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Review

Inflammation and cerebral small vessel disease: A systematic review

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ABSTRACT

Inflammation is increasingly implicated as a risk factor for dementia, stroke, and small vessel disease (SVD). However, the underlying mechanisms and causative pathways remain unclear. We systematically reviewed the existing literature on the associations between markers of inflammation and SVD (*i.e.*, white matter hyperintensities (WMH), lacunes, enlarged perivascular spaces (EPVS), cerebral microbleeds (CMB)) in cohorts of older people with good health, cerebrovascular disease, or cognitive impairment. Based on distinctions made in the literature, markers of inflammation were classified as systemic inflammation (*e.g.* C-reactive protein, interleukin-6, fibrinogen) or vascular inflammation/endothelial dysfunction (*e.g.* homocysteine, von Willebrand factor, Lp-PLA2). Evidence from 82 articles revealed relatively robust associations between SVD and markers of *vascular inflammation*, especially amongst stroke patients, suggesting that alterations to the endothelium and blood-brain barrier may be a driving force behind SVD. Conversely, cross-sectional findings on *systemic inflammation* were mixed, although longitudinal investigations demonstrated that elevated levels of systemic inflammatory markers at baseline predicted subsequent SVD severity and progression. Importantly, regional analysis revealed that systemic and vascular inflammation were differentially related to two distinct forms of SVD. Specifically, markers of vascular inflammation tended to be associated with SVD in areas typical of hypertensive arteriopathy (*e.g.*, basal ganglia), while systemic inflammation appeared to be involved in CAA-related vascular damage (*e.g.*, centrum semiovale). Nonetheless, there is insufficient data to establish whether inflammation is causal of, or secondary to, SVD. Findings have important implications on interventions, suggesting the potential utility of treatments targeting the brain endothelium and blood brain barrier to combat SVD and associated neurodegenerative diseases.

1. Introduction

Global life expectancy has increased dramatically in the last decade, bringing with it a new set of problems, such as the increasing prevalence of age-related dementia and neurodegenerative disorders (Brayne, 2007). In particular, evidence is mounting for the role of cerebral small vessel disease (SVD) and inflammation in promoting neurodegeneration and worsening its consequences (Eikelenboom et al., 2012; Vemuri et al., 2015; Wardlaw et al., 2013), although the causal associations between SVD and neurodegenerative processes are unclear.

SVD is a common condition in older adults and has long been implicated with cognitive impairment, dementia, and stroke, causing up to 45% of dementia cases worldwide, and accounting for approximately one-quarter of all strokes (Pantoni, 2010). At present, the etiological basis of SVD remains controversial, although inflammation has been proposed as a candidate factor. Under many circumstances, inflammation represents a natural biological response to infections and injuries. However, an inflammatory response can have deleterious effects, causing harm to healthy tissue. One of the most widely studied markers of inflammation is C-reactive protein (CRP), a sensitive but non-specific marker of systemic inflammation (Pepys and Hirschfield, 2003). Elevated levels of CRP are a common observation in the brain and serum of patients with neurodegenerative conditions (Frank et al., 2003), and are generally associated with poorer cognitive outcomes in normal ageing (Noble et al., 2010) and neurodegenerative conditions (Schmidt et al., 2002). Another widely investigated inflammatory marker is homocysteine, which is thought to induce damage to the endothelium, and is considered a risk factor of atherosclerosis (Pang et al., 2014). These alterations to the endothelium, as measured by elevated levels of homocysteine and other vascular inflammatory markers, can result in blood-brain barrier (BBB) dysfunctions (Beard et al., 2011).

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Due to the difficulties involved in visualising small cerebral vessels *in vivo*, SVD is often detected through parenchymal alterations visible on magnetic resonance imaging (MRI), rather than perturbations to the small vessels themselves. In particular, four core MRI features have been identified as markers of SVD (Huijts et al., 2013; Staals et al., 2015, 2014; Wardlaw et al., 2013), namely white matter hyperintensities (WMH), lacunes, cerebral microbleeds (CMB), and enlarged perivascular spaces (EPVS).

1.1. White matter hyperintensities

WMH, also known as leukoaraiosis, represent microvascular brain lesions caused by localised changes in tissue composition. On MRI, WMH appear as patchy areas of increased intensity on T2-weighted and fluid-attenuated inversion recovery (FLAIR) sequences, and hypointense areas on T1-weighted imaging. The clinical relevance of WMH has been well-established – increased WMH burden has been found to be related to poorer cognitive outcomes (Gunning-Dixon and Raz, 2000), and heightened risk of mild cognitive impairment (MCI) and dementia (Debette and Markus, 2010). WMH are also common MRI findings amongst healthy older adults – up to 22% of healthy older adults may have moderate WMH, while 9% may have severe WMH (Hunt et al., 1989). The health of white matter is related to cardiovascular health across the lifespan (Fuhrmann et al., 2018), with WMH associated with lower diastolic blood pressure, higher systolic blood pressure, body mass, and heart rate. Even in healthy older adults, such WMH have been found to have detrimental subclinical effects on cognition (Lampe et al., 2019).

1.2. Lacunes

Lacunes are small subcortical fluid-filled cavities thought to result from the occlusion of individual arteries penetrating the deep structures of the brain (*e.g.* basal ganglia, internal/external capsule) (Bamford and Warlow, 1988). On MRI, lacunes appear as small lesions of similar intensity to cerebrospinal fluid (CSF), *i.e.*, hyperintense on T2-weighted images, and hypointense on FLAIR and T1-weighted images. Lacunes have been associated with greater risk of stroke, cognitive decline, and dementia (Vermeer et al., 2007, 2003). Although often assumed to be caused by acute subcortical infarcts, lacunes may also result from deep cerebral haemorrhages (Franke et al., 1991).

1.3. Enlarged perivascular spaces

Virchow-Robin spaces, also known as perivascular spaces (PVS), are microscopic fluid-filled structures surrounding the small penetrating vessels of the brain. Although normally undetectable on conventional MRI, they are visible on T1- and T2-weighted images when enlarged (EPVS), appearing as small, sharply delineated structures of similar intensity to CSF. Although the mechanisms behind PVS dilation remain unclear, EPVS have been found to be associated with older age, hypertension, and stroke (Doubal et al., 2010; Zhu et al., 2010). On the other hand, however, associations between EPVS and cognition have not been consistent (Benjamin et al., 2018; Hilal et al., 2018b). PVS are particularly relevant in this investigation, given their role in leucocyte trafficking and the modulation of immune responses, both of which are implicated in the inflammatory process.

1.4. Cerebral microbleeds

CMB, sometimes referred to as microhaemorrhages, are focal hemosiderin deposits resulting from tiny blood leakages from damaged arteriolar walls (Fazekas et al., 1999). They appear as small, round or ovoid foci of homogeneous signal intensity on T2*-weighted images and susceptibility-weighted imaging (SWI). CMB are linked to poorer clinical outcomes, such as cognitive dysfunction, dementia, and are predictive of mortality in older populations (Altmann-Schneider et al., 2011; Poels et al., 2012; Seo et al., 2007).

Given the uncertainties surrounding the etiological mechanisms behind SVD, this systematic review aims to elucidate the associations between inflammation and SVD, as well as the factors influencing the relationship between the two pathologies. By unravelling the underlying mechanisms leading to neurodegeneration, findings could improve the prediction of disease onset, and lead to the identification of novel treatment approaches to combat SVD.

2. Methods

2.1. Search strategy and selection criteria

We conducted a systematic review to identify studies investigating the relationship between markers of SVD and inflammation in dementia and stroke patients, as well as healthy older adults. The literature search was conducted on PubMed to identify relevant articles from the beginning of the database to 5 November 2018 using the following search terms: (“small vessel disease” OR “white matter hyperintensities” OR “white matter disease” OR "white matter lesions" OR “leukoaraiosis “OR "lacunes" OR “lacunar infarcts” OR “small subcortical infarcts” OR “perivascular spaces” OR "Virchow-Robin spaces" OR “microbleeds” OR “microinfarcts”) AND ("neuroinflammation" OR "inflammation" OR "endothelial dysfunction" OR "interleukin-6" OR "IL-6" OR "C-reactive protein" OR "CRP" OR "tumour necrosis factor" OR "TNF-α" OR "TNFR2" OR "fibrinogen" OR "Matrix metalloproteinase 9" OR "MMP-9" OR "intercellular adhesion molecule 1" OR "ICAM-1" OR "CD40" OR "E-selectin" OR "P-selectin" OR "lipoprotein-associated phospholipase A2" OR "Lp-PLA2" OR "homocysteine" OR "vascular endothelial growth factor" OR "VEGF" OR "von Willebrand factor" OR "vWF" OR "vascular cadherin adhesion molecule-1" OR "VCAM-1" OR "TSPO" OR "microglia") AND ("healthy" OR "community" OR "dementia" OR "Alzheimer's" OR "cognitive impairment" OR "stroke"). The search was limited to include only human studies published in the English language. We further searched the reference lists of relevant articles.

2.2. Inclusion and exclusion criteria

The titles and abstracts of studies identified by this search strategy were screened for relevance and eligibility for this review. Full-texts of relevant articles were read and selected according to the eligibility criteria. Only full-length research papers were considered for inclusion, and were required to include analysis studying the association between at least one MRI marker of SVD, and at least one marker of inflammation. Case studies, review papers, and studies involving multiple sclerosis, kidney failure, and patient cohorts experiencing broad or unspecified neurological discomforts were excluded. Studies were only included if their sample cohorts were made up of healthy controls, cognitively impaired participants, dementia patients, SVD, and/or stroke patients. Only samples comprising of older adults were considered, although exceptions were made for cohort studies following mid-life adults into old age. Studies where sample cohorts comprised primarily of hospitalised general neurology patients, or patients with broad neurological discomforts (*e.g.* vertigo, migraine, diplopia) were excluded. In the case of study duplication (*i.e.*, two articles reporting the same findings from the same sample cohort) the more comprehensive of the two studies was retained, while the other was excluded. Articles reporting findings from the same study sample were included if they provided additional study findings that were not previously reported.

2.3. Data extraction

Several key data indices were obtained from all studies: first author,

year of publication, sample size, sample characteristics (age, gender), measure of inflammation, measure of SVD, imaging characteristics (type of imaging, field strength, sequence(s) used to quantify SVD markers), study design, and results. Inflammatory markers were labelled as being measures of systemic inflammation (CRP, interleukin-6, fibrinogen, tumour necrosis factor receptor-2 (TNFR2), TNF-α, osteoprotegerin, myeloperoxidase) or vascular inflammation/endothelial dysfunction (homocysteine, ICAM-1, VCAM-1, Lp-PLA2, vascular endothelial growth factor, E-selectin, P-selectin, matrix metallopeptidase 9, neopterin, CD40). Classifications were based on distinctions made in existing literature (Ahluwalia et al., 2018; Fonseca and Izar, 2018; Goncharov et al., 2017; Hall et al., 2013; Kressel et al., 2009; Shoamanesh et al., 2015; Szmitko et al., 2003; Walker et al., 2018).

3. Results

Our database search strategy identified 454 studies, of which 298 were excluded based on their title/abstract. The full-text of the remaining 156 articles were assessed for eligibility, removing 81 articles. The remaining 75 articles were cross-checked for repetition of findings, removing 2 articles. Searching the reference lists of relevant articles identified 9 additional studies meeting our inclusion criteria, resulting in a final sample of 82 articles published between 1994 and 2018 which were included in this systematic review. The eligibility screening process and reasons for exclusion are detailed in the flowchart provided (Fig. 1).

Across the literature, the majority of studies investigated inflammation in relation to WMH (n = 66), of which 30 also included some other measures of SVD (lacunes/EPVS/CMB). The next SVD marker most frequently studied was lacunes (n = 37), followed by CMB (n = 15). Only 4 studies on EPVS were found. Principal findings of all studies are summarised in Table 1, organised according to SVD markers.

3.1. White matter hyperintensities

The overall literature on inflammation and WMH was inconclusive, although findings differed based on diagnostic group. Specifically, greater WMH burden was consistently associated with vascular inflammation/endothelial dysfunction in stroke cohorts (Fig. 2), while findings remained mixed in non-stroke cohorts, and with regard to systemic inflammation in general.

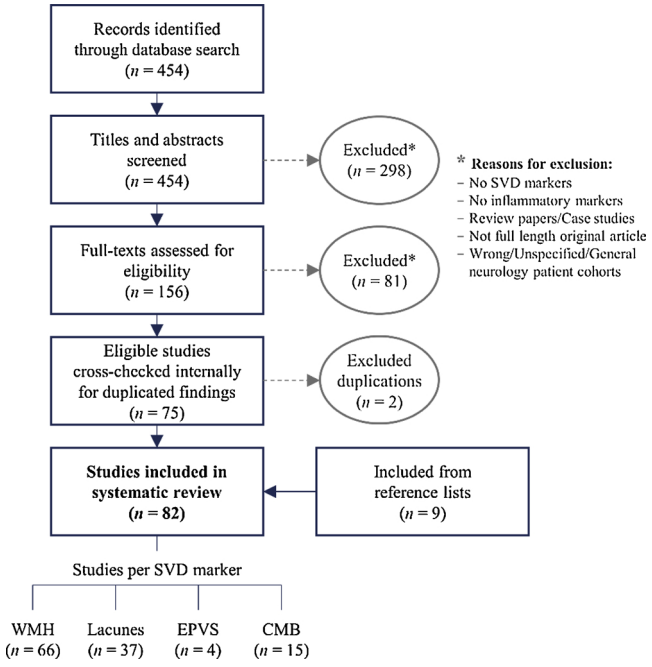

Fig. 1. Flowchart of study selection procedures.

In terms of vascular inflammation/endothelial dysfunction, homocysteine has been the inflammatory marker most widely investigated in conjunction with WMH, and produced vastly contradictory results across literature. Notably, all 5 articles on VCAM-1 reported significant associations with WMH (Arba et al., 2018; de Leeuw et al., 2002; Huang et al., 2015; Rouhl et al., 2012; Tchalla et al., 2015). Although the literature appeared largely inconclusive *overall*, stratification by diagnosis group revealed that WMH and homocysteine were consistently associated amongst stroke cohorts (Fig. 2). With regard to systemic inflammation, associations between WMH and CRP are often cited as evidence of the role of inflammation in SVD. However, this systematic review showed mixed findings of cross-sectional association at best. Inconsistent findings were likewise found with regard to other markers of systemic inflammation, such as fibrinogen, and interleukin-6. To date, only one study has examined SVD in relation to *neuroinflammation* in the human brain, in a post-mortem investigation (Tomimoto et al., 1996). Consistent with animal studies (Farkas et al., 2004; Jalal et al., 2012), this study demonstrated increased microglial and astroglial activation in sites with WMH, providing robust evidence of a relationship between WMH and neuroinflammation in patients with ischaemic cerebrovascular disease and Alzheimer's disease.

Regional differences were also observed, whereby inflammation appeared to be preferentially related to periventricular WMH, but not deep WMH. In terms of lobar regions, higher homocysteine levels also corresponded with greater WMH in the frontal lobe (Gao et al., 2015). This finding is compatible with earlier studies demonstrating that higher CRP/homocysteine levels were significantly associated with reduced fractional anisotropy in the frontal regions (Wersching et al., 2010), and greater frontal-executive cognitive dysfunction (Sachdev, 2004; Wersching et al., 2010).

3.2. Lacunes

Evidence from 37 articles suggested that lacunar burden in healthy older adults and SVD patients was linked to higher levels of vascular inflammation/endothelial dysfunction, but not systemic inflammation. The role of vascular inflammation in lacunar infarctions was evidenced by the majority of studies on homocysteine reporting significant associations with the presence and/or number of lacunes (Fig. 3). Similarly, longitudinal investigations have also reported that higher baseline levels of homocysteine were predictive of greater prevalence and progression of lacunes. On the other hand, findings suggest the absence of a relationship between lacunes and markers of systemic inflammation, as most investigations on CRP did not identify significant associations, including 6 longitudinal investigations (Nylander et al., 2015; Satizabal et al., 2012; Schmidt et al., 2006; Staszewski et al., 2018; Van Dijk et al., 2005; Walker et al., 2017).

3.3. Enlarged perivascular spaces

EPVS appeared to be associated with vascular inflammation/endothelial dysfunction in stroke cohorts, and systemic inflammation in healthy cohorts. Specifically, vascular inflammatory processes appeared to be more closely tied to EPVS in the basal ganglia, while systemic inflammation was more closely associated with EPVS in the centrum semiovale. Studies on stroke/hypertension-based cohorts reported significant relationships between basal ganglia EPVS and the vascular inflammatory markers of neopterin (Rouhl et al., 2012) and von Willebrand factor (Wang et al., 2016b), but not systemic inflammation. On the other hand, studies on community-based cohorts produced contrasting evidence, reporting instead associations between EPVS in the centrum semiovale and CRP (Aribisala et al., 2014). Notably, the relationship between CRP and EPVS were present in community-based cohorts, but not stroke cohorts.

Table 1
Summary of studies.

Authors (Year)	Sample size and patient cohort	Sample characteristics	Measure of inflammation	Measure of SVD	SVD imaging; field strength (FS) and sequence (S)	Study design	Results
White Matter Hyperintensities							
Breteler et al. (1994)	111 community-based subjects Rotterdam Study	Age range: 65–84 Females: 59.5%	**Systemic:** Fibrinogen	WMH (Semi-quantitative)	MRI FS: 1.5T S: T2	Cross-sectional	**Systemic:** 1 Presence of WMH a/w higher fibrinogen levels
Longstreth et al. (1996)	3,301 community-based subjects Cardiovascular Health Study	Age: 65 and older Females: nr	**Systemic:** Fibrinogen	WMH (Semi-quantitative)	MRI FS: 1.5T S: PD, T2	Cross-sectional	**Systemic:** 1 WMH severity not a/w fibrinogen levels
Tomimoto et al. (1996)[#]	Post-mortem brains from 14 ischaemic CVD, 12 AD, 6 healthy controls	**Healthy controls** Age: 76.5 ± 2.8 Females: 16.7% **CVD patients** Age: 79.4 ± 2.5 Females: 50.0% **AD patients** Age: 81.5 ± 2.2 Females: 75.0%	**Systemic:** Fibrinogen **Microglial activation:** HLA-DR **Astroglia:** GFAP	WMH (Semi-quantitative)	CT/MRI FS: nr S: nr	Post-mortem study	**Systemic:** 1 Presence of WMH a/w greater fibrinogen levels **Microglia activation:** 2 In CVD and AD, groups with WMH presented with more microglial activation **Astroglia:** 3 In CVD and AD, groups with WMH presented with greater GFAP
de Leeuw et al. (2002)	29 stroke patients Rotterdam Scan Study	Age: 62.2 ± 12.3 Females: 13.8%	**Vascular:** ICAM-1, VCAM-1, E-selectin, P-selectin	WMH (Semi-quantitative)	MRI FS: 1.5T S: PD, T2	Cross-sectional	**Vascular:** 1 Severe PVH, but not DWMH a/w higher P-selectin and VCAM-1 levels 2 WMH not a/w ICAM-1 or E-selectin levels
Hogervorst et al. (2002)	137 AD patients, 277 healthy controls Oxford Project to Investigate Memory and Ageing (OPTIMA) Study	**Healthy controls** Age: 73.3 ± 7.7 Females: 50% **AD patients** Age: 73.9 ± 9.0 Females: 60%	**Vascular:** Homocysteine	WMH (Semi-quantitative)	CT	Cross-sectional	**Vascular:** 1 Moderate to severe WMH a/w higher homocysteine levels 2 Homocysteine levels more strongly associated with DWMH than PVH
Martí-Fàbregas et al. (2002)	28 patients (12 first-ever lacunar infarction, 16 Binswanger disease)	Age: 71.0 ± 8.6 Females: 25.0%	**Systemic:** Fibrinogen	WMH (Semi-quantitative)	MRI FS: 1.5T S: PD, T2	Cross-sectional	**Systemic:** 1 Greater WMH a/w higher fibrinogen levels
Vermeer et al. (2002)[b]	1,077 healthy subjects Rotterdam Scan Study	Age: 72.2 ± 7.4 Females: 51.5%	**Vascular:** Homocysteine	WMH (PVH – Semi-quantitative; DWMH – Quantitative)	MRI FS: 1.5T S: PD, T2	Cross-sectional	**Vascular:** 1 Presence of severe WMH a/w higher homocysteine levels 2 Severity of PVH and DWMH a/w higher homocysteine levels
Hassan et al. (2003)[b]	110 lacunar stroke patients, 50 community controls	**Healthy controls** Age: 66.5 ± 9.7 Females: 46.0% **Lacunar stroke patients** Age: 67.2 ± 10.2 Females: 35.5%	**Vascular:** ICAM-1, TM	WMH (Semi-quantitative)	CT/MRI FS: nr S: T2/CT	Cross-sectional	**Vascular:** 1 Presence of WMH a/w elevated TM and ICAM-1 levels 2 Severity of WMH a/w TM but not ICAM-1 levels
Dufouil et al. (2003)	1,241 community-based participants Epidemiology of Vascular Ageing (EVA) study	Age: 67.0 ± 3.0 Females: 58.6%	**Vascular:** Homocysteine	WMH (Semi-quantitative)	MRI FS: 1T S: PD, T2	Cohort study	**Vascular:** 1 Cross-sectionally, WMH severity not a/w homocysteine levels

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Table 1 (*continued*)

Authors (Year)	Sample size and patient cohort	Sample characteristics	Measure of inflammation	Measure of SVD	SVD imaging; field strength (FS) and sequence (S)	Study design	Results
Hassan et al. (2004)[b]	172 SVD patients and 172 community controls	**Healthy controls** Age: 66.3 ± 10.2 Females: 41.9% **SVD patients** Age: 67.1 ± 10.3 Females: 40.7%	**Vascular:** Homocysteine	WMH (Semi-quantitative)	MRI FS: nr S: T2	Cross-sectional	**Vascular:** 1 Higher homocysteine observed in patients with WMH, compared to both patients with isolated lacunar infarct and controls
Longstreth et al. (2004)[b]	622 non-stroke, non-TIA participants Cardiovascular Health Study	Age: 65 and above (61.3% above 75) Females: 46.6%	**Vascular:** Homocysteine	WMH (Semi-quantitative)	MRI FS: nr S: T1, T2	Cross-sectional	**Vascular:** 1 WMH not a/w homocysteine levels
Sachdev (2004)	**Sydney Stroke Study** 131 ischaemic stroke patients, 81 healthy subjects **PATH Study** 385 community-dwelling subjects	**Sydney Stroke Study** Age range: 55-87 Females: nr **PATH Study** Age range: 60-64 Male Age: 62.6 ± 1.4 Female Age: 62.6 ± 1.5 Females: 49.1%	**Vascular:** Homocysteine	**Sydney Stroke Study** WMH (Semi-quantitative) **PATH study** WMH (Quantitative)	MRI FS: 1.5T S: FLAIR	Cross-sectional	**Sydney Stroke Study** **Vascular:** 1 DWMH not a/w homocysteine after correcting for age **PATH Study** **Vascular:** 2 Greater DWMH volume a/w higher homocysteine level
Markus et al. (2005)	267 community-based subjects Austrian Stroke Prevention Study	Age: 60.0 ± 6.0 Females: 49.4%	**Vascular:** ICAM-1	WMH (Quantitative + Semi-quantitative)	MRI FS: 1.5T S: PD, T2	Cohort study	**Vascular:** 1 WMH progression a/w ICAM-1
Van Dijk et al. (2005)[b]	1,033 dementia-free, community-based sample Rotterdam Scan Study	Age: 72 ± 7 Females: 51%	**Systemic:** CRP	WMH (Semi-quantitative)	MRI FS: 1.5T S: PD, T2	Cohort study	**Systemic:** 1 Cross-sectionally, presence and greater severity of WMH (both PVH and DWMH) a/w higher CRP levels 2 Greater progression of PVH and DWMH a/w higher CRP levels
Wright et al. (2005)	259 community-based stroke-free participants Northern Manhattan Study (NOMAS)	Mean age: 64.8 Females: 55.2%	**Vascular:** Homocysteine	WMH (Quantitative)	MRI FS: 1.5T S: FLAIR	Cross-sectional	**Vascular:** 1 Greater WMH volume a/w higher homocysteine levels
Gunstad et al. (2006)	37 cardiovascular disease patients (subset of 128)	Age: 69.2 ± 7.6 Females: 41%	**Systemic:** CRP **Vascular:** Homocysteine	WMH (Quantitative)	MRI FS: 1.5T S: FLAIR	Cross-sectional	**Systemic:** 1 WMH not a/w CRP levels **Vascular:** 2 WMH not a/w homocysteine levels
Naka et al. (2006)[d,#]	102 stroke patients	Age: 69.5 ± 10.3 Females: 47.1%	**Vascular:** Homocysteine	WMH (Semi-quantitative)	MRI FS: 1T S: T2	Cross-sectional	**Vascular:** 1 Presence of advanced WMH a/w higher homocysteine levels
Schmidt et al. (2006)[b]	505 community-based participants (subset of 700) Austrian Stroke Prevention Study	Age: 69.9 ± 7.7 Females: 53.7%	**Systemic:** CRP	WMH (Quantitative + Semi-quantitative)	MRI FS: 1.5T S: nr	Cohort study	**Systemic:** 1 Severity or progression of WMH not a/w CRP levels
Wong et al. (2006)[b,#]	57 SVD-related stroke patients	**Non-Hyperhomocysteinemia** Age: 68.3 ± 12.2 Females: 44.2% **Hyperhomocysteinemia** Age: 73.0 ± 6.8 Females: 64.3%	**Vascular:** Homocysteine	WMH (Quantitative)	MRI FS: 1.5T S: T2	Cross-sectional	**Vascular:** 1 Greater WMH a/w higher homocysteine levels

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Table 1 (*continued*)

Authors (Year)	Sample size and patient cohort	Sample characteristics	Measure of inflammation	Measure of SVD	SVD imaging; field strength (FS) and sequence (S)	Study design	Results
Aono et al. (2007)[b,#]	958 community-based participants The Ohasama Study	Age: 66.0 ± 5.7 Females: 68%	**Systemic:** Fibrinogen	WMH (Semi-quantitative)	MRI FS: 0.5T S: T2	Cross-sectional	**Systemic:** 1 Presence of WMH a/w higher fibrinogen levels
Jefferson et al. (2007)	1,926 dementia-free, stroke-free, community-based sample Framingham Heart Study	Mean age: 60 ± 9 Females: 53.6%	**Systemic:** IL-6, TNFα, TNFR2, MCP-1, MPO, OPG **Vascular:** CD40, ICAM-1 P-selectin	WMH (Quantitative)	MRI FS: 1T S: T2	Cross-sectional	1 None of the inflammatory markers a/w WMH
Fornage et al. (2008)	3,644 community-based participants (3073 whites; 571 blacks) Cardiovascular Health Study	**Whites** Age: 75.4 ± 5.0 Females: 57.5% **Blacks** Age: 73.9 ± 5.7 Females: 62.7%	**Systemic:** IL-6, CRP	WMH (Semi-quantitative)	MRI FS: 1.5T S: T2	Cross-sectional	**Systemic:** 1 Presence of moderate to severe WMH a/w greater IL-6 levels in white and blacks, and with greater CRP levels in whites, but not blacks
Khan et al. (2008)	457 black stroke patients, 179 black healthy controls South London Ethnicity and Stroke Study	**Healthy controls** Age: 65.4 ± 7.4 Females: 38.0% **Stroke patients** Age: 65.4 ± 12.2 Females: 44.0%	**Vascular:** Homocysteine	WMH (Semi-quantitative)	CT/MRI FS: nr S: nr	Cross-sectional	**Vascular:** 1 WMH severity a/w higher homocysteine levels
Seshadri et al. (2008)[b]	1,965 healthy older adults Framingham Offspring Study	Age: 62 ± 9 Females: 53.4%	**Vascular:** Homocysteine	WMH (Quantitative)	MRI FS: 1T S: T2	Cohort study	**Vascular:** 1 Presence of extensive WMH at follow-up not a/w baseline or follow-up homocysteine levels
Wada et al. (2008)[b,#]	689 community-based elderly	**Without lacunes** *n* = 493 Age: 67.7 ± 5.0 Females: 55.2% **With lacunes** *n* = 196 Age: 69.9 ± 3.6 Females: 57.1%	**Systemic:** CRP	WMH (Semi-quantitative)	MRI FS: 0.3T/ 0.5T S: FLAIR	Cross-sectional	**Systemic:** 1 WMH severity not a/w CRP levels in multivariate analysis
Zylberstein et al. (2008)[b]	277 women from community sample	Mean age at CT scan: 73.8 Females: 100%	**Vascular:** Homocysteine	WMH (Semi-quantitative)	CT	Cohort study	**Vascular:** 1 Mid-life homocysteine levels not a/w later-life WMH
Baune et al. (2009)[b]	268 community participants Memory and Morbility in Augsburg Elderly (MEMO) Study	Mean age: 72.3 Females: 47.8%	**Systemic:** IL-1β, IL-6, IL-8, IL-10, IL-12, TNF-α	WMH (Quantitative)	MRI FS: 1.5T S: nr	Cross-sectional	**Systemic:** 1 None of the inflammatory markers a/w WMH
Kearney-Schwartz et al. (2009)	198 hypertensive patients with subjective cognitive impairment	Age: 69.3 ± 6.2 Females: 53.0%	**Vascular:** vWF	WMH (Semi-quantitative)	MRI FS: 1.5T S: T2	Cross-sectional	**Vascular** 1 Greater WMH severity a/w greater vWF
Wright et al. (2009)	527 stroke-free participants Northern Manhattan Study (NOMAS)	Mean age: 71.3 Females: 58%	**Systemic:** CRP, MPO **Vascular:** Lp-PLA2	WMH (Quantitative)	MRI FS: 1.5T S: nr	Cross-sectional	**Systemic:** 1 Greater WMH volume a/w higher CRP levels 2 Adjusting for all three biomarkers simultaneously, WMHV association with higher Lp-PLA2 and MPO remained significant, while the association with CRP disappeared.

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Table 1 (*continued*)

Authors (Year)	Sample size and patient cohort	Sample characteristics	Measure of inflammation	Measure of SVD	SVD imaging; field strength (FS) and sequence (S)	Study design	Results
Knottnerus et al. (2010)	149 lacunar stroke patients	**Asymptomatic lacunar infarct without extensive WMH** Age: 60.4 ± 13.0 Female: 30.2% **Isolated lacunar infarct** Age: 58.9 ± 10.0 Female: 39.5% **With extensive WMH** Age: 68.2 ± 9.3 Female: 43.4%	**Vascular:** VWF, PAI-1, TM	WMH (Semi-quantitative)	MRI FS: 1.5T/ 3T S: FLAIR	Cross-sectional	**Vascular:** 1 Presence of extensive WMH a/w lower PA1-1 but was not a/w vWF and TM
Ma et al. (2010)[#]	377 acute ischaemic stroke patients, 106 patients with transient ischaemic attack	**Acute ischaemic stroke** Age: 60.5 ± 11.6 Females: 24.7% **Transient ischaemic attack** Age: 61.3 ± 11.7 Females: 30.2%	**Vascular:** Homocysteine	WMH (Semi-quantitative)	CT/MRI FS: nr S: nr	Cross-sectional	**Vascular:** 1 Greater WMH severity a/w elevated homocysteine level
Oberheiden et al. (2010)	24 SVD patients, 10 healthy controls	**Healthy controls** Age: 64.6 ± 12.9 Females: 40.0% **SVD patients** Age: 77.3 ± 5.8 Females: 58.3%	**Systemic:** IL-6, IL-7 **Vascular:** CD40	WMH (Semi-quantitative)	MRI FS: 1.5T S:FLAIR	Cross-sectional	**Systemic:** 1 Presence of WMH a/w lower IL-7, but not IL-6 **Vascular:** 2 Presence of WMH a/w greater CD40
Romero et al. (2010)[b]	583 stroke-free, dementia-free subjects	Age: 57 ± 9 Females: 57.6%	**Vascular:** MMP-9	WMH (Quantitative)	MRI FS: 1T/1.5T S: T2	Cross-sectional	**Vascular:** 1 Presence of large WMH a/w MMP-9
Wersching et al. (2010)	Framingham Offspring Study 447 community-dwelling, stroke-free individuals	Mean age: 63 Females: 55.5%	**Systemic:** CRP	WMH (Semi-quantitative)	MRI FS: 3T S: FLAIR	Cross-sectional	**Systemic:** 1 Extent of WMH not a/w CRP levels
Narayan et al. (2011)[b]	Systematic Evaluation and Alteration of Risk Factors for Cognitive Health (SEARCH) Health Study 70 hypertensive participants without dementia	Age: 79.1 ± 3.5 Females: 60.0%	**Vascular:** Homocysteine	WMH (Quantitative)	MRI FS: 1.5T S: FLAIR	Cohort study	**Vascular:** 1 Cross-sectionally, WMH not a/w homocysteine 2 WMH progression not a/w homocysteine
Pavlovic et al. (2011)	95 SVD patients, 41 healthy subjects	**Healthy controls** Age: 57.7 ± 10.6 Females: 53.7% **SVD subjects** Age: 59.8 ± 10.9 Females: 42.1%	**Vascular:** Homocysteine	WMH (Semi-quantitative)	MRI FS: 1T S: T2	Cross-sectional	**Vascular:** 1 Greater WMH severity independently a/w increased homocysteine

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Table 1 (*continued*)

Authors (Year)	Sample size and patient cohort	Sample characteristics	Measure of inflammation	Measure of SVD	SVD imaging; field strength (FS) and sequence (S)	Study design	Results
Wada et al. (2011)[b,#]	667 community-dwelling older adults	**Without lacunar infarcts** Age: 67.7 ± 4.9 Females: 57.1% **With lacunar infarct** Age: 70.1 ± 3.5 Females: 51.6%	**Systemic:** Fibrinogen, CRP **Vascular:** vWF, TM	WMH (Semi-quantitative)	MRI FS: nr S: FLAIR	Cross-sectional	**Systemic:** 1 Greater WMH a/w greater vWF activity and fibrinogen, but not CRP **Vascular:** 2 In subjects with high fibrinogen, high vWF activity and high TM increased the risk for the presence of moderate WMH
Raz et al. (2012)	144 healthy subjects	Age: 58.9 ± 9.1 Females: 68.1%	**Systemic:** CRP **Vascular:** Homocysteine	WMH (Quantitative)	MRI FS: 4T S: FLAIR	Cross-sectional	**Systemic:** 1 Larger WMH volume a/w higher CRP levels **Vascular:** 2 Larger WMH volume a/w higher homocysteine levels
Rouhl et al. (2012)[b,c,d]	163 lacunar stroke patients, 183 hypertensive patients, 43 healthy controls	**Healthy controls** Age: 62.0 ± 7.7 Females: 54.5% **Hypertensive patients** Age: 55.3 ± 11.9 Females: 47.5% **Lacunar stoke patients** Age: 63.9 ± 12.0 Females: 39.0%	**Systemic:** CRP **Vascular:** Neopterin, ICAM-1, VCAM-1, E-selectin, P-selectin	WMH (Semi-quantitative)	MRI FS: 1.5T S: FLAIR	Cross-sectional	**Systemic:** 1 Presence of extensive WMH not a/w CRP levels **Vascular:** 2 Presence of high WMH a/w higher levels of neopterin and VCAM-1, but not P-selectin, ICAM-1, and E-selectin 3 Presence of both lacunes and high WMH burden a/w higher neopterin, ICAM-1, and VCAM-1
Satizabal et al. (2012)[b]	1,841 healthy subjects 3C-Dijon Study	Age: 72.5 ± 4.1 Females: 60.4%	**Systemic:** IL-6, CRP	WMH (Quantitative)	MRI FS: 1.5T S: T2	Cohort study	**Systemic:** 1 Cross-sectionally, higher total WMH and PVH, but not DWMH a/w higher IL-6 and CRP levels 2 Longitudinally, WMH progression not a/w baseline IL-6 or CRP levels
Feng et al. (2013b)[#]	228 healthy, community-based subjects Singapore-Longitudinal Aging Brain Study (SLAS)	Age: 65.4 ± 6.2 Females: 53.9%	**Vascular:** Homocysteine	WMH (Quantitative)	MRI FS: 3T S: FLAIR	Cross-sectional	**Vascular:** 1 WMH volume not a/w homocysteine level
Feng et al. (2013a)[b,#]	324 healthy non-stroke subjects	Age: 66.9 ± 10.7 Females: 49.1%	**Vascular:** Homocysteine	WMH (Semi-quantitative)	MRI FS:1.5T/ 3T S: FLAIR	Cross-sectional	**Vascular:** 1 Greater WMH burden a/w higher homocysteine level
Hooshmand et al. (2013)[b]	103 post-mortem brains Vaanta 85+ Study	**Low homocysteine** Age at baseline: 88.4 ± 2.8 Age at death: 92.6 ± 3.3 Females: 84.4% **High homocysteine** Age at baseline: 88.9 ± 3.2 Age at death: 92.6 ± 3.9 Females: 82.0%	**Vascular:** Homocysteine	WMH (Semi-quantitative)	Ex vivo MRI FS: 1.5T S: nr	Post-mortem study	**Vascular:** 1 Higher post-mortem PVH, but not DWMH, a/w higher homocysteine levels at baseline
Pikula et al. (2013)	1,863 stroke-free, dementia-free subjects Framingham Offspring Study	Age: 61 ± 9 Females: 55%	**Vascular:** VEGF	WMH (Quantitative)	MRI FS: 1T / 1.5T S: nr	Cohort study	**Vascular:** 1 WMH volume not a/w VEGF cross-sectionally

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Table 1 (*continued*)

Authors (Year)	Sample size and patient cohort	Sample characteristics	Measure of inflammation	Measure of SVD	SVD imaging; field strength (FS) and sequence (S)	Study design	Results
Aribisala et al. (2014)[c]	634 participants Lothian Birth Cohort 1936	Mean age: 73 Females: nr	**Systemic:** CRP, IL-6, fibrinogen	WMH (Quantitative + Semi-quantitative)	MRI FS: 1.5T S: FLAIR	Cross-sectional	**Systemic:** 1 WMH not a/w CRP, IL-6, or fibrinogen 2 Latent construct of inflammation not a/w the latent variable of WMH
Rizzi et al. (2014)	135 non-stroke outpatients of cardiology clinic (34 cognitive impairment, 101 healthy controls)	Age: 66.6 ± 8.7 Females: 40.0%	**Systemic:** CRP	WMH (Semi-quantitative)	CT	Cross-sectional	**Systemic:** 1 Presence of WMH a/w elevated CRP levels
Bridges et al. (2014)	84 post-mortem brains with minimal AD pathology (Braak 0-2) Thomas Willis Oxford Brain Collection	**Healthy controls post-mortem brains** *n* = 33 Age at death: 81 ± 8 Females: 45% **SVD post-mortem brains** *n* = 51 Age at death: 83 ± 8 Female: 39%	**Systemic:** Fibrinogen	WMH (Semi-quantitative)	In-life CT	Post-mortem study	**Systemic:** 1 WMH severity not a/w fibrinogen levels
Kim et al. (2014)[#]	137 non-stroke participants	Age: 64.9 ± 8.1 Females: 57.6%	**Systemic:** IL-6, TNF-α **Vascular:** MMP-9, PAI-1	WMH (Semi-quantitative)	MRI FS: nr S: FLAIR	Cross-sectional	**Systemic:** 1 WMH not a/w IL-6 or TNF- α **Vascular:** 2 Presence of high WMH a/w higher levels of MMP-9 but not PAI-1
Kloppenborg et al. (2014)[b]	663 patients with symptomatic atherosclerotic disease SMART-MR Study	**Non-Hyperhomocysteinemia** *n* = 533 Age: 57 ± 9 Females: 20.1% **Hyperhomocysteinemia** *n* = 130 Age: 61 ± 10 Females: 13.1%	**Vascular:** Homocysteine	WMH (Quantitative)	MRI FS: 1.5T S: FLAIR	Cohort study	**Vascular:** 1 Elevated homocysteine levels a/w greater WMH progression
Cloonan et al. (2015)	809 acute ischaemic stroke patients	Age: 65.6 ± 14.7 Females: 37%	**Vascular:** Homocysteine	WMH (Quantitative)	MRI FS: 1.5T S: FLAIR	Cross-sectional	**Vascular:** 1 Higher homocysteine levels independently predicted greater WMH volume
Tchalla et al. (2015)	25 community-dwelling participants (subset of 680) Maintenance Of Balance, Independent Living, Intellect, and Zest in the Elderly (MOBILIZE) Boston Study	Age: 77.6 ± 6.3 Females: 68.0%	**Vascular:** ICAM-1, VCAM-1	WMH (Quantitative)	MRI FS: 3T S: PD, T2	Cross-sectional	**Vascular:** 1 Greater WMH volume a/w higher VCAM-1 concentration, controlling for CRP, IL-6, patient characteristics and vascular risk factors

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Authors (Year)	Sample size and patient cohort	Sample characteristics	Measure of inflammation	Measure of SVD	SVD imaging; field strength (FS) and sequence (S)	Study design	Results
Huang et al. (2015)[#]	110 AD and 50 healthy controls	**Healthy controls** *n* = 50 Age: 73.2 ± 6.2 Females: 44.0% **Mild AD** *n* = 60 Age: 75.0 ± 6.6 Females: 53.3% **Moderate to severe AD** *n* = 50 Age: 75.4 ± 6.9 Females: 54.0%	**Vascular:** Homocysteine, ICAM-1, VCAM-1, E-selectin	WMH (Semi-quantitative)	MRI FS: 1.5T S: FLAIR	Cross-sectional	**Vascular:** 1 Severity of WMH (both PVH and DWMH) a/w higherVCAM-1, but not ICAM-1 and E-selectin
Gao et al. (2015)[#]	923 ischaemic stroke patients	Age: 58.9 ± 11.9 Females: 31.6%	**Vascular:** Homocysteine	WMH (Semi-quantitative)	MRI FS: nr S: FLAIR	Cross-sectional	**Vascular:** 1 Greater PVH, but not DWMH, observed in participants in the highest quartile of homocysteine 2 Greater WMH in the left and right frontal lobe observed in participants in the highest quartile of homocysteine
Shoamanesh et al. (2015)[b,d]	1,763 stroke-free participants Framingham Offspring Study	Age: 60.2 ± 9.1 Females: 53.7%	**Systemic:** IL-6, CRP, TNF-α, TNFR2, Fibrinogen, OPG, MCP-1, MPO **Vascular:** ICAM-1, CD40, P-selectin, Lp-PLA2 mass and activity, homocysteine, VEGF	WMH (Quantitative)	MRI FS: 1T/ 1.5T S: nr	Cross-sectional	**Systemic:** 1 Presence of extensive WMH and/or silent cerebral infarcts a/w higher levels of OPG but not IL-6, CRP, TNF- α, TNFR2, fibrinogen, MCP-1, and MPO **Vascular:** 2 Presence of extensive WMH and/or silent cerebral infarcts a/w ICAM-1 and Lp-PLA2 mass, but not CD40, P-selectin, homocysteine, Lp-PLA2 activity, and VEGF
Miwa et al. (2016)[b,d,#]	643 subjects with more than 1 vascular risk factor Osaka Follow-up Study for Carotid Atherosclerosis (OSACA)	Age: 67.2 ± 8.4 Female: 41%	**Vascular:** Homocysteine	WMH (Semi-quantitative)	MRI FS: 1.5T S: FLAIR	Cohort study	**Vascular:** 1 Cross-sectionally, WMH not a/w homocysteine
Mitaki et al. (2016)[b,d,#]	519 neurologically normal subjects	Age: 63.5 ± 10.3 Females: 45.3%	**Systemic:** CRP	WMH (Semi-quantitative)	MRI FS: 1.5T S: FLAIR	Cross-sectional	**Systemic:** 1 WMH severity not a/w CRP levels
Hainsworth et al. (2017)	126 post-mortem brains MRC-Cognitive Function and Ageing Study (CFAS) Neuropathology Study	Age: 86.4 ± 7.7 Females: 54.0%	**Systemic:** Fibrinogen	WMH (Semi-quantitative)	Post-morterm MRI FS: 1T S: T2	Post-mortem study	**Systemic:** 1 Extent of fibrinogen labelling not a/w WMH, both MRI-defined and histologically defined.
Wei et al. (2017)[#]	186 patients with ischaemic stroke and atrial fibrillation	Age: 68.8 ± 12.8 Females: 65.6%	**Systemic:** Fibrinogen	WMH (Semi-quantitative)	MRI FS: 3T S: FLAIR, T2	Cross-sectional	**Systemic:** 1 Fibrinogen independently a/w greater overall WMH, PVH but not DWMH.

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Authors (Year)	Sample size and patient cohort	Sample characteristics	Measure of inflammation	Measure of SVD	SVD imaging; field strength (FS) and sequence (S)	Study design	Results
Chung et al. (2017)[b,#]	337 patients with intracranial atherosclerotic stroke (ICAS) and non-stroke controls	**Non-stroke controls** *n* = 75 Age: 61.7 ± 10.3 Females: 58.7% **ICAS** *n* = 262 Age: 67.0 ± 12.1 Females: 42.0%	**Vascular:** Lp-PLA2	WMH (Semi-quantitative)	MRI FS: 3T S: FLAIR	Cross-sectional	**Vascular:** 1 Severity of WMH not a/w Lp-PLA2
Nam et al. (2017)[b,d,#]	2,875 healthy subjects	Age: 56 ± 9 Females: 45.6%	**Systemic:** NLR	WMH (Quantitative + Semi-quantitative)	MRI FS: 1.5T S: FLAIR	Cross-sectional	**Systemic:** 1 Greater WMH grade and volume a/w higher NLR
Walker et al. (2017)[b,d]	1,485 community participants Atherosclerosis Risk in Communities (ARIC) Study	Age at midlife: 55.5 ± 5.2 Females: 62%	**Systemic:** CRP	WMH (Quantitative)	MRI FS: 3T S: FLAIR	Cohort study	**Systemic:** 1 Midlife CRP a/w greater late-life WMH volume
Arba et al. (2018)[b]	263 acute ischaemic stroke patients	Age: 69 ± 13 Females: 41%	**Vascular:** vWF, ICAM-1, VCAM-1, VEGF	WMH (Semi-quantitative)	CT	Cohort study	**Vascular:** 1 Cross-sectionally, presence of WMH not a/w vWF, ICAM-1, VCAM-1, VEGF 2 Longitudinally, presence of WMH a/w increased vWF, ICAM-1, VCAM-1 levels, but not VEGF
Hilal et al. (2018a)[b,c,d]	2,814 population-based participants Rotterdam Study	Age: 56.9 ± 6.5 Females: 44.8%	**Systemic:** CRP	WMH (Quantitative)	MRI FS: 1.5T S: nr	Cross-sectional	**Systemic:** 1 Larger WMH volume a/w higher CRP levels
You et al. (2018)[#]	200 acute stroke patients	**Without WMH** *n* = 54 Age: 53.2 ± 11.7 Females: 33.3% **With WMH** *n* = 146 Age: 62.4 ± 12.3 Females: 41.8%	**Systemic:** CRP **Vascular:** Homocysteine	WMH (Semi-quantitative)	MRI FS: nr S: nr	Cohort study	**Systemic:** 1 Cross-sectionally, presence of WMH a/w higher levels of CRP **Vascular:** 2 Cross-sectionally, presence of WMH a/w higher levels of homocysteine
Walker et al. (2018)	1,532 community-based participants ARIC Study	Age: 76.5 ± 5.4 Females: 61%	**Systemic:** CRP	WMH (Quantitative)	MRI FS: 3T S: FLAIR	Cohort study	**Systemic:** 1 Higher WMH a/w higher 21-year average CRP 2 Higher WMH a/w early ascending CRP levels spanning middle- to late-life

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Authors (Year)	Sample size and patient cohort	Sample characteristics	Measure of inflammation	Measure of SVD	SVD imaging; field strength (FS) and sequence (S)	Study design	Results
Staszewski et al. (2018)[b]	123 SVD participants (49 with lacunar stroke, 48 with vascular dementia, 26 with vascular parkinsonism) Significance of HEmodynamic and hemostatic Factors in the course of different manifestations of Cerebral Small Vessel Disease (SHEF-SVD) Study	Age: 72.2 ± 8.0 Females: 49%	**Systemic:** CRP, IL-1α, IL-6, TNF-α **Vascular:** ICAM-1, P-selectin, CD40, PF-4, homocysteine	WMH (Semi-quantitative) *SVD progression defined as increase in WMH or development of new lacunes*	MRI FS: 1.5T S: FLAIR	Cohort study	**Systemic:** 1 SVD progression a/w IL-6 and domain z-score for systemic inflammation, but not CRP, TNF-α, IL-1α 2 WMH progression not a/w domain z-score for systemic inflammation, CRP, TNF-α, IL-6, IL-1α **Vascular:** 3 SVD progression a/w CD40, PF-4, homocysteine, but not P-selectin, ICAM-1 4 WMH progression a/w domain z-score for vascular inflammation, PF-4, but not CD40, P-selectin, ICAM-1, homocysteine
Lacunes							
Kario et al. (1996)[#]	178 high-risk healthy older adults, 32 lacunar stroke patients	**Healthy subjects (Non-Lacunar)** Age: 70 ± 7 Females: 71% **Healthy subjects (Lacunar)** Age: 73 ± 7 Females: 57% **Lacunar stroke patients** Age: 73 ± 8 Females: 44%	**Systemic:** Fibrinogen **Vascular:** vWF, TM	Silent lacunar infarcts	MRI FS: 1.5T S: T1, T2	Cross-sectional	**Systemic** 1 Presence of lacunes a/w higher fibrinogen levels **Vascular:** 2 Number of lacunes a/w higher vWF, but not TM
Matsui et al. (2001)[#]	153 community-dwelling older adults	Age: 76.7 ± 5.3 Females: 80.4%	**Vascular:** Homocysteine	Silent brain infarctions	MRI FS: 1T S: T1, T2, FLAIR	Cross-sectional	**Vascular:** 1 Presence of silent brain infarctions a/w higher homocysteine
Vermeer et al. (2002)[a]	1,077 population-based subjects Rotterdam Scan Study	Age: 72.2 ± 7.4 Females: 51.5%	**Vascular:** Homocysteine	Silent brain infarcts	MRI FS: 1.5T S: T1, T2	Cross-sectional	**Vascular:** 1 Presence of silent brain infarcts a/w higher homocysteine
Hassan et al. (2003)[a]	110 lacunar stroke patients, 50 community controls	**Healthy controls** Age: 66.5 ± 9.7 Females: 46.0% **Lacunar stroke patients** Age: 67.2 ± 10.2 Females: 35.5%	**Vascular:** ICAM-1, TM	Isolated lacunar infarcts	CT/MRI FS: nr S: T2/ CT	Cross-sectional	**Vascular:** 1 Greater extent of isolated lacunar infarcts a/w higher TM but not ICAM-1 levels
Hassan et al. (2004)[a]	172 SVD patients and 172 community controls	**Healthy controls** Age: 66.3 ± 10.2 Females: 41.9% **SVD patients** Age: 67.1 ± 10.3 Females: 40.7%	**Vascular:** Homocysteine	Lacunar infarctions	MRI FS: nr S: nr	Cross-sectional	**Vascular:** 1 Higher homocysteine observed in patients with isolated lacunar infarcts, compared to controls
Longstreth et al. (2004)[a]	622 non-stroke, non-TIA older adults Cardiovascular Health Study	Age: 65 and above (61.3% above 75) Females: 46.6%	**Vascular:** Homocysteine	Cortical infarcts	MRI FS: nr S: T1, T2	Cross-sectional	**Vascular:** 1 Cortical infarcts not a/w homocysteine

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Table 1 (*continued*)

Authors (Year)	Sample size and patient cohort	Sample characteristics	Measure of inflammation	Measure of SVD	SVD imaging; field strength (FS) and sequence (S)	Study design	Results
Hoshi et al. (2005)[#]	194 healthy subjects	Age: 67.3 ± 7.5 Females: 52%	**Systemic:** CRP, IL-6	Silent brain infarctions	MRI FS: 1.5T S: T1, T2, FLAIR	Cross-sectional	**Systemic:** 1 Presence of lacunes a/w higher CRP and IL-6 levels
Van Dijk et al. (2005)[a]	1,033 dementia-free, community-based sample Rotterdam Scan Study	Age: 72 ± 7 Females: 51%	**Systemic:** CRP	Lacunar infarcts	MRI FS: 1.5T S: PD, T2	Cohort study	**Systemic:** 1 Lacunar infarcts not a/w CRP levels
Pavlovic et al. (2006)	201 patients with SVD markers	Age: 59.8 ± 12.6 Females: 46.8%	**Systemic:** Fibrinogen **Vascular:** Homocysteine	Lacunar infarcts	MRI FS: 1T S: T1, T2	Cross-sectional	**Systemic** 1 Multiple lacunes not a/w higher fibrinogen levels, compared to those with a single lacune **Vascular** 2 Multiple lacunes a/w higher homocysteine levels, compared to those with a single lacune
Wong et al. (2006)[a,#]	57 SVD-related stroke patients	**Non-Hyperhomocysteinemia** Age: 68.3 ± 12.2 Females: 44.2% **Hyperhomocysteinemia** Age: 73.0 ± 6.8 Females: 64.3%	**Vascular:** Homocysteine	Silent brain infarcts	MRI FS: 1.5T S: T1, DWI	Cross-sectional	**Vascular:** 1 Presence of lacunes not a/w homocysteine levels
Schmidt et al. (2006)[a]	505 community-based participants (subset of 700) Austrian Stroke Prevention Study	Age: 69.9 ± 7.7 Females: 53.7%	**Systemic:** CRP	Lacunes	MRI FS: 1.5T S: nr	Cohort study	**Systemic:** 1 Number of lacunes not a/w CRP levels, both cross-sectionally and longitudinally
Aono et al. (2007)[a,#]	958 community-based participants	Age: 66.0 ± 5.7 Females: 68%	**Systemic:** Fibrinogen	Lacunar infarcts	MRI FS: 0.5T S: T2	Cross-sectional	**Systemic:** 1 Presence of lacunar infarcts a/w higher fibrinogen levels
Seshadri et al. (2008)[a]	1,965 healthy older adults Framingham Offspring Study	Baseline age: 54 ± 10 Follow-up age: 62 ± 9 Females: 53.4%	**Vascular:** Homocysteine	Silent brain infarcts	MRI FS: 1T S: PD, T2	Cohort study	**Vascular:** 1 Presence of silent brain infarcts a/w higher baseline and concurrent homocysteine levels
Wada et al. (2008)[a,#]	689 community-based older adults	**Without lacunar infarcts** n = 493 Age: 67.7 ± 5.0 Females: 55.2% **With lacunar infarcts** n = 196 Age: 69.9 ± 3.6 Females: 57.1%	**Systemic:** CRP	Lacunar infarcts	MRI FS: 0.3T/ 0.5T S: T1, T2	Cross-sectional	**Systemic:** 1 Number of lacunar infarcts not a/w CRP levels in multivariate analysis
Zylberstein et al. (2008)[a]	526 women from community sample	**Without lacunes** Mean age: 74.3 Females: 100% **With lacunes** Mean age: 73.8 Females: 100%	**Vascular:** Homocysteine	Lacunes	CT	Cohort study	**Vascular:** 1 Women with highest tertile of homocysteine levels were almost three times more likely to develop lacunes after 24 years
Baune et al. (2009)[a]	268 older community participants MEMO Study	Mean age: 72.3 Females: 47.8%	**Systemic:** IL-1β, IL-6, IL-8, IL-10, IL-12, TNF-α	Lacunar infarctions	MRI FS: 1.5T S: PD, T1, T2	Cross-sectional	**Systemic:** 1 None of the inflammatory markers a/w presence of lacunar infarctions

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Table 1 (*continued*)

Authors (Year)	Sample size and patient cohort	Sample characteristics	Measure of inflammation	Measure of SVD	SVD imaging; field strength (FS) and sequence (S)	Study design	Results
Gottesman et al. (2009)	196 with silent lacunar infarcts, 214 healthy controls ARIC Study	**Without infarcts** Mean age: 62.5 Females: 59.8% **With infarcts** Mean age: 64.4 Females: 61.2%	**Systemic:** CRP, Fibrinogen **Vascular:** vWF, D-Dimer, plasminogen, PAI-1, β-TG, TM, TPA antigen	Lacunar infarcts	MRI FS: 1.5T S: T1, T2	Cross-sectional	**Systemic:** 1 Presence of lacunar infarcts not a/w fibrinogen or CRP **Vascular:** 2 Presence of lacunar infarct a/w higher vWF, higher D-Dimer, but not plasminogen, β-TG, PAI-1, TPA antigen
Yoshida et al. (2009)[#]	97 healthy older adult volunteers	Age: 65.3 ± 8.6 Females: 52.6%	**Systemic:** CRP, IL-6, S100B **Vascular:** MMP-9	Silent brain infarcts	MRI FS: 1.5T S: T1, T2, FLAIR	Cross-sectional	**Systemic:** 1 Presence of silent brain infarcts a/w higher CRP and IL-6 levels, but not a/w S100B **Vascular:** 2 Silent brain infarcts not a/w MMP-9
Romero et al. (2010)[a]	583 stroke-free, dementia-free subjects Framingham Offspring Study	Mean age: 57 ± 9 Females: 57.6%	**Vascular:** MMP-9	Silent cerebral infarcts	MRI FS: 1T or 1.5T S: PD, T1, T2	Cross-sectional	**Vascular:** 1 Silent cerebral infarcts not a/w MMP-9
Narayan et al. (2011)[a]	70 hypertensive participants without dementia	Age: 791. ± 3.5 Females: 60.0%	**Vascular:** Homocysteine	Lacunes	MRI FS: 1.5T S: nr	Cohort study	**Vascular:** 1 Presence and development of new lacunes not a/w homocysteine (small incidence of lacunes)
Wada et al. (2011)[a,#]	667 community-dwelling older adults	**Without lacunar infarcts** Age: 67.7 ± 4.9 Females: 57.1% **With lacunar infarct** Age: 70.1 ± 3.5 Females: 51.6%	**Systemic:** Fibrinogen, CRP **Vascular:** vWF, TM	Lacunar infarcts	MRI FS: nr S: T1, T2	Cross-sectional	**Systemic:** 1 Presence of lacunar infarcts a/w fibrinogen but not CRP levels 2 Multiple lacunar infarcts (> 2) a/w higher fibrinogen compared to single/no infarcts **Vascular:** 3 Presence of lacunar infarcts a/w TM but not vWF activity
Rouhl et al. (2012)[a,c,d]	163 lacunar stroke patients, 183 hypertensive patients, 43 healthy controls	**Lacunar stoke patients** Age: 63.9 ± 12.0 Females: 39.0% **Hypertensive patients** Age: 55.3 ± 11.9 Females: 47.5% **Healthy controls** Age: 62.0 ± 7.7 Females: 54.5%	**Systemic:** CRP **Vascular:** Neopterin, ICAM-1, VCAM-1, E-selectin, P-selectin	Silent lacunar infarcts	MRI FS: 1.5T S: T2, FLAIR	Cross-sectional	**Systemic:** 1 Presence of lacunes not a/w CRP levels **Vascular:** 2 Presence of lacunes a/w higher levels of neopterin, P-selectin, ICAM-1, and VCAM-1, but not E-selectin 3 Presence of both lacunes and high WMH burden a/w higher neopterin, ICAM-1, and VCAM-1
Satizabal et al. (2012)[a]	1,841 healthy subjects 3C-Dijon Study	Age: 72.5 ± 4.1 Females: 60.4%	**Systemic:** IL-6, CRP	Silent brain infarctions	MRI FS: 1.5T S: T1, T2, PD	Cohort study	**Systemic:** 1 Silent brain infarctions not a/w IL-6 and CRP levels, both cross-sectionally and longitudinally (low occurrence of infarcts)
Feng et al. (2013a)[a,#]	324 healthy non-stroke subjects	Age: 66.9 ± 10.7 Females: 49.1%	**Vascular:** Homocysteine	Silent brain infarctions	MRI FS: 1.5T/ 3T S: T1, T2, FLAIR	Cross-sectional	**Vascular:** 1 Greater number of lacunes a/w higher homocysteine level

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Table 1 (*continued*)

Authors (Year)	Sample size and patient cohort	Sample characteristics	Measure of inflammation	Measure of SVD	SVD imaging; field strength (FS) and sequence (S)	Study design	Results
Hooshmand et al. (2013)[a]	103 post-mortem brains Vantaa 85+ Study	**Low homocysteine** Age at baseline: 88.4 ± 2.8 Age at death: 92.6 ± 3.3 Females: 84.4% **High homocysteine** Age at baseline: 88.9 ± 3.2 Age at death: 92.6 ± 3.9 Females: 82.0%	**Vascular:** Homocysteine (blood sample collected at baseline)	Macroinfarcts (Cavitary lesions or solid cerebral infarcts)	Visual examination of post-mortem brains	Post-mortem study	**Vascular:** 1 Cerebral infarcts not a/w homocysteine
Kloppenborg et al. (2014)[a]	663 patients with symptomatic atherosclerotic disease SMART-MR Study	**Non-Hyperhomocysteinemia** n = 533 Age: 57 ± 9 Females: 20.1% **Hyperhomocysteinemia** n = 130 Age: 61 ± 10 Females: 13.1%	**Vascular:** Homocysteine	Lacunes	MRI FS: 1.5T S: T1, FLAIR	Cohort study	**Vascular:** 1 Elevated homocysteine levels a/w risk of new lacunes
Nylander et al. (2015)	406 community-dwelling older adults Vasculature in Uppsala Seniors (PIVUS) Study	Baseline age: 70 ± 0 Females: 48.3%	**Systemic:** CRP	Lacunar infarcts	MRI FS: 1.5T S: PD, T1, T2	Cohort study	**Systemic:** 1 Lacunar infarcts not a/w CRP
Riba-Llena et al. (2014)	921 hypertensive participants, without stroke or dementia Investigating Silent Strokes in hYpertensives: a magnetic resonance imaging Study (ISSYS)	Mean age: 64 Females: 51.7%	**Vascular:** Lp-PLA2	Silent brain infarcts	MRI FS: 1.5T S: T1, T2, FLAIR	Cross-sectional	**Vascular:** 1 Presence and number of silent brain infarcts a/w higher Lp-PLA2 activity 2 Lp-PLA2 independently predicted silent brain infarcts in women but not men
Shoamanesh et al. (2015)[a,d]	1,763 stroke-free participants Framingham Offspring Study	Age: 60.2 ± 9.1 Females: 53.7%	**Systemic:** IL-6, CRP, TNF-α, TNFR2, Fibrinogen, OPG, MCP-1, MPO **Vascular:** ICAM-1, CD40, P-selectin, Lp-PLA2 mass and activity, homocysteine, VEGF	Silent cerebral infarcts	MRI FS: 1T/ 1.5T S: nr	Cross-sectional	**Systemic:** 1 Presence of extensive WMH and/or silent cerebral infarcts a/w higher levels of OPG but not IL-6, CRP, TNF- α, TNFR2, fibrinogen, MCP-1, and MPO **Vascular:** 2 Presence of extensive WMH and/or silent cerebral infarcts a/w ICAM-1 and Lp-PLA2 mass, but not CD40, P-selectin, homocysteine, Lp-PLA2 activity, and VEGF
Mitaki et al. (2016)[a,d,#]	519 neurologically normal subjects	Age: 63.5 ± 10.3 Females: 45.3%	**Systemic:** CRP	Lacunar infarcts	MRI FS: 1.5T S: T1, T2	Cross-sectional	**Systemic:** 1 Higher number of lacunar infarcts a/w higher CRP levels
Miwa et al. (2016)[a,d,#]	643 subjects with vascular risk factor OSACA Study	Age: 67.2 ± 8.4 Female: 41%	**Vascular:** Homocysteine	Lacunar infarction	MRI FS: 1.5T S: T1, T2, FLAIR	Cohort study	**Vascular:** 1 Cross-sectionally, presence of lacunar infarctions higher in highest tertile of homocysteine, compared to lowest tertile

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Table 1 (*continued*)

Authors (Year)	Sample size and patient cohort	Sample characteristics	Measure of inflammation	Measure of SVD	SVD imaging; field strength (FS) and sequence (S)	Study design	Results
Chung et al. (2017)[a,#]	337 patients with intracranial atherosclerotic stroke (ICAS) and non-stroke controls	**ICAS** *n* = 262 Age: 67.0 ± 12.1 Females: 42.0% **Non-stroke controls** *n* = 75 Age: 61.7 ± 10.3 Females: 58.7%	**Vascular:** Lp-PLA2	Ischaemic brain lesions	MRI FS: 3T S: DWI	Cross-sectional	**Vascular:** 1 Higher Lp-PLA2 a/w larger lesions, greater number of lesions, and larger cortical pattern
Nam et al. (2017)[a,d,#]	2,875 healthy subjects	Age: 56 ± 9 Females: 45.6%	**Systemic:** NLR	Silent brain infarcts	MRI FS: 1.5T S: T1, T2	Cross-sectional	**Systemic:** 1 Presence of silent brain infarcts not a/w NLR
Walker et al. (2017)[a,d]	1,485 community participants ARIC Study	Age at midlife: 55.5 ± 5.2 Females: 62%	**Systemic:** CRP	Lacunar infarcts	MRI FS: 3T S: FLAIR	Cohort study	**Systemic:** 1 Late-life lacunar infarcts not a/w midlife CRP
Arba et al. (2018)[a]	263 acute ischaemic stroke patients	Age: 69 ± 13 Females: 41%	**Vascular:** vWF, ICAM-1, VCAM-1, VEGF	Lacunes	CT	Cohort study	**Vascular:** 1 Cross-sectionally, presence of lacunes not a/w vWF, ICAM-1, VCAM-1, VEGF 2 Longitudinally, pre-existing lacunes a/w increased VEGF levels, but not ICAM-1 or VCAM-1
Hilal et al. (2018a)[a,c,d]	2,814 community participants Rotterdam Study	Age: 56.9 ± 6.5 Females: 44.8%	**Systemic:** CRP	Lacunes	MRI FS: 1.5T S: T1, T2, FLAIR	Cross-sectional	**Systemic:** 1 Higher lacune count a/w higher CRP levels
Staszewski et al. (2018)[a]	123 SVD participants (49 with lacunar stroke, 48 with vascular dementia, 26 with vascular parkinsonism) SHEF-SVD Study	Age: 72.2 ± 8.0 Females: 49%	**Systemic:** CRP, IL-1α, IL-6, TNF-α **Vascular:** ICAM-1, P-selectin, CD40, PF-4, homocysteine	Lacunes *SVD progression defined as increase in WMH or development of new lacunes*	MRI FS: 1.5T S: nr	Cohort study	**Systemic:** 1 SVD progression related to IL-6 and domain z-score for systemic inflammation, but not CRP, TNF-α, IL-1α 2 Development of new lacunes a/w IL-6 and domain z-score for systemic inflammation, but not CRP, TNF-α, IL-1α **Vascular:** 3 SVD progression a/w CD40, PF-4, homocysteine, but not P-selectin, ICAM-1 4 Development of new lacunes a/w homocysteine but not domain z-score for vascular inflammation, CD-40, PF-4, P-selectin, ICAM-1
Enlarged Perivascular Spaces							
Rouhl et al. (2012)[a,b,d]	163 lacunar stroke patients, 183 hypertensive patients, 43 healthy controls	**Healthy controls** Age: 62.0 ± 7.7 Females: 54.5% **Hypertensive patients** Age: 55.3 ± 11.9 Females: 47.5% **Lacunar stoke patients** Age: 63.9 ± 12.0 Females: 39.0%	**Systemic:** CRP **Vascular:** Neopterin, ICAM-1, VCAM-1, E-selectin, P-selectin	EPVS (BG, CSO, sella media level)	MRI FS: 1.5T S: nr	Cross-sectional	**Systemic:** 1 Higher number of BG-EPVS, but not sella media or CSO-EPVS a/w higher neopterin levels 2 EPVS count not a/w CRP levels **Vascular:** 3 Number of EPVS not a/w ICAM-1, VCAM-1, E-selectin, P-selectin

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Table 1 (*continued*)

Authors (Year)	Sample size and patient cohort	Sample characteristics	Measure of inflammation	Measure of SVD	SVD imaging; field strength (FS) and sequence (S)	Study design	Results
Aribisala et al. (2014)[a]	634 participants Lothian Birth Cohort 1936	Mean age: 73 Females: nr	**Systemic:** CRP, IL-6, fibrinogen	EPVS (BG, hippocampus, CSO)	MRI FS: 1.5T S: nr	Cross-sectional	**Systemic:** 1 CSO-EPVS a/w CRP, but not fibrinogen or IL-6 2 Latent construct of inflammation a/w the latent variable of EPVS
Wang et al. (2016b)	100 patients with recent lacunar or ischaemic stroke	Mean age: 69 Females: nr	**Systemic:** IL-6, TNF-α, CRP, fibrinogen **Vascular:** vWF, ICAM-1, D-dimer	EPVS (BG only)	MRI FS: 1.5T S: T2	Cross-sectional	**Systemic:** 1 IL-6, TNF-α, CRP, and fibrinogen not a/w BG-EPVS count or volume **Vascular:** 2 Greater number of BG-EPVS a/w lower vWF, but not ICAM-1 and D-dimer.
Hilal et al. (2018a)[a,b,d]	2,814 community participants Rotterdam Study	Age: 56.9 ± 6.5 Females: 44.8%	**Systemic:** CRP	EPVS (whole brain)	MRI FS: 1.5T S: T1 and T2	Cross-sectional	**Systemic:** 1 Higher EPVS count a/w higher tertiles of CRP levels
Cerebral Microbleeds							
Naka et al. (2006)[a,#]	102 stroke patients	Age: 69.5 ± 10.3 Females: 47.1%	**Vascular:** Homocysteine	CMB (whole brain)	MRI FS: 1T S: T2*	Cross-sectional	**Vascular:** 1 Presence of CMB not a/w homocysteine level
Koh et al. (2011)[#]	206 patients with first acute lacunar stroke	**Without CMB** Age: 64.6 ± 8.7 Females: 43.3% **With CMB** Age: 66.7 ± 11.3 Females: 45.6%	**Systemic:** CRP, fibrinogen **Vascular:** MMP-9, D-dimer	CMB (whole brain)	MRI FS: 1.5T S: GRE	Cross-sectional	**Systemic:** 1 Presence of CMB a/w higher MMP-9 and CRP levels, but not fibrinogen or D-dimer levels **Vascular:** 2 Presence of CMB a/w higher MMP-9, but D-dimer levels
Dassan et al. (2012)	20 acute ischaemic stroke patients	**Without CMB** *n* = 15 Age: 65.3 ± 17.2 Females: 46.7% **With CMB** *n* = 5 Age: 69.4 ± 11.2 Females: 20.0%	**Vascular:** VEGF	CMB (whole brain)	MRI FS: 1.5T S: GRE	Cross-sectional	**Vascular:** 1 Presence of CMB a/w higher VEGF levels
Rouhl et al. (2012)[a,b,c]	163 lacunar stroke patients, 183 hypertensive patients, 43 healthy controls	**Healthy controls** Age: 62.0 ± 7.7 Females: 54.5% **Hypertensive patients** Age: 55.3 ± 11.9 Females: 47.5% **Lacunar stoke patients** Age: 63.9 ± 12.0 Females: 39.0%	**Systemic:** CRP **Vascular:** Neopterin, ICAM-1, VCAM-1, E-selectin, P-selectin	CMB (whole brain)	MRI FS: 1.5T S: GRE	Cross-sectional	**Vascular:** 1 Higher number of CMB a/w higher E-selectin levels, irrespective of location (deep or lobar)

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Table 1 (*continued*)

Authors (Year)	Sample size and patient cohort	Sample characteristics	Measure of inflammation	Measure of SVD	SVD imaging; field strength (FS) and sequence (S)	Study design	Results
Huang et al. (2013)[#]	126 patients with first ever ischaemic stroke	**Without CMB** Age: 63.2 ± 13.3 Females: 41.2% **With CMB** Age: 64.6 ± 12.7 Females: 27.0%	**Vascular:** E-selectin	CMB (lobar, deep, infratentorial)	MRI FS: 3T S: SWI	Cross-sectional	**Vascular:** 1 Presence and number of CMB a/w higher E-selectin levels 2 Higher E-selectin levels in patients with mixed CMB, and severe CMB, compared to those without CMB
Shoamanesh et al. (2015)[a,b]	1,763 stroke-free participants Framingham Offspring Study	Age: 60.2 ± 9.1 Females: 53.7%	**Systemic:** IL-6, CRP, TNF-α, TNFR2, fibrinogen, OPG, MCP-1, MPO **Vascular:** ICAM-1, CD40, P-selectin, Lp-PLA2 mass and activity, homocysteine, VEGF	CMB (lobar-only, deep-only, any-deep)	MRI FS: 1T/ 1.5T S: GRE	Cross-sectional	**Systemic:** 1 Presence of CMB a/w higher TNFR2 and MPO – this was most prominent in persons with only deep CMB 2 Presence of CMB not a/w levels of IL-6, CRP, TNF-α, fibrinogen, OPG, and MCP-1 3 Higher number of CMB a/w higher TNFR2 and MPO, but not IL-6, CRP, TNF-α, fibrinogen, OPG, and MCP-1 **Vascular:** 4 Presence of CMB not a/w CD40, ICAM-1, P-selectin, homocysteine, LP-PLA2 activity and mass, and VEGF
Mitaki et al. (2016)[a,b,#]	519 neurologically normal subjects	Age: 63.5 ± 10.3 Females: 45.3%	**Systemic:** CRP	CMB (subcortical white matter, BG, thalamus)	MRI FS: 1.5T S: GRE	Cross-sectional	**Systemic:** 1 Number of CMB not a/w CRP levels
Miwa et al. (2016)[a,b,#]	643 subjects with vascular risk factor OSACA Study	Age: 67.2 ± 8.4 Female: 41%	**Vascular:** Homocysteine	CMB (strictly lobar, strictly deep, mixed)	MRI FS: 1.5T S: GRE	Cohort study	**Vascular:** 1 Cross-sectionally, presence of total CMB and deep CMB, but not strictly lobar CMB, were more prevalent in the highest tertile of homocysteine, compared to the lowest tertile.
Wang et al. (2016a)	112 ischaemic stroke patients	Mean age: 67.1 Females: 28.6%	**Vascular:** Homocysteine	CMB (lobar, deep, mixed)	MRI FS: 3T S: SWI	Cross-sectional	**Vascular:** 1 Presence and number of CMB a/w higher homocysteine levels
Zhang et al. (2016a)[#]	146 AD patients	Age: 72.1 ± 7.4 Females: 56.8%	**Vascular:** VEGF	CMB (strictly lobar, strictly non-lobar, mixed)	MRI FS: 3T S: SWI	Cross-sectional	**Vascular:** 1 Presence and number of CMB a/w higher VEGF

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Table 1 (*continued*)

Authors (Year)	Sample size and patient cohort	Sample characteristics	Measure of inflammation	Measure of SVD	SVD imaging; field strength (FS) and sequence (S)	Study design	Results
Lu et al. (2017)[#]	201 stroke-free participants	**Non-CMB group** Age: 61.76 ± 11.06 Females: 48.0% **CMB group** Age: 68.61 ± 7.76 Females: 40.8%	**Systemic:** CRP, IL-6 **Vascular:** MMP-9	CMB (deep/infratentorial, lobar)	MRI FS: 3T S: SWI	Cross-sectional	**Systemic:** 1 Presence of deep/infratentorial and deep CMB a/w CRP, IL-6 **Vascular:** 2 Presence of deep/infratentorial and deep CMB a/w MMP-9
Nam et al. (2017)[a,b,#]	2,875 healthy subjects	Age: 56 ± 9 Females: 45.6%	**Systemic:** NLR	CMB (whole brain)	MRI FS: 1.5T S: GRE	Cross-sectional	**Systemic:** 1 Presence of CMB not a/w NLR levels
Walker et al. (2017)[a,b]	1,485 community participants ARIC Study	Age at midlife: 55.5 ± 5.2 Females: 62%	**Systemic:** CRP	CMB (whole brain)	MRI FS: 3T S: GRE	Cohort study	**Systemic:** 1 Presence of late-life CMB not a/w midlife CRP levels
Hilal et al. (2018a)[a,b,c]	2,814 community participants Rotterdam Study	Age: 56.9 ± 6.5 Females: 44.8%	**Systemic:** CRP	CMB (lobar, deep, infratentorial)	MRI FS: 1.5T S: GRE	Cross-sectional	**Systemic:** 1 Elevated CRP a/w greater number of deep/infratentorial CMB, but fewer lobar CMB
Wu et al. (2018)[#]	148 acute ischaemic stroke patients	Age: 69.6 ± 8.2 Females: 47.3%	**Vascular:** ICAM-1	CMB (whole brain)	MRI FS: 1.5T S: SWI	Cross-sectional	**Vascular:** 1 Presence of CMB a/w higher ICAM-1

Abbreviations: AD, Alzheimer's disease; a/w, associated with; BG, basal ganglia; β-TG, β-thromboglobulin; CD40, CD40 ligand; CRP, C-reactive protein; CSO, centrum semiovale; CT, computed tomography; CVD, cerebrovascular disease; DWI, diffusion weighted imaging; DWMH, deep white matter hyperintensities; EPVS, enlarged perivascular spaces; FLAIR, fluid-attenuated inversion recovery; GFAP, glial fibrillary acidic protein; GRE, T2* gradient-recalled echo; ICAM-1, intercellular adhesion molecule-1; IL-6, interleukin-6; LA-DR, human Leukocyte Antigen – DR isotype; Lp-PLA2, lipoprotein-associated phospholipase A2; MCP-1, monocyte chemotactic protein 1; MPO, myeloperoxidase; MRI, magnetic resonance imaging; NLR, neutrophil to lymphocyte ratio; nr, not reported; OPG, osteoprotegerin; PAI-1, plasminogen activator inhibitor-1; PD, proton density; PVH, periventricular white matter hyperintensities; SVD, small vessel disease; SWI, susceptibility weighted imaging; TM, thrombomodulin; TNF-α, tumour necrosis factor-α; TNFR2, tumour necrosis factor receptor-2; TPA, tissue plasminogen activator; VEGF, vascular endothelial growth factor; vWF, von Willebrand factor; WMH, white matter hyperintensities.

[a] Study also covered under WMH.

[b] Study also covered under Lacunes.

[c] Study also covered under EPVS.

[d] Study also covered under CMB.

[#] Studies conducted in Asian cohorts.

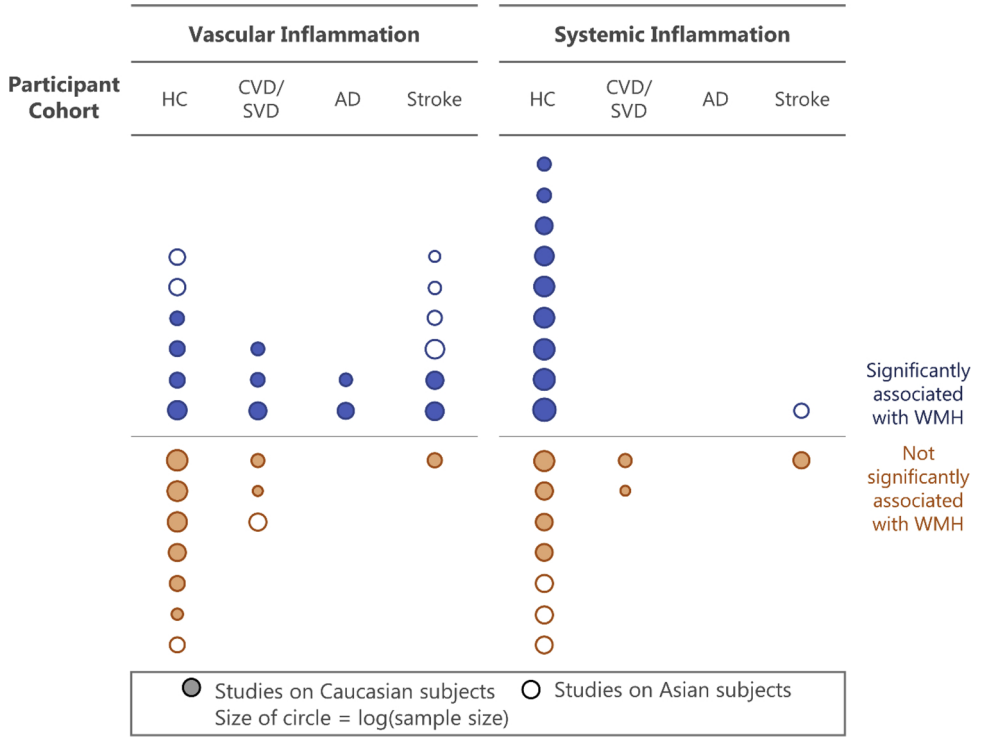

Fig. 2. WMH: Association with vascular inflammation (homocysteine) and systemic inflammation (CRP), stratified by diagnosis, ethnicity, and labelled by sample size.

3.4. Cerebral microbleeds

Greater CMB burden was often accompanied by elevated markers of vascular inflammation/endothelial dysfunction and systemic inflammation, particularly in stroke patients. Although studies on homocysteine were largely divided, evidence of the relationship between CMB and E-selectin and vascular endothelial growth factor (VEGF) provide support of a vascular inflammatory involvement in CMB formation. In terms of systemic inflammation, there was no consensus on the relationship between CRP and CMB in healthy controls. In stroke cohorts, however, there were significant relationships between greater CMB burden and higher levels of CRP and interleukin-6.

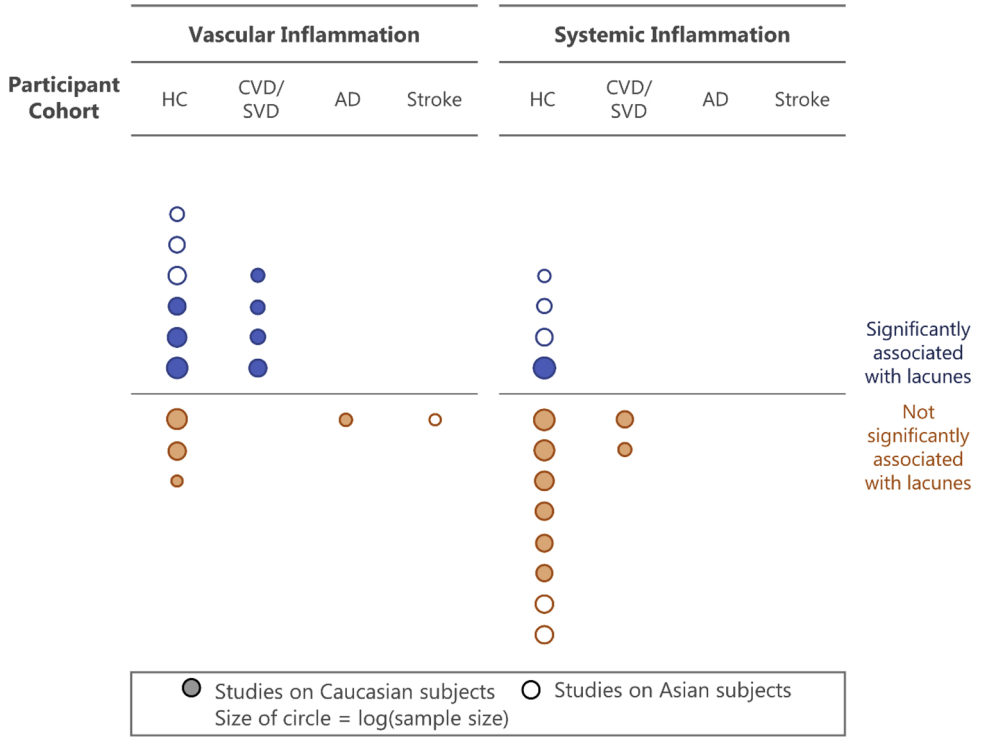

Fig. 3. Lacunes: Association with vascular inflammation (homocysteine) and systemic inflammation (CRP), stratified by diagnosis, ethnicity, and labelled by sample size.

Importantly, findings differed by CMB detection protocols. Although reports were somewhat inconsistent *overall*, it is notable that all 4 studies utilising 3T SWI scans for CMB detection reported consistently robust associations (Huang et al., 2013; Lu et al., 2017; Wang et al., 2016a; Zhang et al., 2016b), as opposed to studies using 1.5T and/or gradient recalled-echo (GRE) scans, which are less capable of detecting CMB reliably (Cheng et al., 2013; Stehling et al., 2008). While this may suggest that the under-detection of CMB may be masking associations between inflammation and SVD, it should also be noted that 3 of the 4 SWI studies were conducted in Alzheimer's disease and stroke cohorts. Further research should be done to examine these associations in healthy cohorts using more reliable CMB detection methods.

Several studies reported region-specific associations between inflammation and deep CMB. Higher levels of CRP, TNFR2, and myeloperoxidase were associated with greater numbers of deep CMB in healthy participants, while greater homocysteine was associated with the presence of deep, but not lobar CMB.

4. Discussion

This systematic review suggests that markers of vascular inflammation/endothelial dysfunction are more strongly and consistently associated with SVD, than those of systemic inflammation. Furthermore, vascular inflammation and systemic inflammation appeared to be differentially related to two distinct forms of SVD – regional differences suggest that vascular inflammatory responses play a more central role in the formation of SVD in brain regions typically associated with hypertensive arteriopathy (*e.g.*, basal ganglia), while systemic inflammation appeared to be involved in CAA-related vascular damage in lobar regions and the centrum semiovale. The existing literature suggests that vascular inflammation and endothelial dysfunction may be the driving force behind SVD *via* BBB disruptions, and can occur in the absence of systemic inflammation. Nevertheless, there is evidence that systemic inflammation is longitudinally associated with SVD progression, especially if the inflammatory response is sustained in the long term.

We discuss how findings support the involvement of BBB and endothelial dysfunction in the pathogenesis of SVD, the various factors influencing the associations between inflammation and SVD (*e.g.*, gender, ethnicity, APOE genotype, diagnosis, duration of inflammation), and implications on therapeutic interventions.

4.1. Blood-brain barrier and endothelial dysfunction

Findings support the position that BBB dysfunction is involved in the pathogenesis of SVD, as a downstream result of endothelial dysfunction – this process appeared particularly relevant in the development of CMB and EPVS. The functions of the BBB include restricting the entry of pathogens and immune cells into the brain. However, given that the BBB is composed of endothelial cells, vascular inflammation and disruptions to endothelial function can cause the BBB to break down, increasing its permeability and allowing the entry of potentially harmful toxins and immune cells into the brain (Beard et al., 2011). In turn, this has been proposed to cause changes to the small vessel structures, parenchyma, and PVS, resulting in SVD (Wardlaw, 2010).

In general, findings are interpreted to suggest that endothelial dysfunction and increased BBB permeability may contribute to the development of SVD, implicating EPVS in particular. EPVS itself is considered a marker of BBB dysfunction (Wardlaw et al., 2009), as well as a marker of neuroinflammation (Wuerfel et al., 2008). Normally, PVS function as a conduit for the drainage of interstitial fluids to the ventricles (Abbott, 2004). Being a direct pathway of interstitial drainage, however, it is also vulnerable as a gateway for harmful foreign antigens (*e.g.* toxins) to enter the brain. Vascular inflammatory processes may be involved in the dilation of PVS, as evidenced by associations between greater EPVS burden with higher levels of neopterin and lower levels of von Willebrand factor expression in plasma. Both of these are considered markers of endothelial dysfunction – (1) neopterin, a product of activated macrophages/monocytes, reflects the degree of oxidative stress induced by immune system activation (Murr et al., 2002), while (2) the von Willebrand factor is a marker of endothelial cell damage and a regulator of BBB permeability (Suidan et al., 2013). Taken together, findings demonstrate a close coupling between EPVS, endothelial dysfunction, and BBB permeability. However, due to the cross-sectional designs of the studies, it remains unclear as to whether PVS dilation is a cause, effect, or secondary process of endothelial dysfunction and increased BBB permeability.

It is noteworthy that two important markers of endothelial dysfunction, E-selectin and VEGF, were found to be exclusively associated with CMB, but not the other markers of SVD (*i.e.*, WMH, lacunes, EPVS). Soluble E-selectin is shed from damaged endothelial cells, and due to its exclusively endothelial source, it is considered to be one of the most specific measures of endothelial damage (Deanfield et al., 2007). As such, the associations demonstrated between E-selectin and the presence (Huang et al., 2013) and number (Rouhl et al., 2012) of CMB provides strong support that endothelial dysfunction plays a key role in the development of CMB. As a result of the increased BBB permeability brought about by endothelial dysfunction, CMB may result from 'leakage' of red blood cells into the parenchyma (Nachman and Rafii, 2008), as opposed to ruptured vessels. This is further supported by evidence demonstrating associations between CMB and VEGF, a potent inducer of vascular leakage, in Alzheimer's disease (Zhang et al., 2016b) and stroke patients (Dassan et al., 2012). Somewhat surprisingly, almost all investigations on other SVD markers (*i.e.* WMH, lacunes, EPVS) did not find any significant associations with E-selectin or VEGF. The largely exclusive associations of CMB with E-selectin and VEGF suggests a disproportionately central role of endothelial dysfunction in CMB formation, compared to other SVD markers. However, given the limited literature, more investigations should be done to investigate the role of E-selectin in WMH, lacunes, and EPVS.

Although the relationship between inflammation and BBB dysfunction has been well-documented, the direction of causality remains a topic of debate. Several studies have found evidence of BBB damage preceding inflammation (Minagar et al., 2006; Tonra et al., 2001), suggesting that increased BBB permeability exposes the brain to harmful toxins and immune cells, thereby damaging the vessel walls and parenchyma of the brain, while others believe that inflammation is responsible for damages to the BBB (Varatharaj and Galea, 2017). Longitudinal investigations and more direct measures of BBB integrity are needed to elucidate the mechanistic involvement of the BBB in SVD.

4.2. Longitudinal associations

Cross-sectionally, the literature pertaining to associations between SVD and systemic inflammation has been inconsistent. However, longitudinal investigations demonstrated that higher levels of systemic inflammation predicted WMH progression, although it was unrelated to lacune progression. Importantly, there was evidence to suggest that the *prolongation* of systemic inflammation may be a key propagator of subsequent SVD progression. Findings from the Atherosclerosis Risk in Communities study found that *sustained* elevation of CRP levels across midlife increased the risk of SVD two decades later (Walker et al., 2018). Notably, participants who experienced high levels of CRP at baseline, followed by low CRP in later years were not at greater risk of developing WMH, which was in agreement with previous evidence that reduction in CRP levels in healthy older adults predicted better white matter microstructure, as measured by fractional anisotropy (Bettcher et al., 2015). It is plausible that short-term elevation of systemic inflammation may not be sufficient to induce a vascular inflammatory cascade leading to SVD, but when prolonged, could promote the development of SVD downstream. The significance of the *prolongation* of inflammation may in part explain the inconsistent findings obtained in

cross-sectional studies, highlighting the inadequacy of single-time measurements.

Somewhat contrasting results were obtained with regard to longitudinal associations between vascular inflammation/endothelial dysfunction and SVD. While heightened baseline levels of vascular inflammation predicted lacune progression, findings were inconclusive in relation to WMH progression. The differential involvement of the two forms of inflammation in WMH and lacunes suggests that WMH may be linked to elevations in non-specific inflammatory markers, while lacunes could stem from focal damage to the endothelium.

Although current literature is yet unable to establish whether inflammation is causal of, or merely secondary to SVD, basic research studies suggest that inflammation/endothelial dysfunction are responsible, at least in part, in the pathogenesis of SVD. Recently, a single-nucleotide polymorphism in ATP11B has been identified in human SVD patients and was found to be associated with WMH. Importantly, the mutation of this gene is rats has been shown to lead to endothelial dysfunction, suggesting the involvement of inflammation/endothelial dysfunction in SVD. Nevertheless, this has yet to be established in humans. To address this, future studies would benefit from repeated measurements of inflammation alongside SVD progression, and the use of Mendelian randomisation to study the effects of genetic variants associated with inflammation on SVD (*e.g.*, Rutten-Jacobs et al., 2016).

4.3. Regional distribution of small vessel disease

The markers recognised to represent vascular inflammation and systemic inflammation seemed to be differentially associated with two distinct types of SVD, namely hypertensive arteriopathy and cerebral amyloid angiopathy (CAA), as classified by Pantoni's etiological classification of Type 1 and Type 2 SVD (Pantoni, 2010). Inflammation, especially vascular inflammation, appeared to be preferentially associated with SVD in the periventricular area, basal ganglia, and brainstem, which are linked to hypertensive arteriopathy. Conversely, systemic inflammation, but not vascular inflammation, seemed to be involved in cortical regions, which are commonly associated with CAA. The differential vulnerability to vascular damage may be attributed to features of the cerebrovascular network making certain regions more vulnerable to endothelial dysfunction.

4.3.1. Type 1: hypertensive arteriopathy (arteriolosclerosis)

Several studies reported stronger associations between inflammation and SVD occurring in regions characteristic of hypertensive arteriopathy. This includes lesions occurring in areas supplied by deep perforating arteries, such as WMH in the periventricular region (as opposed to deep WMH), deep CMB (as opposed to lobar CMB), and EPVS occurring in the basal ganglia (as opposed to EPVS in the centrum semiovale). Anatomically, these regions are supplied by long arterioles and arteries which are susceptible to luminal narrowing resulting from atherosclerosis, especially in hypertension and diabetes mellitus. These long arteries are susceptible to twisting/looping, which can be exacerbated by hypertension, typically affecting the small perforating end-arteries. As such, lesions occurring in these regions are often attributed to hypertensive pathology, including lacunes (Kario et al., 2001), CMB (Greenberg et al., 2009), and EPVS (Charidimou et al., 2013).

Given the detrimental effects of hypertension on BBB integrity (Biancardi et al., 2014), the involvement of endothelial activation in SVD positions it as a possible mediator explaining the mechanisms leading from hypertension to increased risk of SVD, especially in regions supplied by deep perforating arteries. However, the association of SVD with hypertension is qualified by the opposing effects of diastolic and systolic pressure (Fuhrmann et al., 2018), suggesting that pulse pressure may also be relevant rather than just hypertension.

4.3.2. Type 2: cerebral amyloid angiopathy

Findings from this systematic review offer new insights into the mechanisms behind CAA-related SVD, implicating systemic inflammation as a contributor to CAA-related damage. An examination of regional differences found that systemic inflammation was preferentially associated with vascular damage in regions commonly linked to CAA pathology – these are lobar regions and areas supplied by cortical and leptomeningeal vessels, which are commonly affected by CAA. For instance, systemic inflammation was associated with EPVS occurring specifically in the centrum semiovale, a pattern often observed in Alzheimer's disease and CAA. This is in line with prior research suggesting that EPVS in the centrum semiovale, but not in the basal ganglia, may be attributed to systemic inflammation (Miyata et al., 2017). CAA results from the deposition of β-amyloid within the walls of cortical and leptomeningeal blood vessels, and preferentially affects lobar regions. This accumulation of β-amyloid plaques in the cerebral cortex activate the immune response, inducing the activation of microglia and cytokine production (Meyer-Luehmann et al., 2008), contributing to downstream damage to the parenchyma and vessels in the brain through the release of neurotoxic factors (Lucin and Wyss-Coray, 2009), perhaps explaining the findings observed. Other SVD markers occurring in this area have also been associated with CAA, including lobar CMB (Greenberg et al., 2009; Vernooij et al., 2008). While studies in this review have not reported any exclusive associations between systemic inflammation and lobar CMB, recent mouse models have demonstrated bidirectional associations between the two, whereby CMB may be induced by systemic inflammation, and also heighten levels of inflammation (Ahn et al., 2018; Sumbria et al., 2018). However, more studies are required to reach a definitive conclusion in human populations.

4.4. Factors influencing associations between inflammation and SVD

4.4.1. Diagnostic group differences

The association between inflammation and SVD were largely confined to patient cohorts, but was not observed in healthy older adults. For instance, the relationship between WMH and homocysteine was inconclusive within healthy older adults, although stratification by diagnosis group revealed that majority of studies on stroke and Alzheimer's disease cohorts demonstrated significant associations (Fig. 2). Similarly, the relationship between homocysteine and lacunes was not conclusive in healthy older adults, while all four studies in SVD cohorts reported significant associations (Fig. 3). Evidence of associations between inflammation and CMB and EPVS were also more robust in stroke cohorts. The lack of a relationship in healthy cohorts may perhaps be attributed to low or minimal levels of pathology.

4.4.2. Sex differences

Levels of inflammation and cerebrovascular damage differed significantly between males and females, although there was insufficient evidence to determine whether sex influenced the association between SVD and inflammation. In general, studies in this review reported higher levels of systemic (CRP, NLR) and vascular inflammation (homocysteine) in males, compared to females (L. Feng et al., 2013; Hassan et al., 2004; Hogervorst et al., 2002; Ma et al., 2010; Matsui et al., 2001; Nam et al., 2017; Wright et al., 2005). In relation to cerebrovascular damage, however, females displayed greater WMH burden than males (Cloonan et al., 2015; Hogervorst et al., 2002; Sachdev, 2004; Wright et al., 2005).

However, few studies investigated the effect of sex on the association between SVD and inflammation, reporting contrasting findings. Some studies found exclusive associations between SVD and inflammation in females, but not males (Hogervorst et al., 2002; Riba-Llena et al., 2014), and vice versa (Sachdev, 2004), while others found that the relationship between SVD and inflammation was not influenced by gender (Aono et al., 2007; Khan et al., 2008; Wright et al.,

2009). On top of distinct sex differences in brain structure and function (Cosgrove et al., 2007), males and females also differ in terms of cerebrovascular health (Gallart-Palau et al., 2016; Sachdev et al., 2009) and the immune response (Khera et al., 2005; Oertelt-Prigione, 2012). By examining how sex influences the association between the two processes, researchers may better elucidate the underlying mechanisms involved and identify key contributing factors, e.g. hormonal changes (Hogervorst et al., 2002; Tallova et al., 1999).

4.4.3. Cross-ethnic differences

Ethnic differences appeared to influence the relationship between inflammation and SVD. In healthy controls, associations between systemic inflammation and WMH were commonly reported in Caucasian cohorts, but was largely absent in Asian cohorts (Fig. 2). With regard to lacunes, however, almost all studies conducted in Caucasian cohorts reported an absence of association between lacunes and CRP, while findings were mixed in Asian cohorts (Fig. 3). Comparing blacks and whites, the significance of ethnicity was inconclusive. While some have found that blacks display stronger associations between inflammation and SVD (Khan et al., 2008; Khera et al., 2005; Walker et al., 2017), contrasting evidence exists (Fornage et al., 2008).

4.4.4. APOE genotype

There was some evidence to suggest that APOE genotype moderated the association between inflammation and SVD. Significant associations in APOE ε2 and APOE ε4 carriers, but not non-carriers, suggests a heightened sensitivity to abnormal inflammatory levels amongst those in possession of these alleles (Romero et al., 2012; Walker et al., 2017). This may be explained by the increased propensity of APOE ε2 and APOE ε4 to promote inflammation, notably through distinct processes. While APOE ε2 heightens inflammation through defective receptor binding and delayed lipid clearance (Kuhel et al., 2013), APOE ε4 has been found to increase inflammation by accelerating endoplasmic reticulum stress and reducing macrophage function (Cash et al., 2012). Moreover, this may be further accentuated by the tendency for APOE ε4 carriers to produce a stronger neuroinflammatory response to peripheral systemic inflammation (Lynch et al., 2003; Ophir et al., 2005).

4.5. Evidence from animal studies

While existing human studies have been unable to ascertain the direction of causality between inflammation and SVD, evidence from animal studies may help bridge the gap between basic and clinical research, suggesting that SVD may be caused by inflammation. Investigations based on rat models have generally reported robust associations between inflammation and SVD (e.g., Jalal et al., 2012; Kaiser et al., 2014; Rajani et al., 2018; Rajani and Williams, 2017), with histological studies showing activated microglia and increased expression of vascular inflammatory markers (e.g. MMP-9, TNF-α) within regions of white matter lesions (Farkas et al., 2004; Jalal et al., 2012).

Animal studies have also shed light on the direction of causality, providing strong support that inflammation and endothelial dysfunction precedes, and causes, SVD (Jalal et al., 2015; Kaiser et al., 2014; Rajani et al., 2018). This is demonstrated especially by the reversal of white matter damage following the use of drugs targeting inflammation and the endothelium, as well as the identification of a single-nucleotide polymorphism of a gene in SVD patients – a gene shown to be responsible for endothelial dysfunction in rats when mutated (Jalal et al., 2015; Rajani et al., 2018).

4.6. Therapeutic interventions

Although findings suggest the potential of anti-inflammatory drugs in combating SVD, there is weak evidence to support their efficacy in preventing SVD and related neurodegeneration (Bath and Wardlaw, 2015; Meyer et al., 2019; Mok and Kim, 2015; Yoon et al., 2017). While further research is currently being undertaken to assess the efficacy of anti-inflammatory drugs in SVD (Bath and Wardlaw, 2015), the lack of success thus far suggests that such drugs might be treating the symptom of inflammation, but not its underlying cause. On the other hand, interventions targeting the endothelium have shown promising results in rat models, whereby the stabilisation of endothelial cells was found to reverse white matter abnormalities (Rajani et al., 2018). Combined with evidence from this systematic review, this highlights the need to further assess the therapeutic efficacy of interventions targeting the endothelium and blood brain barrier in humans.

4.7. Future directions

4.7.1. Differentiation of vascular inflammation and systemic inflammation

At present, scientists use the term 'inflammation' to describe both systemic and vascular inflammation. However, the variability in the associations between SVD and the two forms of inflammation suggests distinct roles and vascular outcomes in SVD, despite the fact that they can occur simultaneously. In acknowledging their differences, future research should aim to characterise and distinguish between the two inflammatory responses.

4.7.2. Need for more longitudinal studies

Majority of the studies identified employed cross-sectional designs. Of the limited cohort studies, all but 2 studies measured inflammation at only one time point. Furthermore, all studies examined inflammation as a predictor of SVD, while none examined the opposite direction of causality. These limitations hinder our ability to draw reliable conclusions on the directionality of effects, or account for fluctuations in inflammation levels. This is particularly important considering the importance of *prolonged* systemic inflammation in propagating SVD.

4.7.3. Blood-brain barrier measurements

Although the relationship between inflammation and BBB dysfunction has been well-established, the direction of causality remains a topic of debate. Longitudinal investigations, and the use of more direct measures of BBB integrity (*e.g.* dynamic contrast-enhanced MRI) are required to elucidate the involvement of the BBB in SVD.

4.7.4. Need for high-resolution imaging for reliable SVD detection

The MRI parameters employed for the detection of SVD markers should also be considered, especially in relation to CMB detection, which most studies performed using T2*-weighted GRE scans on 1.5T MRI. However, CMB detection is known to vary dramatically depending on the field strength and scan sequence adopted – SWI scans detect 25% more CMB than GRE scans (Cheng et al., 2013), while 3T scans detect 30% more CMB than 1.5T scans (Stehling et al., 2008). As such, further research employing more reliable and consistent CMB detection is required to ensure the accurate estimation of SVD severity.

4.7.5. Simultaneous investigation of markers

To distil the independent associations involved, multiple markers of inflammation and SVD should be investigate simultaneously. A number of studies limited their analysis to single markers of inflammation, which is problematic due to the strong relationships between inflammatory markers. Furthermore, in instances whereby multiple inflammatory markers were examined simultaneously, investigations often focused on either vascular or systemic inflammation, but rarely both. The same can be said about SVD markers - out of the 82 articles identified, only 2 articles have investigated all four SVD markers in tandem (Hilal et al., 2018a; Rouhl et al., 2012).

4.7.6. Inflammation and SVD in dementia

Despite increasing recognition of the role of both inflammation and SVD in dementia, only four studies on dementia cohorts were identified, although an abundance of research has been conducted in healthy

adults and other disorders such as multiple sclerosis. Further investigations on the associations of inflammation and SVD in dementia will be valuable in elucidating the underlying mechanisms of dementia.

4.8. Strengths and limitations

Publication bias is a problem inherent in academic literature and, by extension, systematic reviews. This systematic review was able to overcome some extent of publication bias, by virtue of the simultaneous analysis of multiple markers in many studies, reporting non-significant findings alongside significant results. In this review, we classified the various inflammatory markers into systemic and vascular inflammation based on distinctions emerging in recent research (Hall et al., 2013; Kressel et al., 2009; Shoamanesh et al., 2015). However, the various biological markers are recognised to be closely interconnected, and overlaps may exist. Further research to make distinctions between the two forms of inflammation are required for more definite assignment of inflammation type. Finally, we examined the effect of sample sizes on previous findings. However, sample size was not a major determinant of a study's reported significance/non-significance (Figs. 2 and 3).

4.9. Conclusion

Biological markers of vascular inflammation/endothelial dysfunction appear to be involved in the pathogenesis of SVD in stroke patients, and may be linked to underlying hypertensive arteriopathology. While cross-sectional associations with systemic inflammation have been inconclusive, heightened systemic inflammatory responses appeared to be capable of promoting the subsequent development of SVD, especially if prolonged. Combined with reports from emerging animal studies, these findings have important implications for therapeutic interventions, suggesting the potential of treatments targeting the endothelium and blood brain barrier to combat SVD, and by extension, SVD-related neurodegeneration.

Authors' contributions

Audrey Low conducted the literature searches and wrote the paper. Elijah Mak reviewed the drafts, and contributed to the writing of the paper. James Rowe, Hugh Markus and John O'Brien reviewed the data and manuscript, provided critical feedback, and made revisions to the manuscript.

Transparency document

The Transparency document associated with this article can be found in the online version.

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