the studies used healthy control participants, instead comparing lacunar stroke patients with other patients with a variety of diseases. Comparison groups varied even within specific analyses (e.g. the general lacunar stroke analysis contained patients with six different disease types). As each one of the studies had a different comparison groups, the group differences likely differed between studies, thus confounding the meta-analysis. This is exemplified by the high statistical heterogeneity, which limits the conclusions that can be drawn from the analyses. However, it must be appreciated that the comparison groups in these studies had an increased risk of depression compared to healthy controls. Chronic and acute cardiovascular diseases and stroke, lacunar or not, are risk factors for depression. Our data suggest that the risk of depression in lacunar stroke and deep white matter disease is similar to other causes of stroke such as atherosclerotic large artery disease, even though motor outcomes and survival rates are better in lacunar stroke than these other stroke types (Sacco *et al.*, 1994). By extension, our data also suggest that the risk of depression following lacunar stroke is quite high compared to the healthy population because the prevalence of depression is comparable to that in other cardiovascular diseases.

A second issue with this data is the low number of studies included in the analyses. While the general lacunar stroke analysis had six studies and the deep white matter and thalamic lacunes analyses had three, the rest only contained two studies each. This reduced the power of the statistical analyses, and introduced uncertainty into the results. Additionally, there was insufficient data in the included studies to analyze the impact of other brain regions such as the frontal lobes and subcortical structures including the caudate nucleus, both of which have been implicated in depression (Provinciali and Coccia, 2002; Buijs *et al.*, 2012). However, this was a result of the relatively low number of studies available, which was exacerbated in this meta-analysis by the necessary exclusion criteria. This study serves to indicate the relative infancy of this field.

Lastly, studies used different methods of reporting results: some provided raw data from which OR or RR could be calculated, while others provided either adjusted or unadjusted OR, RR, or other forms of statistical measures. This variability presented compatibility problems for analyses, and led to the inability to include certain studies in the analyses due to a lack of usable data. Additionally,

https://doi.org/10.1017/S1041610214000568 Published online by Cambridge University Press

some studies did not control for co-variables, while others that performed multivariable analyses differed in the co-variables they included, thus affecting the meta-analyses. The details of co-variables used are presented in supplemental Table S1.

More research is necessary to establish whether the general presence, location-specific, or the accumulation of lacunes and other microvascular lesions can lead to the development of depression. Further, lacunar stroke and deep white matter disease patients need to be examined separately to determine their specific contributions to depression. This meta-analysis hinted that lacunar stroke and deep white matter disease is associated with depression, with rates comparable to other cardiovascular diseases. However, the heterogeneity between studies and the patient populations, the low number of studies analyzed, and the low number of region-specific lesion analyses prevented the formation of any decisive conclusions. From a clinical standpoint, this study had a narrow focus on groups of patients originating from specialized clinical centres, which limits the generalizability of the results. Nevertheless, it indicates the importance for screening patients with microvascular, not just macrovascular pathologies for depressive symptoms, and providing appropriate treatment. Future work can also elucidate whether depressive symptom profiles differ between different vascular pathologies, and whether treating cardiovascular risk factors reduce the risk of lacunar stroke and deep white matter disease, and subsequently depression.

Conflict of interest

None.

Description of authors' roles

P.E. completed the systematic literature search and review, data extraction and analyses, and wrote the paper and prepared the figures and tables. E.E.S. contributed to the paper preparation, and provided important feedback and edits of the paper. Z.I., C.E.F., E.E.S. and T.A.S. provided important feedback and edits of the paper.

Acknowledgments

This work was supported by a Personnel Award from the Heart and Stroke Foundation of Canada and an Early Researcher Award from the Ontario Ministry of Research and Innovation to T.A.S., the Heather and Eric Donnelly Endowment from St. Michael's Hospital Foundation to C.E.F., and E.E.S. holds the Kathy Taylor Chair in Vascular Dementia at the University of Calgary and receives salary support from Alberta Innovates - Health Solutions and the Canadian Institutes for Health Research.

References

Aharon-Peretz, J., Kliot, D. and Tomer, R. (2000). Behavioral differences between white matter lacunar dementia and Alzheimer's disease: a comparison on the neuropsychiatric inventory. *Dementia and Geriatric Cognitive Disorders*, 11, 294–298.

American Psychiatric Association. (1994). *Diagnostic and Statistical Manual of Mental Disorders*. Washington, DC, American Psychiatric Press.

Appelros, P. and Viitanen, M. (2004). Prevalence and predictors of depression at one year in a swedish population-based cohort with first-ever stroke. *Journal of Stroke and Cerebrovascular Diseases*, 13, 52–57.

Arnone, D., Mcintosh, A. M., Ebmeier, K. P., Munafo, M. R. and Anderson, I. M. (2012). Magnetic resonance imaging studies in unipolar depression: systematic review and meta-regression analyses. *European Neuropsychopharmacology*, 22, 1–16.

Bailey, E. L., Smith, C., Sudlow, C. L. and Wardlaw, J. M. (2012). Pathology of lacunar ischemic stroke in humans–a systematic review. *Brain Pathology*, 22, 583–591.

Begg, C. B. and Mazumdar, M. (1994). Operating characteristics of a rank correlation test for publication bias. *Biometrics*, 50, 1088–1101.

Bella, R. *et al.* (2010). Clinical presentation and outcome of geriatric depression in subcortical ischemic vascular disease. *Gerontology*, 56, 298–302.

Bhogal, S. K., Teasell, R., Foley, N. and Speechley, M. (2004). Lesion location and poststroke depression: systematic review of the methodological limitations in the literature. *Stroke*, 35, 794–802.

Brodaty, H., Withall, A., Altendorf, A. and Sachdev, P. S. (2007). Rates of depression at 3 and 15 months poststroke and their relationship with cognitive decline: the sydney stroke study. *The American Journal of Geriatric Psychiatry*, 15, 477–486.

Brookes, R. L., Willis, T. A., Patel, B., Morris, R. G. and Markus, H. S. (2013). Depressive symptoms as a predictor of quality of life in cerebral small vessel disease, acting independently of disability; a study in both sporadic small vessel disease and cadasil. *International Journal of Stroke*, 8, 510–517.

Buijs, J. E., Greebe, P. and Rinkel, G. J. (2012). Quality of life, anxiety, and depression in patients with an unruptured intracranial aneurysm with or without aneurysm occlusion. *Neurosurgery*, 70, 868–872.

Carson, A. J. *et al.* (2000). Depression after stroke and lesion location: a systematic review. *Lancet*, 356, 122–126.

Chatterjee, K., Fall, S. and Barer, D. (2010). Mood after stroke: a case control study of biochemical, neuro-imaging

https://doi.org/10.1017/S1041610214000568 Published online by Cambridge University Press

and socio-economic risk factors for major depression in stroke survivors. *BMC Neurology*, 10, 125.

Chen, Y., Chen, X., Mok, V. C., Lam, W. W., Wong, K. S. and Tang, W. K. (2009). Poststroke depression in patients with small subcortical infarcts. *Clinical Neurology and Neurosurgery*, 111, 256–260.

Edwards, J. D., Jacova, C., Sepehry, A. A., Pratt, B. and Benavente, O. R. (2013). A quantitative systematic review of domain-specific cognitive impairment in lacunar stroke. *Neurology*, 80, 315–322.

Everson, S. A., Roberts, R. E., Goldberg, D. E. and Kaplan, G. A. (1998). Depressive symptoms and increased risk of stroke mortality over a 29-year period. *Archives of Internal Medicine*, 158, 1133–1138.

Farrall, A. J. and Wardlaw, J. M. (2009). Blood-brain barrier: ageing and microvascular disease–systematic review and meta-analysis. *Neurobiology of Aging*, 30, 337–352.

Fazekas, F. *et al.* (1993). Pathologic correlates of incidental MRI white matter signal hyperintensities. *Neurology*, 43, 1683–1689.

Fernando, M. S. *et al.* (2006). White matter lesions in an unselected cohort of the elderly: molecular pathology suggests origin from chronic hypoperfusion injury. *Stroke*, 37, 1391–1398.

Firbank, M. J. *et al.* (2012). Relationship between progression of brain white matter changes and late-life depression: 3-Year results from the ladis study. *The British Journal of Psychiatry*, 201, 40–45.

Fu, J. H. *et al.* (2010). Neuroimaging predictors for depressive symptoms in cerebral small vessel disease. *International Journal of Geriatric Psychiatry*, 25, 1039–1043.

Gouw, A. A. *et al.* (2011). Heterogeneity of small vessel disease: a systematic review of MRI and histopathology correlations. *Journal of Neurology, Neurosurgery, and Psychiatry*, 82, 126–135.

Grool, A. M., Van Der Graaf, Y., Mali, W. P., Geerlings, M. I. and Group, S. S. (2011a). Location of cerebrovascular and degenerative changes, depressive symptoms and cognitive functioning in later life: the smart-medea study. *Journal of Neurology, Neurosurgery, and Psychiatry*, 82, 1093–1100.

Grool, A. M., Van Der Graaf, Y., Mali, W. P., Witkamp, T. D., Vincken, K. L. and Geerlings, M. I. (2011b). Location and progression of cerebral small-vessel disease and atrophy, and depressive symptom profiles: the second manifestations of arterial disease (Smart)-medea study. *Psychological Medicine*, 42, 1–12.

Grool, A. M. *et al.* (2012). Mood problems increase the risk of mortality in patients with lacunar infarcts: the Smart-Mr study. *Psychosomatic Medicine*, 74, 234–240.

Grool, A. M., Gerritsen, L., Zuithoff, N. P., Mali, W. P., Van Der Graaf, Y. and Geerlings, M. I. (2013). Lacunar infarcts in deep white matter are associated with higher and more fluctuating depressive symptoms during three years follow-up. *Biological Psychiatry*, 73, 169–176.

Hackett, M. L., Yapa, C., Parag, V. and Anderson, C. S. (2005). Frequency of depression after stroke: a systematic review of observational studies. *Stroke*, 36, 1330–1340.

Hamilton, M. (1960). A rating scale for depression. *Journal of Neurology, Neurosurgery, and Psychiatry*, 23, 56–62.

Herrmann, L. L., Le Masurier, M. and Ebmeier, K. P. (2008). White matter hyperintensities in late life depression: a systematic review. *Journal of Neurology, Neurosurgery, and Psychiatry*, 79, 619–624.

Higgins, J. P., Thompson, S. G., Deeks, J. J. and Altman, D. G. (2003). Measuring inconsistency in meta-analyses. *BMJ*, 327, 557–560.

Huijts, M., Duits, A., Staals, J. and Van Oostenbrugge, R. J. (2012). Association of Vitamin B12 deficiency with fatigue and depression after lacunar stroke. *PloS One*, 7, e30519.

Huijts, M., Van Oostenbrugge, R. J., Rouhl, R. P., Menheere, P. and Duits, A. (2013). Effects of Vitamin B12 supplementation on cognition, depression, and fatigue in patients with lacunar stroke. *International Psychogeriatrics*, 25, 508–510.

Hutter, B. O. and Kreitschmann-Andermahr, I. (2013). Subarachnoid hemorrhage as a psychological trauma. *Journal of Neurosurgery*. doi:10.3171/2013.11.JNS121552.

Jokinen, H. *et al.* (2006). Cognitive Profile of subcortical ischaemic vascular disease. *Journal of Neurology, Neurosurgery, and Psychiatry*, 77, 28–33.

Jokinen, H. *et al.* (2009). MRI-Defined subcortical ischemic vascular disease: baseline clinical and neuropsychological findings. the ladis study. *Cerebrovascular Diseases*, 27, 336–344.

Kim, H. J. *et al.* (2013). The effects of small vessel disease and amyloid burden on neuropsychiatric symptoms: a study among patients with subcortical vascular cognitive impairments. *Neurobiology of Aging*, 34, 1913–1920.

Komaki, S., Nagayama, H., Ohgami, H., Takaki, H., Mori, H. and Akiyoshi, J. (2008). Prospective study of major depressive disorder with white matter hyperintensity: comparison of patients with and without lacunar infarction. *European Archives of Psychiatry and Clinical Neuroscience*, 258, 160–164.

Lavretsky, H. *et al.* (2008). The MRI brain correlates of depressed mood, anhedonia, apathy, and anergia in older adults with and without cognitive impairment or dementia. *International Journal of Geriatric Psychiatry*, 23, 1040–1050.

Lavretsky, H. *et al.* (2010). Association of depressed mood and mortality in older adults with and without cognitive impairment in a prospective naturalistic study. *American Journal of Psychiatry*, 167, 589–597.

Makin, S. D., Turpin, S., Dennis, M. S. and Wardlaw, J. M. (2013). Cognitive impairment after lacunar stroke: systematic review and meta-analysis of incidence, prevalence and comparison with other stroke subtypes. *Journal of Neurology, Neurosurgery, and Psychiatry*, 84, 893–900.

Man, B. L. *et al.* (2011). Cognitive and functional impairments in ischemic stroke patients with concurrent small vessel and large artery disease. *Clinical Neurology and Neurosurgery*, 113, 612–616.

Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G. and Group, P. (2009). Preferred reporting items for systematic reviews and meta-analyses: the prisma statement. *PLoS Medicine*, 6, e1000097.

O'Brien, J. T. *et al.* (2006). White matter hyperintensities rather than lacunar infarcts are associated with depressive symptoms in older people: the ladis study. *The American Journal of Geriatric Psychiatry*, 14, 834–841.

https://doi.org/10.1017/S1041610214000568 Published online by Cambridge University Press

Ogata, J. (1999). The arterial lesions underlying cerebral infarction. *Neuropathology*, 19, 112–118.

Ogawa, Y. *et al.* (2013). Association of cerebral small vessel disease with delusions in patients with Alzheimer's disease. *International Journal of Geriatric Psychiatry*, 28, 18–25.

Paolucci, S., Gandolfo, C., Provinciali, L., Torta, R., Toso, V. and Group, D. S. (2006). The italian multicenter observational study on post-stroke depression (Destro). *Journal of Neurology*, 253, 556–562.

Provinciali, L. and Coccia, M. (2002). Post-stroke and vascular depression: a critical review. *Neurological Sciences*, 22, 417–428.

Ramasubbu, R., Robinson, R. G., Flint, A. J., Kosier, T. and Price, T. R. (1998). Functional impairment associated with acute poststroke depression: the stroke data bank study. *The Journal of Neuropsychiatry and Clinical Neurosciences*, 10, 26–33.

Ramos-Estebanez, C. *et al.* (2008). Vascular cognitive impairment: prodromal stages of ischemic vascular dementia. *Dementia and Geriatric Cognitive Disorders*, 25, 451–460.

Sacco, R. L., Shi, T., Zamanillo, M. C. and Kargman, D. E. (1994). Predictors of mortality and recurrence after hospitalized cerebral infarction in an Urban community: the Northern Manhattan Stroke Study. *Neurology*, 44, 626–634.

Sacco, S., Marini, C., Totaro, R., Russo, T., Cerone, D. and Carolei, A. (2006). A population-based study of the incidence and prognosis of lacunar stroke. *Neurology*, 66, 1335–1338.

Santos, M. *et al.* (2009a). Differential impact of lacunes and microvascular lesions on poststroke depression. *Stroke*, 40, 3557–3562.

Santos, M. *et al.* (2009b). The neuroanatomical model of post-stroke depression: towards a change of focus? *Journal of the Neurological Sciences*, 283, 158–162.

Santos, M. *et al.* (2010). Neuropathological analysis of lacunes and microvascular lesions in late-onset depression. *Neuropathology and Applied Neurobiology*, 36, 661–672.

Soriano-Raya, J. J., *et al.* (2012). Deep versus periventricular white matter lesions and cognitive function in a community sample of middle-aged participants. *Journal of the International Neuropsychological Society*, 18, 874–885.

Staekenborg, S. S. *et al.* (2010). Behavioural and psychological symptoms in vascular dementia; differences between small- and large-vessel disease. *Journal of Neurology, Neurosurgery, and Psychiatry*, 81, 547–551.

Stang, A. (2010). Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *European Journal of Epidemiology*, 25, 603–605.

Sudlow, C. L. and Warlow, C. P. (1997). Comparable studies of the incidence of stroke and its pathological types: results from an international collaboration. International stroke incidence collaboration. *Stroke*, 28, 491–499.

Tang, W. K. *et al.* (2011). Cerebral microbleeds and depression in lacunar stroke. *Stroke*, 42, 2443–2446.

Teodorczuk, A. *et al.* (2010). Relationship between baseline white-matter changes and development of late-life depressive symptoms: 3-Year results from the ladis study. *Psychological Medicine*, 40, 603–610.

Thomas, A. J., Perry, R., Kalaria, R. N., Oakley, A., Mcmeekin, W. and O'Brien, J. T. (2003). Neuropathological evidence for ischemia in the white matter of the dorsolateral prefrontal cortex in late-life depression. *International Journal of Geriatric Psychiatry*, 18, 7–13.

Troisi, E. *et al.* (2012). Altered cerebral vasoregulation predicts the outcome of patients with partial anterior circulation stroke. *European Neurology*, 67, 200–2005.

Van Der Flier, W. M. *et al.* (2005). Small vessel disease and general cognitive function in nondisabled elderly: the ladis study. *Stroke*, 36, 2116–2120.

Van Norden, A. G., Van Den Berg, H. A., De Laat, K. F., Gons, R. A., Van Dijk, E. J. and De Leeuw, F. E. (2011). Frontal and temporal microbleeds are related to cognitive function: the Radboud University Nijmegen Diffusion Tensor and Magnetic Resonance Cohort (Run Dmc) study. *Stroke*, 42, 3382–3386.

Van Norden, A. G. *et al.* (2013). Cerebral microbleeds are related to subjective cognitive failures: the Run Dmc Study. *Neurobiology of Aging*, 34, 2225–2230.

Van Uden, I. W. *et al.* (2011). Depressive symptoms and amygdala volume in elderly with cerebral small vessel disease: the Run Dmc study. *Journal of Aging Research*, 2011, 647869.

Wells, G. A. *et al.* (2011). *The Newcastle-Ottawa Scale (Nos) for Assessing the Quality of Nonrandomised Studies in Meta-Analyses*. [Online]. Ottawa: Ottawa Hospital Research Institute. [Accessed October 10, 2013].

White, C. L. *et al.* (2011). The correlates and course of depression in patients with lacunar stroke: results from the secondary prevention of small subcortical strokes (Sps3) study. *Cerebrovascular Diseases*, 32, 354–360.

Whyte, E. M., Mulsant, B. H., Vanderbilt, J., Dodge, H. H. and Ganguli, M. (2004). Depression after stroke: a prospective epidemiological study. *Journal of the American Geriatrics Society*, 52, 774–778.

Wolfson, L. *et al.* (2013). Rapid buildup of brain white matter hyperintensities over 4 Years linked to ambulatory blood pressure, mobility, cognition, and depression in old persons. *The Journals of Gerontology. Series A*, 68, 1387–1394.

Xiong, Y. Y. *et al.* (2011). Frequency and predictors of proxy-confirmed post-stroke cognitive complaints in lacunar stroke patients without major depression. *International Journal of Geriatric Psychiatry*, 26, 1144–1151.

Young, V. G., Halliday, G. M. and Kril, J. J. (2008). Neuropathologic correlates of white matter hyperintensities. *Neurology*, 71, 804–811.

https://doi.org/10.1017/S1041610214000568 Published online by Cambridge University Press